A review of the possible prognostic values of biochemical changes in patients with SARS-CoV-2 infections

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Abstract:

Because of high mortality and long-term hospital stay among patients with SARS-CoV-2 infections, it is important to search for biochemical changes in different organs and systems that could be useful in diagnosis and prognosis of COVID-19. We conducted a literature search of online databases including PubMed, Web of Science, Scopus and Google scholar for relevant materials on biochemical changes in SARS-CoV-2 infections published between December 2019 and March 2021. The review shows that SARS-CoV-2 uses the angiotensin converting enzyme 2 (ACE2) for attachment and entry into host cells. These ACE2 are abundantly expressed by the epithelial cells of the respiratory tract and moderately expressed by the epithelial cells of the esophagus, stomach, duodenum, ileum, rectum, cholangiocytes, liver hepatocytes, pancreatic beta cells, and kidney tubular cells. This explains the systemic nature of SARS-CoV-2 infection, and the high morbidity and mortality associated with COVID-19. Although, tests to assess biochemical changes are not specific enough for the diagnosis of SARS-CoV-2 infection, they may be useful for predicting outcome of COVID-19. This review highlights biochemical parameters that are significantly elevated or reduced in SARS-CoV-2 infections, and which can be used as predictive factors of the severity and prognosis in COVID-19 patients.

Keywords: SARS-CoV-2; COVID-19; ACE2; Biomarkers; Diagnosis; Prognosis

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Un examen des valeurs pronostiques possibles des changements biochimiques chez les patients infectés par le SRAS-CoV-2

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Abstract:

En raison de la mortalité élevée et du séjour à l’hôpital à long terme chez les patients infectés par le SRAS-CoV-2, il est important de rechercher des changements biochimiques dans différents organes et systèmes qui pourraient être utiles pour le diagnostic et le pronostic de COVID-19. Nous avons effectué une recherche documentaire dans des bases de données en ligne, notamment PubMed, Web of Science, Scopus et Google Scholar, pour rechercher des documents pertinents sur les changements biochimiques dans les infections par le SRAS-CoV-2 publiés entre décembre 2019 et mars 2021. La revue montre que le SRAS-CoV-2 utilise l’enzyme de conversion de l’angiotensine 2 (ACE2) pour la fixation et l’entrée dans les cellules hôtes. Ces ACE2 sont abondamment exprimés par les cellules épithéliales des voies respiratoires et modérément exprimés par les cellules épithéliales de l’œsophage, de...
Introduction:

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is responsible for the current coronavirus disease-2019 (COVID-19) pandemic. Like other coronavirus, it is a highly pathogenic and transmissible virus (1). Millions of people globally have been affected since the World Health Organization (WHO) declared it a pandemic on March 11, 2020 (2, 3). The earliest coronaviruses (called infectious bronchitis virus) were grown from infected chickens (4). Subsequent isolates grown from the anterior nares of man were called coronavirus 229E and OC43 (4). A few other members of this family have also been branded, including SARS-CoV, CoV-NL63, HKU1, MERS-CoV, and 2019-nCoV, now known as SARS-CoV-2 (4). Almost all of these have been linked to severe respiratory tract infections. The SARS-CoV-2 is considered a relative of the deadly SARS and the Middle East respiratory syndrome (MERS) coronaviruses, both of which are characterized by flu-like symptoms, including fever, cough, and nasal congestion, and have the potential of transmission from animals to humans (5). Other studies suggested that bats and snakes could be the potential natural reservoirs of SARS-CoV-2 (6,7,8).

The guidelines for diagnosis and treatment of this novel coronavirus infection have clear criteria for severe COVID-19, including respiratory rate, hemoglobin oxygen saturation (SaO2), and oxygenation index (PaO2/FiO2) (9). However, these criteria are highly subjective and lack objectivity, which may lead to an extended time for diagnosis and the possibility of misdiagnosis in severe COVID-19. Therefore, it is pertinent to search for biochemical parameters associated with this virus infection that could effectively aid in the early diagnosis and prompt management of COVID-19.

Methodology:

Online databases including PubMed, Web of Science, Scopus and Google scholar were comprehensively searched for published articles from December 2019 to March 2021 using the keywords and Boolean search terms; ["laboratory" OR "chemistry" OR "clinical"] AND ["coronavirus 2019" OR "COVID-19" OR "2019-nCoV" OR "SARS CoV-2"], and the PRISMA guidelines for selection of relevant materials. We searched for biochemical features seen in patients with COVID-19 in the published articles including C-reactive protein, interleukin-6, triglycerides, and other biomarkers responsible for hyper-inflammatory or 'cytokine storm syndromes' associated with COVID-19.

Initially, with greatest sensitivity search, we found 310 articles on external databases collected using Endnote software. Then unifying the articles from all the cited databases and bringing out duplicate articles, we separately reviewed all the articles and excluded the articles that were not related to the topic. After further review of the titles and abstracts, several other articles were excluded, leaving 70 eligible articles. The reference lists of all the eligible articles were also scrutinized, from which 6 additional articles were identified, given a total of 76 eligible published articles for the review (Fig 1).
Results and Discussion:

Biology of SARS-COV-2

Coronaviruses are enveloped, positivesense single-stranded RNA viruses with helical nucleocapsid symmetry (10). They are members of the order Nidovirales, family Coronaviridae, and sub-family Coronavirinae, which contains four genera; alpha, beta, gamma and deltacoronaviruses (4). This classification is on the basis of their phylogenetic relationships and genomic structures. Alpha and beta-coronaviruses are mammalian pathogens while the gamma and delta-coronaviruses infect birds, but some of them can also infect mammals (11).

Alpha and beta-coronaviruses are respiratory tract pathogens of man and enteric pathogens in animals. SARS-CoV (beta-coronavirus), 229E (alpha-coronavirus), HKU1 (beta-coronavirus), NL63 (alpha-coronavirus), OC43 (betacoronavirus), and MERS-CoV (betacoronavirus) can all cause infections in humans (4).

Inflammatory markers in COVID-19

It has been demonstrated that there is direct cytopathic effect of SARS-CoV-2 on lymphocytes, along with a number of morphological changes seen on the peripheral blood smear of infected patients with 'cytokine storm syndrome' (12). Secondary haemophagocytic lymphohistiocytosis (shLH) is an under recognized hyper inflammatory syndrome characterized by a fulminant and fatal hypercyto-}

kinaemia with multi-organ failure, and is most commonly triggered by viral infections (12). A cytokine profile resembling shLH is associated with COVID-19 severity, characterized by increased interleukin (IL)-2, IL-7, granulocyte colony stimulating factor (GCSF), interferon-γ inducible protein 10 (IGIP-10), monocyte chemotacttractant protein 1 (MCP-1), macrophage inflammatory protein 1-α (MIP-1α), and tumor necrosis factor-α (TNF-α) (13). It is therefore plausible that measurement of some of these inflammatory biomarkers will be crucial for early and accurate identification of COVID-19 patients who may be at high risk of unfavorable progression.

C-reactive protein (CRP) is a commonly measured nonspecific biomarker of inflammation. Increased CRP concentration has consistently been shown to be associated with poor outcome in SARS-CoV-2 infection (14). Ferritin is a positive acute phase protein, which is easily measured and may be a marker of adverse outcomes in individuals infected with SARS-CoV-2 (15). Procalcitonin (PCT) is also a main inflammatory marker routinely measured in clinical practice. However, it has been reported that the overall number of COVID-19 patients with increased PCT values seem limited (16).

Biomarkers of cardiovascular functions in COVID-19

COVID-19 patients who are co-morbid with hypertension, heart failure and coronary artery disease are at greater risk of serious
illness and ICU admission (17). Cardiac troponin (cTnI) is the 'gold standard' necrotic biomarker for risk assessment of myocardial injury worldwide (18). It is released exclusively in the presence of myocardial injury irrespective of the mechanism of insult. SARS-CoV-2 has been shown to induce expression of multiple cytokines and chemokines, resulting in vascular inflammation, plaque instability and myocardial inflammation (13). Several studies have shown that the blood levels of cardiac troponins are higher in patients with more severe illness, compared to those with milder disease (19). An increased cardiac troponin in COVID-19 patients is probably reflecting an acute myocardial injury caused by either the virus or host immune response, rather than myocardial infarction due to rupture of an atherosclerotic plaque (20). Other cardiac biomarkers, including creatine kinase-MB, myoglobin and atrial natriuretic peptides have been shown to have similar relationships (21).

**Physiological parameters of respiratory functions in COVID-19**

Severe COVID-19 is associated with hypoxemia and metabolic acidosis (22), which may lead to acute respiratory distress syndrome (ARDS). Hence the need for the measurement of arterial blood gas parameters especially pH, pO₂, pCO₂, HCO₃ and lactate (23). COVID-19 is adjudged to be severe if respiratory rate is ≥ 30 breaths/min, SpO₂ < 93% while breathing room air or PaO₂/FIO₂ ≤ 300 mmHg or 40 kPa (24).

**Biomarkers of muscle injury in COVID-19**

Oxidative stress, which is preceded by excessive production of proinflammatory cytokines in hypercatabolic conditions, is associated with production of corrosive molecules that cause severe myocyte damage (25). Myokines and adipokines produced by sarcopenic muscle and adipose tissue stimulate signaling pathway of inflammation and oxidative stress resulting in hyper-catabolism, especially in people with advanced age and those with metabolic disorders (26). Remarkable elevation in biomarkers of muscle loss, such as creatine kinase (CK), in up to 27% of hospitalized COVID-19 patients, was a condition described as hyperCKemia (27, 28). In a meta-analytical study, report shows elevated levels of CK, LDH, and myoglobin in severe than mild COVID-19 cases (29).

**Fluid and electrolytes disturbances in COVID-19**

The kidneys and gastrointestinal (GI) involvement in COVID-19 result in fluid and electrolyte disturbances. The notable disturbances are hyponatremia, hypernatremia, hypokalemia, hypocalcemia, hypochloremia, hypervolemia, and hypovolemia, which if left unattended to, can lead to high mortality. Fluid and electrolyte disturbances are more common among hospitalized patients and those in intensive care units. Deranged renal function leads to fluid and electrolyte disturbances (30), and many studies on COVID-19 have confirmed electrolyte disturbances such as sodium, potassium, chloride, and calcium imbalances (13, 31). However, the most common electrolyte disorder is hyponatremia, which is associated with increased risk of mortality among hospitalized COVID-19 patients (32).

Some drugs used in the treatment for patients with COVID-19 such as chloroquine and hydroxychloroquine, have also been implicated to cause electrolyte imbalance (33). Hypokalemia, another complication in COVID-19, can exacerbate acute respiratory distress syndrome (ARDS) and increase the risk of heart injuries (34). Hypocalcemia has also been observed as one of the electrolytes disorders in patients with COVID 19, which if not controlled, can increase mortality rate (35). Syndrome of inappropriate antidiuretic hormone (SIADH) has been reported in some COVID-19 patients and implicated in causing fluids and electrolyte disturbances (36).

**Effects of SARS-CoV-2 on the liver and biomarkers of hepatic injury in COVID-19**

The liver performs protective functions in host defense against microbes. Therefore, SARS-CoV-2 infections can be associated with liver injury during disease progression and treatment in COVID-19 patients with or without preexisting liver disease. Elevated serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin, and low albumin and prealbumin concentrations have all been associated with poor outcome of COVID-19 (37). It was reported in a study that some drugs used in treatment of COVID-19 were associated with elevated biomarkers of liver injury (38).

SARS COV-2 RNA has been detected in stool highlighting the possible means of transmission of the virus from the gut through the portal circulation to the liver. SARS-COV-2 may directly bind to ACE2 positive cholangiocytes to exert a cytopathic effect. The disruption of cholangiocyte function is associated with hepatobiliary damage (39). Multiple factors are responsible for liver dysfunction or damage in patients with COVID-19. This includes a direct cytopathic effect of SARS-COV-2 from conti-
uous replication of the virus inside the hepatocytes, indirect effects following drug-induced liver injury (DILI) from the current armory of therapeutic agents deployed against SARS-COV-2, and liver injury related to accentuated immune response such as ‘cytokine storm syndrome’ and immune mediated hepatitis. Also, hypoxia and shock induced by COVID-19-related complications such as systemic inflammatory response syndrome and multiple organ failure, may cause hepatic ischaemia and hypoxia-reperfusion dysfunction (40).

Between 37.2 and 76.3% of COVID-19 patients have abnormal liver function (41), and the commonly elevated parameters are aspartate transaminases (AST), alanine transaminases (ALT), alkaline phosphatase (ALP), total bilirubin, and the gamma glutamyl transferase (GGT) while albumin is usually reduced (42). Liver test abnormalities defined using the Yale New Haven Health System (YNHHS) laboratory reference range standards include; AST >33 U/L, ALT > 34 U/L, ALP > 122 U/L, total bilirubin > 1.2 mg/dL, and albumin < 3.5 mg/dL (43). Abnormal liver function in COVID-19 is more common in adult males than females, and less common in children (44). Liver dysfunction in COVID-19 is usually mild in majority of the patients with many parameters returning to normal without treatment. However, severe liver injury (AST 1445 U/L and ALT 7590 U/L) have been reported, with 61.5% of intensive care unit (ICU) patients having higher number of liver injury than non-ICU patients (25%). Among non-survivors, the incidence of liver injury might reach as high as 58%-78% (45, 46,47). Therefore, liver function could be used as an indicator of disease progression, and special attention should be given to any liver dysfunction while managing COVID-19 patients (48).

In a study of 417 patients with COVID-19 in Shenzhen, China by Cai et al., (41), 76.3% of them were found to have abnormal liver tests results and 21.5% had liver injury during hospitalization. The patterns of the liver abnormalities were hepatocellular, cholestatic or mixed. Hepatocellular abnormalities resulted in elevations of ALT and/or AST, cholestatic type resulted in elevation of ALP and/or GGT, while mixed type was associated with elevation of combination of the liver enzymes. On the other hand, a decrease in serum albumin level and/or prolonged prothrombin time was considered synthetic type of liver abnormality (41). Similarly, a study done by Fan et al., (44) on 148 COVID-19 patients reported incidence of abnormal liver function tests as lactate dehydrogenase (35.1%), AST (21.6%), ALT (18.2%), GGT (17.6%), total bilirubin (6.1%) and ALP (4.1%).

A review of more than 20 publications showed abnormal levels of transaminases in COVID-19 patients (48,49), with a correlation between the level of liver dysfunction and severity of the disease (48). The incidence of raised ALT and AST ranged from 2.5%-50.0% to 2.5%-61.1% respectively (44,47,49,50). These studies reported elevation of the hepatocellular markers of liver abnormalities (AST and ALT) in 14%-53% of patients (45,46,51). In a large cohort study of 1099 patients from 552 hospitals, Guan et al., (52) observed elevated levels of only AST in 18.2% of COVID-19 patients with mild to moderate disease, and 56% with severe disease. Moreover, in the same study, 28.1% of patients with severe disease were observed to have abnormal ALT compared to 19.8% of mild cases. Lei et al., (53) reported AST to be the first elevated marker on hospital admission for COVID-19, and this was also associated with the highest mortality. A retrospective study done Xu et al., (7) reported a patient with severe hepatitis due to COVID-19 having ALT of 7590 U/L and AST of 1445 U/L. AST elevation is the commoner of the transaminases, reflecting the extrahepatic contribution of this enzyme (54).

Other studies have reported abnormal levels of parameters of liver dysfunction such as LDH and albumin in COVID-19, with Kukla et al., (55) reporting 76% and 98% of their patients with abnormal LDH and albumin levels respectively. SARS-COV-2 caused decrease in albumin secretion in severe COVID-19 cases in their study to values of about 26.3-30.9 g/L. In a systematic review and meta-analysis of 128 studies (17), the most frequent liver function abnormalities were hypoalbuminemia (61.3%), and elevated GGT (27.9%), AST (23.4%) and ALT (23.3%). Another large systematic review of 11 studies (56) which evaluated liver parameters of 2541 patients with SARS-COV-2 infection, reported elevated AST and/or ALT (25%), LDH (20%), bilirubin (3%), but normal ALP in almost all the COVID-19 patients (56). Patients with chronic liver disease who contract SARS-COV-2 are at increased risk of severe COVID and a sizable number of them tend to develop decompensated liver as a systemic inflammatory response induced by the virus (57).

**Effects of SARS-COV-2 on the kidneys and biomarkers of renal dysfunctions in COVID-19**

The involvement of kidneys in COVID-19 has been said to be multifactorial. Cytopathic effects of kidney-resident cells and the ‘cytokine storm syndrome’ damage are known
modes of tubular damage (58). Elevations of both serum creatinine and urea (blood urea nitrogen, BUN) have been associated with unfavorable clinical outcome (14). SARS-COV-2 uses the angiotensin converting enzyme 2 (ACE2), which is highly expressed in the kidneys, as receptors for cellular entry (59). The viral spike protein (S) binds to renal ACE2, enabling membrane fusion and endocytosis processes through the cellular transmembrane serine protease 2 (TMPRSS2), and within the cell, viral polyproteins are synthesized, assembled and released (60). The mechanisms by which SARS-COV-2 causes renal injury include the release of nephrotoxic substances from ‘cytokine storm syndrome’, prothrombotic coagulopathy, and an imbalance of the renin-angiotensin-aldosterone system (RAAS) with negative haemodynamic effects (61). Naicker (62) outlined other possible aetio-pathological mechanisms for renal injury during the course of COVID-19 as renal hypoperfusion-related acute tubular necrosis or cellular damage, dys-regulated inflammatory response, micro-circulatory dysfunction, metabolic reprogramming, ‘cytokine storm syndrome’ precipitated by sepsis, and direct viral injury.

SARS-CoV-2 causes kidney injury that typically involves the glomerulus and tubules. Impaired glomerular filtration manifests as increased blood urea nitrogen and creatinine while tubular damage manifests as abnormalities in urinalysis (63,64). Proteinuria in patients with COVID-19 is often mild. In a study by Li et al., (65), 27% of COVID-19 patients had elevated urea nitrogen while 19% of same group of patients had elevated creatinine. Another study on 99 patients showed 6% of them had elevated serum urea nitrogen, 3% had elevated serum creatinine and incidence of acute kidney injury (AKI) was 3% (66). The incidence of abnormal renal function, defined as an increase in serum creatinine reported by Zhu et al., (67) in a meta-analysis of 3062 COVID-19 was found to be 25.5%.

The prevalence of kidney injury among hospitalized COVID-19 patients vary from one study to another with a reported highest prevalence of 69% (68). Kidney injury is identified with any of increased serum creatinine levels, proteinuria, and haematuria, with some of the patients requiring renal replacement therapy (69). A large proportion of COVID-19 patients manifest kidneys dysfunction manifesting as proteinuria, haematuria, elevated serum creatinine and blood urea nitrogen (BUN) (22). In a review of 24 studies with 10,180 COVID-19 patients by Yang et al., (70), the pooled prevalence of acute kidney injury (AKI) was 16.2%, increased serum creatinine 8.3%, increased BUN 6.2%, increased D-dimer 49.8%, proteinuria 50.1%, and haematuria 30.3%. They also observed that these analytes were higher in ICU/severe cases in comparison with non-ICU/non-severe patients, with serum creatinine 6.4-folds, BUN 1.8-folds, D-dimer 0.67-folds and AKI 30-folds (70). Wald et al., (69) also observed that majority of COVID-19 patients admitted into the ICU had AKI with 20% of them receiving renal replacement therapy. Survivors of AKI due to COVID-19 often have incomplete recovery of kidney function at the time of hospital discharge (71).

On admission and/or during hospitalization, studies (56,62) have shown that COVID-19 patients present with massive albuminuria (34%), elevated BUN (27%) along with haematuria (44%), and increased serum creatinine (15.5%). Importantly, signs of kidney dysfunction were found in a large percentage of patients on hospital admission for COVID-19 including 44 - 65% with proteinuria, 27 - 44% with haematuria, and 10-14% with increased serum creatinine (58,70,72). Different studies have observed proteinuria in 7% - 63% of COVID-19 patients (61,65) who present either as low abundance proteinuria attributed to tubular injury or as abundant proteinuria which is suggestive of glomerular impairment. Activation of RAAS, injury to podocytes and nephron endothelial dysfunction with consequent increase in glomerular permeability may be responsible for proteinuria (73). Kaliuresis with hypokalaemia due to activation of RAAS in a cohort of 175 COVID-19 patients was associated with the most severe forms of SARS-COV-2 infection (74). Mabillard and Sayer, reported 26.7% of haematuria in COVID-19 patients (36).

AKI is reported in 6.0-36.6% of COVID-19 cases and has been reported to be an independent predictor of in-hospital mortality in COVID-19 patients (45,52,75). Several factors contribute the onset and progression of AKI in COVID-19, some of which include ventilricular dysfunction due to COVID-19 pneumonia, renal endothelial damage, rhabdomyolysis, activation of RAAS and ‘cytokine storm’ following SARS-COV-2 replication (76). A study of 710 COVID-19 patients in Huazhong, China reported 44% with proteinuria and haematuria, 26.9% of whom had simple haematuria, 15.5% had elevated serum creatinine, and 14.1% had elevated BUN. Elevations in serum creatinine, BUN levels and occurrence of AKI increase hospital mortality rate by 3.61, 2.51 and 2.21 respectively (45,48).
**Conclusion:**

SARS-CoV-2 infection affects multiple organs and systems of the body, from which several biochemical substances are released as a result of damage to these organs. The knowledge of the biochemical parameters associated with prognosis in COVID-19 is very important to prevent lengthy stay in ICU and mortality associated with dreaded disease. This review has highlighted various biochemical markers (Table 1) that are significantly elevated or reduced as evidence of serious damage to the organs involved, and which can be explored for diagnostic and prognostic purposes, as well as monitoring of COVID-19 patients on therapy.

It is however important to concentrate more on those parameters that have been found to be strongly associated with worse outcomes. These include elevated levels of C-reactive protein (CRP), ferritin, cardiac troponins (cTnI), serum creatinine, creatinine kinase, LDH and BUN. On the other hand, values of PaO₂/FIO₂ ≤ 300 mmHg or 40 kPa, and SpO₂ < 93% while breathing room air are associated with poor pulmonary function.

**Table 1: Biochemical parameters of organ dysfunctions in COVID-19**

| Organ/system of the body     | Elevated parameters                                                                 | Reduced parameters                                      |
|------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------|
| Inflammatory and immune system | Interleukin (IL)-2                                                                  |                                                        |
|                              | Interleukin (IL)-7                                                                  |                                                        |
|                              | Granulocyte colony stimulating factor                                              |                                                        |
|                              | Interferon-γ inducible protein 10                                                   |                                                        |
|                              | Monocyte chemoattractant protein 1                                                 |                                                        |
|                              | Macrophage inflammatory protein 1-α                                                 |                                                        |
|                              | Tumor necrosis factor-α                                                             |                                                        |
|                              | *C-reactive protein (CRP)                                                           |                                                        |
|                              | *Ferritin                                                                            |                                                        |
| Cardiovascular system         | *Cardiac troponins (cTnI)                                                           |                                                        |
|                              | Creatine kinase-MB                                                                  |                                                        |
|                              | Myoglobin                                                                            |                                                        |
|                              | Natriuretic peptides                                                                |                                                        |
| Liver                        | Aspartate aminotransferase (AST)                                                   |                                                        |
|                              | Alanine aminotransferase (ALT)                                                      |                                                        |
|                              | Bilirubin                                                                            |                                                        |
| Kidneys                      | *Serum creatinine,                                                                   |                                                        |
|                              | *Blood urea nitrogen (BUN)                                                           |                                                        |
|                              | *Lactate dehydrogenase (LDH)                                                        |                                                        |
| Respiratory system            | Respiratory rate ≥30 breaths/min                                                    |                                                        |
|                              | *PaO₂/FIO₂ ≤ 300 mmHg/40 kPa,                                                       |                                                        |
|                              | *SpO₂ < 93% while breathing room air                                                |                                                        |
| Fluid and electrolytes        | *Creatinine kinase                                                                  |                                                        |
|                              | LDH                                                                                  |                                                        |
|                              | Myoglobin                                                                            |                                                        |
| Muscle                       | *Creatinine kinase                                                                  |                                                        |
|                              | Hyponatraemia                                                                        |                                                        |
|                              | Hypocalcaemia                                                                         |                                                        |
|                              | Hypochloraemia                                                                        |                                                        |
|                              | *Hypocalcemia                                                                         |                                                        |

* = parameters associated with higher probability of the need for intensive unit (ICU) care and high mortality rate.
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