International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 16, Special Issue 5, 2024

Review Article

LITERATURE REVIEW: THE OMICS STUDY FOR DETERMINING BIOMARKERS IN HUMAN SERUM AND PLASMA WITH DIFFERENT COVID-19 SEVERITY

WAHYU UTAMI[1*], NAUFAL FARRAS[1,2]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Universitas Muhammadiyah Surakarta, Sukoharjo-57162, Indonesia.
[2]Master in Pharmaceutical Science, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta-55281, Indonesia
*Corresponding author: Wahyu Utami; *Email: wahyu.utami@ums.ac.id

Received: 06 May 2024, Revised and Accepted: 05 Sep 2024

ABSTRACT

The severity of COVID-19 provides information on various stages of changes in the body's normal state in various parameters called biological markers (biomarkers) as the initial identification that facilitates management, selection, and total outcomes in therapy. These biomarkers were selected from the selection of samples that are often used in the advanced diagnosis of COVID-19, serum and plasma. This study aims to determine what biomarkers are measured in serum and plasma samples of COVID-19 patients. This literature review is classified as non-experimental, qualitative, and descriptive research. The inclusion criteria are the full-text journals published within the last two years regarding biomarkers in the serum and plasma of COVID-19 patients. Based on these criteria, 49 relevant articles were obtained. The results show that changes occur in the protein, lipid, and metabolite in serum and plasma by the omics approach. These alterations can be in the form of increasing or decreasing levels of each parameter determined through various analytical methods. The biomarkers profile correlates with the severity of COVID-19 as well as with host cells.

Keywords: COVID-19, Severity, Serum, Plasma, Omics

DOI: https://dx.doi.org/10.22159/ijap.2024.v16s5.52474 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

In late 2019, the world was shocked by a new respiratory disease isolated from a pneumonia patient in Wuhan, Hubei Province, China. This pathophysiological condition shows that there are viral variants that have a high homology level to the human Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV) of 82%. The variant was later called Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) is known as Coronavirus Disease 2019 (COVID-19) [1–3]. Clinical manifestations in COVID-19 patients vary depending on the severity [4]. The severity of COVID-19 is divided into three levels based on improvement in symptoms, the response of patients in therapy, clinical findings and results, including stage I (mild)-the first initial phase of infection; stage II (moderate)-pulmonary phase, and stage III (severe)-hyperinflammatory phase [5]. Another classification system shown that there are three periods and 5 phases in SARS-CoV-2 infection, including the pre-exposure period, the incubation period, the period of virus replication being detected, and the viral symptom phase, also, the initial inflammation phase, the secondary infectious phase, the multisystem inflammatory phase, and the final phase [6]. This classification system refers to the severity of symptoms, immune response, and physiological conditions. The diagnosis and severity of COVID-19 is determined through the laboratory tests [7]. Laboratory supporting examinations were obtained through three methods, namely molecular tests Nucleic Acid Amplification Test (NAAT), Reverse Transcriptase-Polymerase Chain Reaction Test (RT-PCR Test), and Loop-mediated Isothermal Amplification (LAMP Test), antigen test, and antibody test (serological test). There are differences in sampling from each method, such as the nose, nasopharynx, saliva, and blood. Laboratory data information through accurate examinations can help in tracking the spreading of SARS-CoV-2, knowing case information and the strategy to handle it. The use of molecular tests and antigen tests is carried out for diagnostic purposes, but serological tests are recommended for research and surveillance purposes [8]. Based on the findings of serologic and plasma data, biological markers (biomarkers) in patients with confirmed COVID-19 will be known easily. Investigation of biomarkers on biological samples (serum and plasma) can be carried out through various methods, one of which is the omics approach. Omics are defined as an analysis study in molecular biology approaches in the genome to metabolite. This study is usually used to analyze biological samples wholly and comprehensively. The omics study classifies many subjects according to the focus of analysis, such as transcriptomic, genomic, metabolomic, proteomic, and lipidomic. This study uses an omics approach to determine the biomarkers of human serum and plasma. Thus, the biomarkers are easy to find and valuable for further analysis and diagnosis [9]. Biomarkers play an important role in laboratory results of COVID-19 patients that can provide an overview of the body's condition against SARS-CoV-2 exposure and state the patient's health status through many parameters [10-13]. White blood cells (WBC), lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase were also increased compared to healthy individuals significantly [14]. Therefore, it is necessary to study the biomarkers as key in determining the severity of COVID-19 through serum and plasma samples of COVID-19 patients compared with serum and plasma in healthy individuals based on omics profiling studies.

MATERIALS AND METHODS

This research uses a literature review study method classified as non-experimental, qualitative, and descriptive research. Descriptive analysis is needed to systematically describe the data or information obtained through relevant research journals and provide exposure to the study results of the facts or findings. Sources were obtained through the database in Google Scholar and PubMed. The keywords used are "omics and biomarkers FOR serum and plasma and COVID-19 OR Coronavirus-2 OR SARS CoV-2". References or publication articles are taken for data and information such as author, year of publication, title, and journal media. Journals conducted through Google Scholar and PubMed found 267 and 493 articles spanning the last two years. The articles obtained were then identified based on the relevance of the research being carried out by examining the titles and abstracts of research articles with inclusion and exclusion criteria. The inclusion criteria were selected based on full-text journals published in the last two years (2019-2021) regarding biomarkers in the serum and plasma of COVID-19 patients. Meanwhile, the exclusion criteria are the samples are out of serum and plasma profiles in COVID-19 patients compared to healthy individuals. The results are shown in fig. 1, found 49 scientific articles relevant to the research as in table 1 on February 23, 2022.

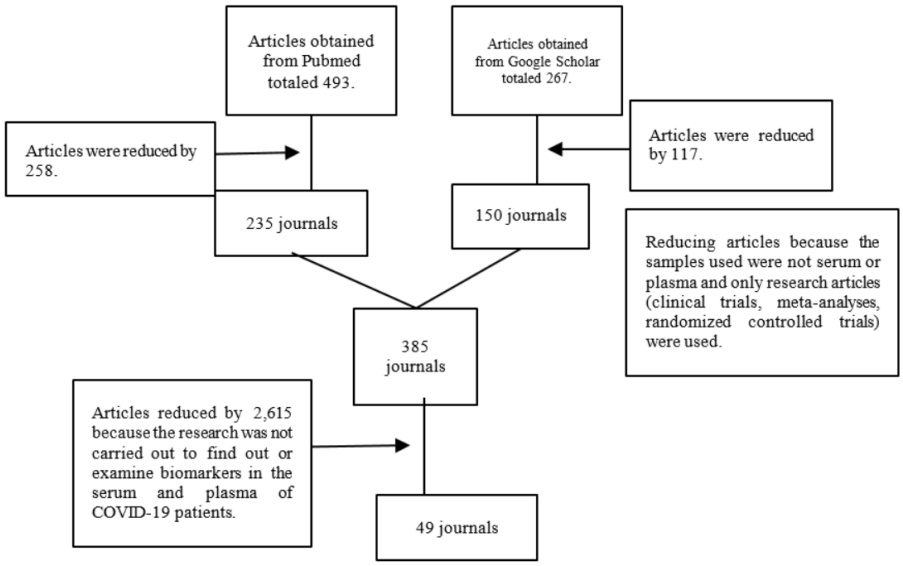

Fig. 1: The process of article analysis on Google Scholar and PubMed

Table 1: Search results and review of published journals

Reference	Research study	Method	Parameter	Result
[15]	Lipid serum sampling from patients.	LC-MS/MS	Increasing lipid parameters	PGE 2 ↑, PS ↑, and PE ↑
[16]	Plasma samples were taken from HC and children with mild stages of COVID-19.	LC-MS/MS	Increasing proinflammatory signal	D-dimer and IL-1β ↑. Dysregulation of proteins coagulation IX and XI, FGA, and FGG.
[17]	Serum protein was taken from 33 patients with severe COVID-19 and HC	LC-MS/MS	Increasing protein parameters	HRG ↑, FETUB ↑, and KNG1 ↑
[18]	Serum was obtained from 72 COVID-19 patients with details of severe (23), mild (28), and critical (21), as well as 20 HCs.	LC-MS/MS and MALDI-TOF MS	Increasing protein parameters	SAA2 ↑ (mild and severe), SAA1, CRP, FGG, and LBP ↑ (all severity)
[19]	Plasma samples from 66 COVID-19 patients and 17 HC patients.	LC-MS/MS	Decreasing immune response	Severe: CD3 (383.38 cells/ml), CD4 T cells (208.63 cells/ml); Mild: CD3 (937.24 cells per ml), CD4 T cells (344.96 cells/ml)
[16]	Plasma samples in moderate recovered asymptomatic and severe and critical patients	LC-MS	Increasing protein parameters	Severe and critical: Succinate uracil ↑, taurine uracil ↑, inosine uracil ↑, cyclic adenosine 3', hypoxanthine, cAMP ↑, hippurate ↑, IMP ↑, and abscisic acid ↑.
[20]	Plasma was collected from 39 HC, 34 moderately recovered, 18 asymptomatic recovered, and 44 recovered severe patients.	LC-MS	Increasing protein parameters	Recovered severe: Taurine ↑, hippuric acid ↑, succinic acid ↑, and indole ↑
[21]	The plasma of COVID-19 patients was obtained from HC and severe	LC-MS	Increasing proinflammatory signal	Severe: IFN-1 ↑ and TLR ↑
[22]	A cohort study on 102 COVID-19 patients and 26 healthy patients.	HRMS	Increasing chemokines and growth factors	CRP ↑, VEGF ↑, FN ↑
[23]	Plasma was taken from moderate (n = 21), control patients (n = 27), critical (n = 28), and mild (n = 23)	GC-MS and UPLC-MS	Increasing protein parameters	Severe: arabinose ↑, ribose ↑, maltose ↑, aspartic acid ↑, arginine ↑, phenylalanine ↑, glutamic acid ↑, and tyrosine ↑
[24]	Serum was taken from patients with COVID-19 (n = 39) and HC (n = 20)	UPLC-MS	Increasing proteinogenic amino	Mild-severe: Glutamate ↑, cysteine-S-sulfate ↑, palmitoleic acid ↑, uracil ↑, lysophosphatidylethanolamine ↑, and myristic acid ↑
[25]	Serum and plasma were taken from 16 HC, 33 negative patients, and 10 COVID-19 positive patients	UPLC-MS	Increasing proteinogenic amino parameters	Mild-severe: Glutamic acid ↑, quinolinic acid ↑, nicotinic acid ↑, kynurenine ↑, aspartic acid ↑, neopterin, phenylalanine ↑, taurine ↑
[26]	Cohort study on plasma samples of 120 COVID-19 and HC patients.	UPLC-MS/MS	Increasing protein parameters	Mild-severe: Cytokines ↑, Kinurenin ↑, Nicotinic Acid ↑, Arginine ↑, Asparagine ↑, and Carnitine ↑
[7]	Plasma samples were obtained from patients who were in hospital and patients with 1 mo post-infection.	UPLC-MS/MS	Increasing proteinogenic amino parameters	Mild-severe: BCAAs ↑, AAAs ↑, and methionine ↓
[9]	Plasma samples were obtained from 44 HC and 6 COVID-19 patients	UPLC-MS/MS	Increasing proteinogenic amino parameters	Mild-severe: AA ↑ and linoleic acid ↑
[27]	Serum in COVID-19 patients to determine the role of LDL serum in COVID-19	ELISA	Increasing lipid parameters	Mild-severe: LDH ↑, platelet degranulation ↑, and pyruvate ↑
[28]	Plasma was obtained from healthy controls (n = 31), hospitalized-mild (n = 29), hospitalized-severe (n = 12)	ELISA	Alteration immune response	Mild and severe: MBL ↑, CD8+↓, FASLG ↓
[29]	Plasma samples obtained from COVID-19 patients through a cohort study	ELISA	Increasing lipid parameters	LPS ↑ and LBP ↑
[30]	Serum samples were obtained from mild or moderate COVID-19 patients, 62 PCR-confirmed non-hospitalised, and 624 negative samples patients.	ELISA	Increasing immunoglobulin and lipid parameter	Mild-severe: IgA ↑, IgG ↑, and IgM ↑, bilirubin ↑, hemoglobin ↑, and triglycerides ↑
[31]	Plasma collected from mild and severe patients	ELISA	Increasing proinflammatory signal	TNF-α ↑ (mild = 52.60 pg/ml; severe = 70.80 pg/ml), IL-2R (mild = 622.0 U/ml; severe = 879.6 U/ml), IL-1β (mild = 107.2 pg/ml; severe = 139.8 pg/ml)

Reference	Research study	Method	Parameter	Result
[32]	Proteomic plasma taken from HC patients, asymptomatic, mild, severe (early), severe (late).	ELISA	Increasing antioxidant gene	Severe (early and late): SOD1↑, PRDX2 ↑, and LDHA ↑
[33]	Serum draw from 93 patients with COVID-19 and 186 HC	ELISA	Decreasing micronutrient serum	Zinc serum ↓
[34]	Serum collected from 60 COVID-19 patients in hospital.	ELISA	Decreasing micronutrient serum	Serum Vitamin B9 ↓, B12↓, C↓, D↓, Magnesium↓, Iron ↓
[35]	32 confirmed COVID-19 patients with severity	ELISA	Decreasing immunoglobulin G	Mild and moderate: IgG ↓
[36]	Serum lipids were obtained from 53 COVID-19 patients with different severity who were compared with healthy patients.	MS	Increasing lipid parameters	Severe: Serum glycophospholipid ↑, sphingolipids ↑, glycosylceramides ↓
[37]	Plasma was obtained from 3 mild and 5 severe COVID-19 patients.	MS	Overexpression of neutrophil	Severe: Neutrophil ↑
[38]	Serum peptides were obtained from 146 COVID-19 patients, 73 negative and 46 healthy patients.	MALDI-TOF-MS	Increasing immune response	Cytokines IP-10 ↑ and MCP-3 ↑
[39]	Plasma samples were taken from healthy patients (n = 25) and COVID-19 patients (n = 17).	NMR-MS and LC-MS	Increasing lipid parameters	Kynurenine ↑, tryptophan ↑, HDL ↑, triglycerides ↑, LDL ↑, HDL ↑, apo A1 ↑, and VLDL ↑
[40]	Plasma samples were taken from COVID-19 patients (n = 34) and HC (n = 35)	NMR	Increasing proinflammatory signal	Cytokine protein ↑, MIP-1β ↑, IL-22 ↑, SDF-1α ↑, and IL-1α ↑
[41]	Cohort study of serum metabolomic and lipidomic in COVID-19 patients.	NMR	Increasing proteinogenic amino parameters	Amino acid (phenylalanine) ↑, ketones ↑, phospholipids ↑, and triglycerides ↑
[42]	Serum was taken from patients of varying severity.	NMR	Increasing proteinogenic amino parameters	Mild and moderate: glucose ↓, glutamate ↓, formate ↓, and CD8+↓
[43]	Ethylene EDTA plasma was collected in 30 patients stratified by gender and age.	NMR	Increasing lipid parameters	VLDL ↑,HDL3 ↑, HDL-4 ↑, LDL-4 ↑, LDL-5 ↑
[44]	Blood plasma samples were obtained from 251 COVID-19 patients.	NMR	Increasing lipid and proteinogenic amino parameters	Glycoprotein acetylation ↑, Lipoprotein concentrations ↑, and Amino acid concentrations (leucine and phenylalanine) ↑, Triglycerides ↑
[45]	Plasma lipids were obtained from severe (n=217), moderate (n=364), and mild (n=215) patients with COVID-19.	Biomedical test	Increasing lipid parameters	Mild-severe: TC ↑ and HDL-C ↑
[46]	Samples were obtained from COVID-19 patients (n = 22)	Biomedical test	Increasing proinflammatory parameters	Mild-severe: fibroblast growth factor-2 ↑, IFN-γ ↑, and platelet-derived growth factors ↑
[47]	Serum was obtained from patients with COVID-19 and HC.	Biomedical test	Increasing proinflammatory signal	Mild-severe: IL-6 ↑, IL-1β ↑, and IL-8 ↑
[48]	Serum protein samples were obtained from COVID-19 patients with differentiation of severity, already negative patients, and HC.	Single center registry study	Increasing lipid parameters	Mild-severe: GRN ↑
[49]	Plasma and serum samples were obtained from COVID-19 patients of different severity	Multiparametric Flow Cytometry	Increasing immune response and protein	Mild-severe: Albumin ↓ (mild/moderate = 4,55 g/dl; severe = 3,80 g/dl), CD8+↓ (mild/moderate = 72,21 cell/µl; severe = 61,22cell/µl), Th1 cells ↓ (mild/moderate = 100,05 cell/µl; severe = 50,14 cell/µl)
[50]	Samples were obtained from 52 COVID-19 patients	Multiparametric Flow Cytometric	Increasing immune response	Mild-severe: CD19+↑
[51]	Serum was taken from 125 normal patients and 17 COVID-19 patients.	The direct-surfactant removal method and the immunoturbidimetric method.	Increasing lipid parameters	Mild-severe: HDL-C ↑, TC ↑, ApoA1 ↑ and LDL-C ↑
[52]	Plasma taken from a COVID-19 patient in the ICU	Serological test	Increasing immune response	Severe: IgG ↑
[53]	200 COVID-19 participants in Brazil with 65.8% mild, 21% moderate, and 6.1% severe	Serology test	Increasing immune response	Mild-moderate: IgG ↑
[54]	35 COVID-19 patients (28 mild patients and 7 severe patients)	Serology Test	Increasing immune response	Severe: IgA ↑ and IgG ↑
[55]	Cohort study on 9 COVID-19 and 6 non-COVID-19 patients.	Metagenomic analysis	Decreasing proteinogenic amino	Mild-severe: Lactic acid ↓, L-proline ↓, and CME ↓
[56]	Longitudinal study on father (severe) and child (mild) COVID-19 patients.	PCA	Increasing protein inhibitors	Mild-severe: Serpin ↑
[57]	Serum collected from 6 fatal, 7 severe, and 10 mild	Multiplex Detection of CCGFs	Increasing protein, chemokines, and cytokines plasma	Severe and moderate: SCGF, MIF, CCL27, and CXCL1 (>500 pg/ml). IL-12 p40, VEGF, G-CSF, IL16, and TNF-α (50–500 pg/ml), CCL11, CXCL12, and CCL27
[58]	Serum from different COVID-19 severity	Cohort Observational	Decreasing micronutrient serum	Dp-µcMGP levels in COVID-19 patients were higher than controls in healthy patients (776.5 ng/ml vs 549.8 ng/ml)
[59]	Observational study of VDD patients (COVID-19) and HC.	Cohort Observational	Decreasing micronutrient serum	Mild-severe: Serum 25(OH)D ↓
[60]	Blood drawn from COVID-19 patients and HC.	Colorimetric	Increasing lipid parameters	Mild-severe: Cholesterol ↑, LDL ↑, and triglycerides ↑

RESULTS AND DISCUSSION

Measurement of protein, lipid, and metabolite data in samples is a valuable method to identify biomarkers of COVID-19 severity. Protein regulation plays a role in determining the severity of disease because protein is one of the building blocks of the human immune system. The changes in protein or amino acid are significantly present in early-stage infection or health to mild stage [61]. Another parameter that can be used as a marker of severity is lipid. Downregulation of lipids also occurs in mild to moderate and moderate to severe severity. Increasing the production of CCL7, Interleukin 10, and 6 (IL-10 and IL-6) was significantly measurable at moderate and severe stages [62, 63]. Serum 25-hydroxyvitaminD (25(OH)D) has a correlation between COVID-19 and vitamin D deficiency infection and mortality by the biochemical processes approaching. The lower serum 25(OH)D value makes it easier for the patient to be infected. Other biological markers include C-reactive protein (CRP), serum ferritin, serum amyloid A (SAA), and

procalcitonin as markers of acute severity. Detection of dysregulation in the pathogenesis of COVID-19 severity occurs after the patient's serum lipids are found at the elevation of monosialodihexosyl ganglioside (GM3s) level [64]. The appropriate method in identifying the presence of each biomarker is using omics study. The use of this analytical method is suitable for determining biomarkers [65, 66]. This identification can be made by knowing the biomarker at random and untargeted. Thus, all the protein, lipid, and metabolite alterations can be identified [67, 68].

Proteomic

SARS-CoV-2 classifies as a positive-sense single-stranded RNA (+ssRNA) virus that includes a large group of coronavirus types. Genomic identification revealed that there was an approximately 89% similarity with SARS-likeCoV in bats and 82% in human SARS-CoV. Similarities can be seen in the molecular and characteristics such as E (envelope), S (spike), N (nucleocapsid) and M (membrane) [69]. SARS-CoV 2 has a concave and wavy surface (resembling hills and valleys), which results in its high surface affinity for N-terminal helical-like receptors on ACE 2 cells [70]. This also explains the beta (β) and lambda (λ) variants in many epithelial cells. Through immunology science, the body has an excellent immune system in fighting pathogenic organisms that are harmful to the body, including COVID-19 virus. This protection mechanism is present by the WBCs function. WBCs will be distributed through the blood circulation to the target places in the body. Humans have 3 kinds of immune systems, including innate immunity, adaptive immunity, and passive immunity [71]. SARS-CoV 2 infection for the first time in patients will cause symptoms because of a slower immune response (adaptive immunity). These responses distinguish between people with COVID-19 symptoms and people without symptoms (OTG) [72]. Most of the COVID-19 mortality is caused by respiratory failure from acute respiratory distress syndrome (ARDS) [73]. SARS-CoV 2 infection triggers secondary hemophagocytic lymphohistiocytosis (sHLH) leading to fulminant hypercytokinemia and organ failure [2, 74]. This condition was also equated with the cytokine profile on the severity of COVID-19 (cytokine storm), characterized by elevated IL-2, IL-7, interferon-induced proteins, and other proinflammatory factors [75-77]. Data showed that COVID-19 patients showed lymphopenia and decreased CD3 T cells by the PD-1 expression by T cells, especially at a severe stage [19].

The same data in severe cases compared with healthy patients is an increase in the proinflammatory factors such as IL-1β, TNF-α, and IL-2 receptor (IL-2R). In addition, the value of triglycerides and LDL-C. Therefore, reduction of T cell counts and function were identified at all levels of COVID-19 severity, especially at the severe level [31]. Cell natural killer (NK) and T cells expressing immunoglobulin (Ig) T cells and mucin domain-3 (TIM-3) and CD69 excessively. NK cell overexpression is associated with an increased frequency of programmed cell death protein 1 (PD-1) and a decreased frequency of natural killer group 2 member D (NKG2D), the accessory molecule DNAX-1 (DNAM-1), and sialic acid binding to the Ig-like lectin. 7 (Siglec-7), which expresses NK cells. This process is associated with decreased ability to secrete interferon-gamma (IFN-γ). Elevated serum IL-6 levels were also identified in mortal patients compared to survivors. A hyperactive/fatigued immune response predominates in severe SARS-CoV-2 infection, possibly driven by the uncontrolled secretion of inflammatory cytokines by monocytes [78]. Therefore, the kinetic profile of immunoglobulin (Ig) antibodies is important in the search for biomarkers in COVID-19. In every stage of COVID-19, IgA and IgG increased especially in severe stages. IgA also occurred high in severe patients on the 11th day after infection [54]. Meanwhile, IgG serum level in mild and moderate patients showed a low peak. It caused the different response of each patient while the researcher drew their serum [35]. Based on these findings, it can be concluded that in cases of COVID-19, the severity can be used as a marker (biomarker) seen in the increase in IgA, IgM, and IgG production at an average time of onset between 2-4 w after infection by the appropriate method.

Another critical component is the level of albumin in the serum. The serum albumin samples from COVID-19 patients with initial albumin administration of 3.50 g/dl and 4.05 g/dl in each patient. Through meta-analysis, it was concluded that hypoalbuminemia was associated with clinical manifestations in severe patients, such as increased severity, increased capillary permeability, and increased cytokines. Hypoalbuminemia conditions with levels<3.3 g/dl in 109 patients (60.2% of the sample population) studied showed an increased risk of SARS-CoV-2 infection compared to patients with normal albumin values [79]. Normal albumin values reduce the risk of venous thromboembolism by 72% for every 1 g/dl increase in serum albumin levels, reducing the risk of Acute Respiratory Distress Syndrome (ARDS), decreased admissions to the ICU, and had a low probability of re-infection with SARS-CoV-2 within 90 days. In addition, a higher albumin value will reduce the total side effects of treatment [4]. Similar results were also shown through a cohort study on serum albumin of 79 COVID-19 patients who stated that there was a significant decrease in serum albumin levels from severe and non-severe patients and experienced hypoalbuminemia. These comorbidities play a clinical role in the form of fever, weakness, lethargy, headache, and dizziness. This condition also correlates with levels of lymphocytes, erythrocytes, prealbumin, and T cell counts so it can be concluded that hypoalbuminemia increases the risk of infection and severity of COVID [32]. Another study said that 106 (35.5% of the sample population) COVID-19 patients experienced hypoalbuminemia with albumin values <3.5 g/dl, potentially experiencing an increase in the severity of COVID-19 and the risk of developing COVID-19 infection. This is also represented by the value of lymphocytes and neutrophils [80]. A cohort study of COVID-19 mortality on hypoalbuminemia in hospitalized and non-hospitalized observed of 300 patients with an average albumin level of 2.86±0.5 g/dl showed that mortality in hospitalized patients higher than non-hospitalized patients in terms of albumin levels (2.6±0.49 vs. 2.9±0.48 g/dl). These phenomenons confirm that one of the markers of COVID-19 mortality is the patient's serum albumin level [81].

Albumin is also associated with serum globulin levels because both values are protein parameters that have representation on T cells, especially immunoglobulins in the inflammatory response [82]. The β2-microglobulin (β2-m) was assayed in 34 COVID-19 patients. As a result, moderate patients had low β2-m levels of 3.57±1.39 mg/l and severe patients had β2-m levels of 2.27±0.64 mg/l, which were indicators (markers) of the severity of COVID-19 [83]. Procalcitonin (PC) is an important amino acid precursor in the regulation of the hormone calcitonin. PC also provides biomarker information in markers of various infections through increasing serum levels in the blood (>0.5 ng/dl) including in COVID-19. In severe patients, serum PC levels increased four times higher than moderate patients and critical patients had very high serum PC values so that increased serum PC levels were correlated with the severity of COVID-19 [84]. Geriatric patients (>75 y) which stated that an increase in serum PC levels would increase the risk of mortality in elderly COVID-19 patients. This is indicated by the severity of symptoms, respiratory failure, and comorbidities [8]. Serum PC levels are usually compared with levels of C-reactive protein (CRP) and white blood cells. The study revealed that serum PC (AUC = 0.815) can be used as a biomarker of COVID-19 infection and low immune response [85].

Lipidomic

Typically, lipids hold the key to biological structures, mediators of cell signaling, and energy sources. The lipid profile in serum undergoes specific changes that can be observed as the impact of SARS-CoV-2 infection on the body's biological system. TC, LDL-C, apoA-I and HDL-C in severe patients are high. HDL-C and apoA-1 levels correlated with CRP, length of patient incubation in hospital, and severity of COVID-19. Mortality rates in hospitalized patients also depended on the CRP/HDL-C (>77.39) or CRP/apoA-I (>72.37) values associated with cardiovascular events. Besides CRP, usually HDL-C and apoA-1 data are represented by monocyte values, namely monocyte/HDL-C ratio (0.43±0.03). Therefore, the increase in severity of COVID-19 can be assessed by serum lipoprotein levels [86, 87]. This can occur due to cholesterol dysregulation in cell biochemical processes. Serum lipids in COVID-19 patients bear a resemblance to membranes of certain membrane-bound extracellular vesicle types, which are rich in GM-3 (monosialody hexose ganglioside) and Sphingomyelins (SM) [64]. SARS-CoV-2 infection changes the lipid composition of infected cells.

In addition, these changes also play a role in signaling errors in lipid biosynthesis and energy sources [38, 88]. Prediction of the infection and severity of COVID-19 can be seen from the triglyceride profile.

Triglycerides can also be a marker of lipid conditions in COVID-19. The plasma lipid profile also changes during SARS-CoV-2 infection. Lipid dysregulation (synthesis and metabolism) also plays an important role in the severity of COVID-19 through specialized pro-resolving mediators (SPM), omega-3 derivatives, that are naturally present in the body and regulate macrophage infiltration and inflammation [89, 90]. Cytokines increased in severe patients and decreased in critically ill patients. This happens because the body condition of critical patients has decreased function so that severe patients can still survive COVID-19 compared to critical patients. Changes in phospholipids (PL), total fatty acids (TFA), palmitic acid, non-esterified fatty acids (NEFAs), and stearic acid decreased, which the virus could use to make membrane changes during the replication process. Meanwhile, the oleic acid parameter increased production which can modulate the inflammatory process, necrosis, apoptosis, cytokine release, and an increase in the amount of oxygen oxide. Enhancement of linoleic acid in TFA and a decrease in PL was the impact of damage to the mitochondrial inner membrane of the host cell. Arachidonic acid increased in TFA which may contribute to the inflammatory process. Metabolites of cholesterol, LDL, and triglycerides have increased [60]. Basically, lipids are useful materials in cells, such as the formation of cell membranes, cell interactions, and energy sources. Viruses utilize this function to replicate during infection [51, 91, 92].

Metabolomic

Vitamins and minerals are known as micronutrients that are beneficial in maintaining the body's homeostatic conditions. Vitamins can be classified according to their solubility in water (Vitamins B and C) and fat (Vitamins A, D, E, K) [93]. Vitamin A is a lipophilic vitamin that is useful in preventing ARDS such as COVID-19. Retinoic acid plays a role in antagonizing IL1-β and IL-1 receptors with macrophages and neutrophils [27]. Similar to vitamin A, the role of vitamin D is also often associated with the ease of infection with SARS-CoV-2 and the severity of COVID-19. Vitamin D receptors (VDRs) are distributed on lung epithelial cells and immune cells (B cells, T cells, macrophages). Vitamins that enter the body will be converted into an active form of 1,25-dihydroxyvitamin D by 25-hydroxyvitamin D (25OHD) through the enzyme 1α-Hydroxylase (CYP27B1) [94]. Serum 25(OH)D levels are relevant to 1,25-dihydroxyvitamin D levels, which will decrease in the presence of infection [95]. In addition, the metabolite 1,25-dihydroxyvitamin D was reported to stimulate the formation of type-II alveolar cells [96–98]. High doses of 250,000–500,000 IU are safe in the treatment of COVID-19. This administration can increase the amount of hemoglobin so that oxygen transport is getting better [99,100]. The value of vitamin D deficiency (VDD) in COVID-19 patients was higher (41.9%) compared to healthy patients (11.1%). The serum level of 25(OH)D needed to protect against COVID-19 is 41.19 nmol/l. Serum 25(OH)D is also used as a parameter in increasing the severity of COVID-19 [101].

Vitamin K also plays an important role in regulating body conditions, especially in protective mechanisms. Vitamin K is categorized as a group of lipophilic vitamins. It is categorized into phylloquinone (vitamin K1) and menaquinones (vitamin K2). Vitamins K1 and K2 act as cofactors for several coagulation proteins and calcium. Its distribution pathway in lipoproteins has led to the identification of its levels correlated with triglycerides (vitamin K1) and LDL (vitamin K2) [102]. COVID-19 patients (34% mild, 51% moderate and 15% severe) showed that Dp-µcMGP levels were higher than controls in healthy patients (776.5 ng/ml vs 549.8 ng/ml; P<.0001) with a normal value of dp-µcMGP<780 ng/ml. The vitamin K deficiency marker used was vitamin K-dependent dephosphorylated uncarboxylated µ-matrix Gla protein (dp-µcMGP) [58]. COVID-19 patients showed that through the parameters Prothrombin induced by vitamin K absence-II (PIVKA II) or des-γ-carboxy prothrombin which will increase its production in the liver if the body is deficient in vitamin K, it increases in COVID-19 patients. 19 (72.3% in men and 36.8% in women). In addition, PIVKA II serum can also represent IL-6 levels in COVID-19 patients (66.2 pg/ml and 15.4 pg/ml). Therefore, vitamin K is useful as a marker of COVID-19 [103]. The role of vitamin C in disease therapy has been very popularly used. The use of vitamin C in critical illness is very necessary because the level of vitamin C consumed by patients is low so that high doses of vitamin C are needed [104, 105].

A randomized controlled trial (RCT) in acute respiratory distress syndrome (ARDS) patients revealed that administering vitamin C at a dose of 200 mg/kgBW per day for 4 days resulted in 30% patient mortality data in patients taking vitamin C than patients given placebo with a higher mortality rate of 46% [106]. In COVID-19 levels severely increased numbers of cytokines (cytokine storm) and an increase in inflammation through hypersecretion of inflammatory mediators [107, 108]. Vitamin C can reduce the amount of IL-6 significantly. Measurement of serum vitamin C in 21 critically ill COVID-19 patients in the ICU has decreased. This low serum vitamin C level causes an increased risk of infection and an increase in severity [109]. In resting neutrophils, intracellular vitamin C levels are about 1-2 mmol. This level will increase if neutrophils are activated due to infection or in the inflammatory response [110, 111]. Vitamin B and its derivatives have a mechanism as a cofactor for the enzyme pyruvate. The decrease in the concentration of vitamin B in cells causes acetyl-Coenzyme A (acetyl-CoA) not to be optimally produced, resulting in a decrease in aerobic respiration function, which causes an increase in lactic acid levels and a decrease in NADH in the glutathione (GSH) pathway [70, 112, 113]. Measurement of the concentration of folic acid (β=-0.27, P=0.02) and vitamin B (β =-0.24, P=0.04) in patients with Chronic Obstructive Pulmonary Disease (COPD) is low [114].

In addition to vitamin serum analysis, mineral serum analysis is also needed to determine other important parameters. Zinc plays an essential role in the process of proliferation, differentiation, and improvement of leukocyte and lymphocyte function. The measurement of zinc levels in COVID-19 patients experienced a significant decrease (P<0.0001). In addition, the patient's serum zinc also had an inverse relationship with the Blood Urea Nitrogen (BUN) parameter (P= 0.021). The measured serum calcium also experienced a significant decrease in P<0.0001 [33]. The levels of serum with the Acute Physiology and Chronic Health Evaluation (APACHE) value which is commonly used as a comparison in acute and chronic disease [34]. The measured serum iron value was 48.00 g/dl with a normal value of 60.00 g/dl so that the serum iron level decreased significantly. In addition, serum selenium levels are also a marker in the severity of COVID-19. Measurement of serum selenium levels in 84 COVID-19 patients with mild, moderate, and severe severity obtained an average of 47.07±20.82 ng/ml, 47.36±25.6 ng/ml, and 29.86±11.48 ng/ml. There was a significant decrease when compared to the normal value (70–150 ng/ml) at all three severity levels [115].

Plasma plays an important role in determining markers in COVID-19. Measurement of metabolites such as cytokines, chemokines, and growth factors (CCGFs) were conducted to identify the parameters that are changed from normal condition (homeostasis) in 7 patients COVID-19 severe and 10 patients COVID-19 mild. Measurement of cytokines including Interleukin 1α, 1β, 4, 5, 7, 12 p40, 13, 16, TNF-α, Interferon-α2 (IFN-α2), and TNF-related apoptosis-inducing ligand (TRAIL). Measurement of chemokines in the form of CXC ligand 1 (CXCL1)/growth-regulated oncogene-α (GRO-α), stromal cell-derived factor 1 (SDF-1α)/CXC motif ligand 12 (CXCL12), CCL11/Eotaxin, CC Chemokine motifs Ligand 27 (CCL27)/CTACK, G-CSF. Meanwhile, measurements of CCGFs, including migration inhibitory factor (MIF), anti-leukemia inhibitory factor (LIF), Vascular endothelial growth factor (VEGF) and stem cell factor (SCF)showed that SCGF, MIF, CCL27, and CXCL1 levels were>500 pg/ml. The levels of IL-12 p40, VEGF, G-CSF, IL16, and TNF-α were in the range of 50–500 pg/ml and other parameters were in the range<50 pg/ml. While the values of CCL11, CXCL12, and CCL27 increased 10 times higher in COVID-19 patients, especially in moderate and severe patients [116]. The cohort study in critical (n=5), severe (n=7), mild (n=10), and healthy (n=8) patients showed that platelet degranulation and coagulation pathways were processes that were measurably high in critical patients and severe. In addition, amino acid synthesis pathways and glycerophospholipid metabolism are also pathways for detecting the severity of COVID-

19 through metabolite measurements [117]. Enhancement in triglycerol, phosphatidylcholine, prostaglandin E2, and arginine as well as a decrease in betaine and adenosine are often associated with this pathway [57].

CONCLUSION

According to the comprehensive literature study above, it concludes that the severity of COVID-19 affects the metabolism in the human body. These alterations lead to determination of biomarkers by the omics study. The COVID-19 severity can be assessed by the different profiles in serum and plasma through the protein, lipid, and metabolite profiles. Generally, IL, TNF, Ig (A and G), procalcitonin, CRP, cytokines, LDL-C, HDL-C, TC, ApoA-1, VVD, Dp-µcMGP, PIVKA II, D-dimer, CCL, CXCL, triglycerol, prostaglandin E2, arginine, and oleic acid will increase during the infection. Meanwhile, globulin, serum vitamin C, serum minerals (zinc, selenium, and iron), betaine, adenosine, TFA, PL, NEFAs, palmitic acid, and fatty acids occur low in every stage of COVID-19. Specifically, In mild: CD3 (937.24 cells per ml), CD4 T cells (344.96 cells/ml), TNF-α (52.60 pg/ml), IL-2R (622.0 U/ml), IL-1β (107.2 pg/ml), Albumin (4,55 g/dl), CD8 (72,21 cell/µl), Th cells (100,05 cell/µl), Dp-ucMGP (776.5 ng/ml); moderate: Albumin (4,55 g/dl), CD8 (72,21 cell/µl), Th cell (100,05 cell/µl); severe: CD3 (383.38 cells/ml), CD4 T cells (208.63 cells/ml), TNF-α (70.80 pg/ml), IL-2R (879.6 U/ml), IL-1β 139.8 pg/ml), Albumin (3,80 g/dl), CD8 (61,22cell/µl), Th cell (0,14 cell/µl). Identification of biomarkers in serum and plasma samples is known through an omics approach to facilitate the comprehensive analysis. It is necessary to conduct a more in-depth search on serum and plasma biomarkers in COVID-19 related to its severity so that it can support therapy, enrich data and information, and choose treatment management for further research.

FUNDING

The funding for this research was obtained through the research grant Hibah Integrasi Tridharma (HIT), which was granted by Universitas Muhammadiyah Surakarta in Indonesia.

AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Bloom JD, Chan YA, Baric RS, Bjorkman PJ, Cobey S, Deverman BE. Investigate the origins of COVID-19. Science. 2021;372(6543):694. doi: 10.1126/science.abj0016, PMID 33986172.
2. Karakike E, Giamarellos Bourboulis EJ. Macrophage activation like syndrome: a distinct entity leading to early death in sepsis. Front Immunol. 2019;10:55. doi: 10.3389/fimmu.2019.00055, PMID 30766533.
3. MA H, Zeng W, HE H, Zhao D, Jiang D, Zhou P. Serum IgA IgM and IgG responses in COVID-19. Cell Mol Immunol. 2020;17(7):773-5. doi: 10.1038/s41423-020-0474-z, PMID 32467617.
4. Kheir M, Saleem F, Wang C, Mann A, Chua J. Higher albumin levels on admission predict better prognosis in patients with confirmed COVID-19. PLOS ONE. 2021;16(3):e0248358. doi: 10.1371/journal.pone.0248358, PMID 33725003.
5. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical therapeutic staging proposal. J Heart Lung Transplant. 2020;39(5):405-7. doi: 10.1016/j.healun.2020.03.012, PMID 32362390.
6. Griffin DO, Brennan Rieder D, Ngo B, Kory P, Confalonieri M, Shapiro L. The importance of understanding the stages of COVID-19 in treatment and trials. AIDS Rev. 2021;23(1):40-7. doi: 10.24875/AIDSRev.200001261, PMID 33556957.
7. WU J, Zhao M, LI C, Zhang Y, Wang DW. The SARS-CoV-2 induced targeted amino acid profiling in patients at hospitalized and convalescent stage. Biosci Rep. 2021;41(3):BSR20204201. doi: 10.1042/BSR20204201, PMID 33625490.
8. Ticinesi A, Nouvenne A, Prati B, Guida L, Parise A, Cerundolo N. The clinical significance of procalcitonin elevation in patients over 75 y old admitted for COVID-19 pneumonia. Mediators Inflamm. 2021;2021:5593806. doi: 10.1155/2021/5593806, PMID 34326704.
9. Mc Reynolds CB, Cortes Puch I, Ravindran R, Khan IH, Hammock BG, Shih PB. Plasma linoleate diols are potential biomarkers for severe COVID-19 infections. Front Physiol. 2021;12:663869. doi: 10.3389/fphys.2021.663869, PMID 33868029.
10. Saadh MJ. SARS-COV-2 3CL-protease inhibitors as antiviral agent against COVID-19. Int J App Pharm. 2022;14(6):18-20. doi: 10.22159/ijap.2022v14i6.46015.
11. Singh S, Monika MR, Mazumder R, Mazumder A. Review of SARS-corona virus-2 repercussions on thyroid gland in the context of hyperthyroidism. Int J App Pharm. 2023;15(5):17-26. doi: 10.22159/ijap.2023v15i5.47937.
12. Suklan J, Cheaveau J, Hill S, Urwin SG, Green K, Winter A. Utility of routine laboratory biomarkers to detect COVID-19: a systematic review and meta-analysis. Viruses. 2021;13(5):803. doi: 10.3390/v13050803, PMID 33946171.
13. Vibhute S, Kasar A, Mahale H, Gaikwad M, Kulkarni M. Niclosamide: a potential treatment option for COVID-19. Int J App Pharm. 2023;15(1):50-6. doi: 10.22159/ijap.2023v15i1.45850.
14. Keykavousi K, Nourbakhsh F, Abdollahpour N, Fazeli F, Sedaghat A, Soheili V. A review of routine laboratory biomarkers for the detection of severe COVID-19 disease. Int J Anal Chem. 2022;2022:9006487. doi: 10.1155/2022/9006487, PMID 36267156.
15. Schwarz B, Sharma L, Roberts L, Peng X, Bermejo S, Leighton I. Cutting edge: severe SARS-CoV-2 infection in humans is defined by a shift in the serum lipidome resulting in dysregulation of eicosanoid immune mediators. J Immunol. 2021;206(2):329-34. doi: 10.4049/jimmunol.2001025, PMID 33277388.
16. Wang C, LI X, Ning W, Gong S, Yang F, Fang C. Multi-omic profiling of plasma reveals molecular alterations in children with COVID-19. Theranostics. 2021;11(16):8008-26. doi: 10.7150/thno.61832, PMID 34335977.
17. Vollmy F, Van den Toorn H, Zenezini Chiozzi R, Zucchetti O, Papi A, Volta CA. A serum proteome signature to predict mortality in severe covid-19 patients. Life Sci Alliance. 2021;4(9):e202101099. doi: 10.26508/lsa.202101099, PMID 34226277.
18. Gomila RM, Martorell G, Fraile Ribot PA, Domenech Sanchez A, Alberti M, Oliver A. Use of matrix-assisted laser desorption ionization time of flight mass spectrometry analysis of serum peptidome to classify and predict coronavirus disease 2019 severity. Open Forum Infect Dis. 2021;8(6):ofab222. doi: 10.1093/ofid/ofab222, PMID 34109258.
19. Chen YM, Zheng Y, YU Y, Wang Y, Huang Q, Qian F. Blood molecular markers associated with COVID-19 immunopathology and multi-organ damage. EMBO J. 2020;39(24):e105896. doi: 10.15252/embj.2020105896, PMID 33140861.
20. Zhang J, Rao X, LI Y, Zhu Y, Liu F, Guo G. Pilot trial of high dose vitamin C in critically ill COVID-19 patients. Ann Intensive Care. 2021;11(1):5. doi: 10.1186/s13613-020-00792-3, PMID 33420963.
21. Reyes L, A Sanchez Garcia M, Morrison T, Howden AJ, Watts ER, Arienti S. A type I IFN prothrombotic hyperinflammatory neutrophil signature is distinct for COVID-19 ARDS. Wellcome Open Res. 2021;6:38. doi: 10.12688/wellcomeopenres.16584.2, PMID 33997298.
22. Overmyer KA, Shishkova E, Miller IJ, Balnis J, Bernstein MN, Peters Clarke TM. Large-scale multi-omic analysis of COVID-19 severity. Cell Syst. 2021;12(1):23-40.e7. doi: 10.1016/j.cels.2020.10.003, PMID 33096026.
23. Danlos FX, Grajeda Iglesias C, Durand S, Sauvat A, Roumier M, Cantin D. Metabolomic analyses of COVID-19 patients unravel stage-dependent and prognostic biomarkers. Cell Death Dis. 2021;12(3):258. doi: 10.1038/s41419-021-03540-y, PMID 33707411.
24. Cai Y, Kim DJ, Takahashi T, Broadhurst DI, MA S, Rattray NJ. Kynurenic acid underlies sex-specific immune responses to COVID-19. MedRxiv. 2020. doi: 10.1101/2020.09.06.20189159, PMID 32935119.

25. LI Y, Zhang Y, LU R, Dai M, Shen M, Zhang J. Lipid metabolism changes in patients with severe COVID-19. Clin Chim Acta. 2021;517:66-73. doi: 10.1016/j.cca.2021.02.011, PMID 33639119.
26. Roberts I, Wright Muelas M, Taylor JM, Davison AS, XU Y, Grixti JM. Untargeted metabolomics of COVID-19 patient serum reveals potential prognostic markers of both severity and outcome. Metabolomics. 2021;18(1):6. doi: 10.1007/s11306-021-01859-3, PMID 34928464.
27. Yang C, Yang X, DU J, Wang H, LI H, Zeng L. Retinoic acid promotes the endogenous repair of lung stem/progenitor cells in combined with simvastatin after acute lung injury: a stereological analysis. Respir Res. 2015;16:140. doi: 10.1186/s12931-015-0300-9, PMID 26561298.
28. Krishnan S, Nordqvist H, Ambikan A, Gupta S, Sperk M, Svensson Akusjarvi S. Implications of central carbon metabolism in sars-COV-2 replication and disease severity. BioRxiv. 2021. doi: 10.1101/2021.02.24.432759.
29. Giron LB, Dweep H, Yin X, Wang H, Damra M, Goldman AR. Plasma markers of disrupted gut permeability in severe COVID-19 patients. Front Immunol. 2021;12:686240. doi: 10.3389/fimmu.2021.686240, PMID 34177935.
30. Cook AM, Faustini SE, Williams LJ, Cunningham AF, Drayson MT, Shields AM. Validation of a combined ELISA to detect IgG, IgA and IgM antibody responses to SARS-COV-2 in mild or moderate non-hospitalised patients. J Immunol Methods. 2021;494:113046. doi: 10.1016/j.jim.2021.113046, PMID 33775672.
31. Mahmoodpoor A, Hosseini M, Soltani Zangbar S, Sanaie S, Aghebati Maleki L, Saghaleini SH. Reduction and exhausted features of T lymphocytes under serological changes and prognostic factors in COVID-19 progression. Mol Immunol. 2021;138:121-7. doi: 10.1016/j.molimm.2021.06.001, PMID 34392110.
32. XU Y, Yang H, Wang J, LI X, Xue C, Niu C. Serum albumin levels are a predictor of COVID-19 patient prognosis: evidence from a single cohort in Chongqing China. Int J Gen Med. 2021;14:2785-97. doi: 10.2147/IJGM.S312521, PMID 34194238.
33. Elham AS, Azam K, Azam J, Mostafa L, Nasrin B, Marzieh N. Serum vitamin D calcium and zinc levels in patients with COVID-19. Clin Nutr ESPEN. 2021;43:276-82. doi: 10.1016/j.clnesp.2021.03.040, PMID 34024527.
34. Beigmohammadi MT, Bitarafan S, Abdollahi A, Amoozadeh L, Salahshour F, Mahmoodi Ali Abadi M. The association between serum levels of micronutrients and the severity of disease in patients with COVID-19. Nutrition. 2021;91-92:111400. doi: 10.1016/j.nut.2021.111400, PMID 34388583.
35. Eberhardt KA, Meyer Schwickerath C, Heger E, Knops E, Lehmann C, Rybniker J. RNA emia corresponds to disease severity and antibody response in hospitalized COVID-19 patients. Viruses. 2020;12(9):1045. doi: 10.3390/v12091045, PMID 32962125.
36. Caterino M, Gelzo M, Sol S, Fedele R, Annunziata A, Calabrese C. Dysregulation of lipid metabolism and pathological inflammation in patients with COVID-19. Sci Rep. 2021;11(1):2941. doi: 10.1038/s41598-021-82426-7, PMID 33536486.
37. Park J, Kim H, Kim SY, Kim Y, Lee JS, Dan K. In depth blood proteome profiling analysis revealed distinct functional characteristics of plasma proteins between severe and non-severe covid-19 patients. Sci Rep. 2020;10(1):22418. doi: 10.1038/s41598-020-80120-8, PMID 33376242.
38. Yan L, YI J, Huang C, Zhang J, FU S, LI Z. Rapid detection of covid-19 using MALDI-TOF-based serum peptidome profiling. Anal Chem. 2021;93(11):4782-7. doi: 10.1021/acs.analchem.0c04590, PMID 33656857.
39. Kimhofer T, Lodge S, Whiley L, Gray N, Loo RL, Lawler NG. Integrative modeling of quantitative plasma lipoprotein metabolic and amino acid data reveals a multiorgan pathological signature of SARS-COV-2 infection. J Proteome Res. 2020;19(11):4442-54. doi: 10.1021/acs.jproteome.0c00519, PMID 32806897.
40. Lodge S, Nitschke P, Kimhofer T, Coudert JD, Begum S, Bong SH. NMR spectroscopic windows on the systemic effects of SARS-COV-2 infection on plasma lipoproteins and metabolites in relation to circulating cytokines. J Proteome Res. 2021;20(2):1382-96. doi: 10.1021/acs.jproteome.0c00876, PMID 33426894.
41. Bruzzone C, Bizkarguenaga M, Gil Redondo R, Diercks T, Arana E, Garcia de Vicuna A. SARS-CoV-2 infection dysregulates the metabolomic and lipidomic profiles of serum. iScience 2020 Oct 23;23(10)101645. I Science. 2020;23(10):101645. doi: 10.1016/j.isci.2020.101645, PMID 33043283.
42. Singh Y, Trautwein C, Fendel R, Krickeberg N, Berezhnoy G, Bissinger R. SARS-CoV-2 infection paralyzes cytotoxic and metabolic functions of the immune cells. Heliyon. 2021;7(6):e07147. doi: 10.1016/j.heliyon.2021.e07147, PMID 34075347.
43. Meoni G, Ghini V, Maggi L, Vignoli A, Mazzoni A, Salvati L. Metabolomic/lipidomic profiling of COVID-19 and individual response to tocilizumab. Plos Pathog. 2021;17(2):e1009243. doi: 10.1371/journal.ppat.1009243, PMID 33524041.
44. Dierckx T, Van Elslande J, Salmela H, Decru B, Wauters E, Gunst J. The metabolic fingerprint of COVID-19 severity. MedRxiv. 2020. doi: 10.1101/2020.11.09.20228221.
45. Wei C, Wan L, Zhang Y, Fan C, Yan Q, Yang X. Cholesterol metabolism impact for SARS-CoV-2 infection prognosis entry and antiviral therapies. MedRxiv. 2020. doi: 10.1101/2020.04.16.20068528.
46. Petrey AC, Qeadan F, Middleton EA, Pinchuk IV, Campbell RA, Beswick EJ. Cytokine release syndrome in COVID-19: innate immune, vascular and platelet pathogenic factors differ in severity of disease and sex. J Leukoc Biol. 2021;109(1):55-66. doi: 10.1002/JLB.3COVA0820-410RRR, PMID 32930456.
47. Varchetta S, Mele D, Oliviero B, Mantovani S, Ludovisi S, Cerino A. Unique immunological profile in patients with COVID-19. Cell Mol Immunol. 2021;18(3):604-12. doi: 10.1038/s41423-020-00557-9, PMID 33060840.
48. Rieder M, Wirth L, Pollmeier L, Jeserich M, Goller I, Baldus N. Serum protein profiling reveals a specific upregulation of the immunomodulatory protein progranulin in coronavirus disease 2019. J Infect Dis. 2021;223(5):775-84. doi: 10.1093/infdis/jiaa741, PMID 33249471.
49. Torres Ruiz J, Perez Fragoso A, Maravillas Montero JL, Llorente L, Mejia-Dominguez NR, Paez Franco JC. Redefining COVID-19 severity and prognosis: the role of clinical and immune biotypes. Front Immunol. 2021;12:689966. doi: 10.3389/fimmu.2021.689966, PMID 34566957.
50. Sosa Hernandez VA, Torres Ruiz J, Cervantes Diaz R, Romero Ramirez S, Paez Franco JC, Meza Sanchez DE. B cell subsets as severity-associated signatures in COVID-19 patients. Front Immunol. 2020;11:611004. doi: 10.3389/fimmu.2020.611004, PMID 33343585.
51. Zhu Z, Yang Y, Fan L, YE S, Lou K, Hua X. Low serum level of apolipoprotein A1 may predict the severity of COVID-19: a retrospective study. J Clin Lab Anal. 2021;35(8):e23911. doi: 10.1002/jcla.23911, PMID 34260764.
52. Oja AE, Saris A, Ghandour CA, Kragten NA, Hogema BM, Nossent EJ. Divergent SARS-CoV-2-specific T and B-cell responses in severe but not mild COVID-19 patients. Eur J Immunol. 2020;50(12):1998-2012. doi: 10.1002/eji.202048908, PMID 33073359.
53. Bichara CD, Da Silva Graca Amoras E, Vaz GL, Da Silva Torres MK, Queiroz MA, DO Amaral IP. Dynamics of anti-SARS-CoV-2 IgG antibodies post-COVID-19 in a Brazilian Amazon population. BMC Infect Dis. 2021;21(1):443. doi: 10.1186/s12879-021-06156-x, PMID 33992073.
54. Sun J, Tang X, Bai R, Liang C, Zeng L, Lin H. The kinetics of viral load and antibodies to SARS-CoV-2. Clin Microbiol Infect. 2020;26(12):1690.e1-4. doi: 10.1016/j.cmi.2020.08.043, PMID 32898715.
55. Liu J, Liu S, Zhang Z, Lee X, WU W, Huang Z. Association between the nasopharyngeal microbiome and metabolome in patients with COVID-19. Synth Syst Biotechnol. 2021;6(3):135-43. doi: 10.1016/j.synbio.2021.06.002, PMID 34151035.
56. Hausburg MA, Banton KL, Roshon M, Bar Or D. Clinically distinct COVID-19 cases share notably similar immune response progression: a follow-up analysis. Heliyon Heliyon. 2021;7(1):e05877. doi: 10.1016/j.heliyon.2020.e05877, PMID 33437888.

57. XU ZS, Shu T, Kang L, WU D, Zhou X, Liao BW. Temporal profiling of plasma cytokines chemokines and growth factors from mild severe and fatal COVID-19 patients. Signal Transduct Target Ther. 2020;5(1):100. doi: 10.1038/s41392-020-0211-1, PMID 32561706.
58. Desai AP, Dirajlal Fargo S, Durieux JC, Tribout H, Labbato D, Mc Comsey GA. Vitamin K and D deficiencies are independently associated with COVID-19 disease severity. Open Forum Infect Dis. 2021;8(10):ofab408. doi: 10.1093/ofid/ofab408, PMID 34642636.
59. YE K, Tang F, Liao X, Shaw BA, Deng M, Huang G. Does serum vitamin D level affect COVID-19 infection and its severity a case control study. J Am Coll Nutr. 2021;40(8):724-31. doi: 10.1080/07315724.2020.1826005, PMID 33048028.
60. Perez Torres I, Guarner Lans V, Soria Castro E, Manzano Pech L, Palacios-Chavarria A, Valdez Vazquez RR. Alteration in the lipid profile and the desaturases activity in patients with severe pneumonia by SARS-CoV-2. Front Physiol. 2021;12:667024. doi: 10.3389/fphys.2021.667024, PMID 34045976.
61. Thomas T, Stefanoni D, Reisz JA, Nemkov T, Bertolone L, Francis RO. COVID-19 infection alters kynurenine and fatty acid metabolism correlating with IL-6 levels and renal status. JCI Insight. 2020;5(14):e140327. doi: 10.1172/jci.insight.140327, PMID 32559180.
62. Lucas C, Wong P, Klein J, Castro TB, Silva J, Sundaram M. Longitudinal analyses reveal immunological misfiring in severe COVID-19. Nature. 2020;584(7821):463-9. doi: 10.1038/s41586-020-2588-y, PMID 32717743.
63. Stone MR, O Neill A, Lovering RM, Strong J, Resneck WG, Reed PW. Absence of keratin 19 in mice causes skeletal myopathy with mitochondrial and sarcolemmal reorganization. J Cell Sci. 2007;120(22):3999-4008. doi: 10.1242/jcs.009241, PMID 17971417.
64. Song JW, Lam SM, Fan X, Cao WJ, Wang SY, Tian H. Omics driven systems interrogation of metabolic dysregulation in COVID-19 pathogenesis. Cell Metab. 2020;32(2):188-202.e5. doi: 10.1016/j.cmet.2020.06.016, PMID 32610096.
65. You R, Dai J, Zhang P, Barding GA, Raftery D. Dynamic metabolic response to adriamycin induced senescence in breast cancer cells. Metabolites. 2018;8(4):95. doi: 10.3390/metabo8040095, PMID 30558288.
66. Segers K, Declerck S, Mangelings D, Heyden YV, Eeckhaut AV. Analytical techniques for metabolomic studies: a review. Bioanalysis. 2019;11(24):2297-318. doi: 10.4155/bio-2019-0014, PMID 31845604.
67. Manchester M, Anand A. Metabolomics: strategies to define the role of metabolism in virus infection and pathogenesis. Adv Virus Res. 2017;98:57-81. doi: 10.1016/bs.aivir.2017.02.001, PMID 28433052.
68. Henkel R, Agarwal A, Samanta L. Oxidants antioxidants and impact of the oxidative status in male reproduction. ScienceDirect; 2018. p. 287-98. doi: 10.1016/C2016-0-03860-3.
69. Chan JF, Yuan S, Kok KH, TO KK, Chu H, Yang J. A familial cluster of pneumonia associated with the 2019 novel corona virus indicating person to person transmission: a study of a family cluster. Lancet. 2020;395(10223):514-23. doi: 10.1016/S0140-6736(20)30154-9, PMID 31986261.
70. Mallat J, Lemyze M, Thevenin D. Do not forget to give thiamine to your septic shock patient. J Thorac Dis. 2016;8(6):1062-6. doi: 10.21037/jtd.2016.04.32, PMID 27293820.
71. Boechat JL, Chora I, Morais A, Delgado L. The immune response to SARS-CoV-2 and COVID-19 immunopathology current perspectives. Pulmonology. 2021;27(5):423-37. doi: 10.1016/j.pulmoe.2021.03.008, PMID 33867315.
72. Schultze JL, Aschenbrenner AC. COVID-19 and the human innate immune system. Cell. 2021;184(7):1671-92. doi: 10.1016/j.cell.2021.02.029, PMID 33743212.
73. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan China. Intensive Care Med. 2020;46(5):846-8. doi: 10.1007/s00134-020-05991-x, PMID 32125452.
74. Ramos Casals M, Brito Zeron P, Lopez Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet. 2014;383(9927):1503-16. doi: 10.1016/S0140-6736(13)61048-X, PMID 24290661.
75. Huang C, Wang Y, LI X, Ren L, Zhao J, HU Y. Clinical features of patients infected with 2019 novel corona virus in Wuhan China. Lancet. 2020;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5, PMID 31986264.
76. Hao Y, Zhang Z, Feng G, Chen M, Wan Q, Lin J. Distinct lipid metabolic dysregulation in asymptomatic COVID-19. iScience. 2021;24(9):102974. doi: 10.1016/j.isci.2021.102974, PMID 34396083.
77. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X. COVID-19 infection: the perspectives on immune responses. Cell Death Differ. 2020;27(5):1451-4. doi: 10.1038/s41418-020-0530-3, PMID 32205856.
78. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology transmission diagnosis and treatment of corona virus disease 2019 (COVID-19): a review. JAMA. 2020;324(8):782-93. doi: 10.1001/jama.2020.12839, PMID 32648899.
79. Aziz M, Fatima R, Lee Smith W, Assaly R. The association of low serum albumin level with severe COVID-19: a systematic review and meta-analysis. Crit Care. 2020;24(1):255. doi: 10.1186/s13054-020-02995-3, PMID 32456658.
80. Huang J, Cheng A, Kumar R, Fang Y, Chen G, Zhu Y. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. J Med Virol. 2020;92(10):2152-8. doi: 10.1002/jmv.26003, PMID 32406952.
81. Abdeen Y, Kaako A, Ahmad Amin Z, Muhanna A, Josefine Froessl L, Alnabulsi M. The prognostic effect of serum albumin level on outcomes of hospitalized COVID-19 patients. Crit Care Res Pract. 2021;2021:9963274. doi: 10.1155/2021/9963274, PMID 34367693.
82. Feketea GM, Vlacha V. The diagnostic significance of usual biochemical parameters in coronavirus disease 19 (COVID-19): albumin to globulin ratio and CRP to albumin ratio. Front Med (Lausanne). 2020;7:566591. doi: 10.3389/fmed.2020.566591, PMID 33224959.
83. Conca W, Alabdely M, Albaiz F, Foster MW, Alamri M, Alkaff M. Serum β2-micro globulin levels in coronavirus disease 2019 (COVID-19): another prognosticator of disease severity. PLOS ONE. 2021;16(3):e0247758. doi: 10.1371/journal.pone.0247758, PMID 33647017.
84. HU R, Han C, Pei S, Yin M, Chen X. Procalcitonin levels in COVID-19 patients. Int J Antimicrob Agents. 2020;56(2):106051. doi: 10.1016/j.ijantimicag.2020.106051, PMID 32534186.
85. Dolci A, Robbiano C, Aloisio E, Chibireva M, Serafini L, Falvella FS. Searching for a role of procalcitonin determination in COVID-19: a study on a selected cohort of hospitalized patients. Clin Chem Lab Med. 2020;59(2):433-40. doi: 10.1515/cclm-2020-1361, PMID 33554505.
86. HU X, Chen D, WU L, HE G, YE W. Low serum cholesterol level among patients with COVID-19 infection in Wenzhou China. SSRN Journal. doi: 10.2139/ssrn.3544826.
87. HU X, Chen D, WU L, HE G, YE W. Declined serum high density lipoprotein cholesterol is associated with the severity of COVID-19 infection. Clin Chim Acta. 2020;510:105-10. doi: 10.1016/j.cca.2020.07.015, PMID 32653486.
88. Casari I, Manfredi M, Metharom P, Falasca M. Dissecting lipid metabolism alterations in SARS-CoV-2. Prog Lipid Res. 2021;82:101092. doi: 10.1016/j.plipres.2021.101092, PMID 33571544.
89. Masana L, Correig E, Ibarretxe D, Anoro E, Arroyo JA, Jerico C. Low HDL and high triglycerides predict COVID-19 severity. Sci Rep. 2021;11(1):7217. doi: 10.1038/s41598-021-86747-5, PMID 33785815.
90. Palmas F, Clarke J, Colas RA, Gomez EA, Keogh A, Boylan M. Dysregulated plasma lipid mediator profiles in critically ill COVID-19 patients. PLOS ONE. 2021;16(8):e0256226. doi: 10.1371/journal.pone.0256226, PMID 34437568.
91. V kovski P, Al Mulla H, Thiel V, Neuman BW. New insights on the role of paired membrane structures in coronavirus replication. Virus Res. 2015;202:33-40. doi: 10.1016/j.virusres.2014.12.021, PMID 25550072.
92. Abu Farha M, Thanaraj TA, Qaddoumi MG, Hashem A, Abubaker J, Al Mulla F. The role of lipid metabolism in COVID-19 virus

infection and as a drug target. Int J Mol Sci. 2020;21(10):3544. doi: 10.3390/ijms21103544, PMID 32429572.
93. Akram M, Munir N, Daniyal M, Egbuna C, Gaman MA, Onyekere PF. Vitamins and minerals: types sources and their functions. Functional Food and Neutraceutical; 2020. p. 149-72. doi: 10.1007/978-3-030-42319-3_9.
94. Pfeffer PE, Hawrylowicz CM. Vitamin D and lung disease. Thorax. 2012;67(11):1018-20. doi: 10.1136/thoraxjnl-2012-202139, PMID 22935474.
95. Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. Nutrients. 2015;7(6):4240-70. doi: 10.3390/nu7064240, PMID 26035247.
96. Bombardini T, Picano E. Angiotensin converting enzyme 2 as the molecular bridge between epidemiologic and clinical features of COVID-19. Can J Cardiol. 2020;36(5):784.e1-2. doi: 10.1016/j.cjca.2020.03.026, PMID 32299780.
97. Phokela SS, Peleg S, Moya FR, Alcorn JL. Regulation of human pulmonary surfactant protein gene expression by 1alpha, 25-dihydroxyvitamin D3. Am J Physiol Lung Cell Mol Physiol. 2005;289(4):L617-26. doi: 10.1152/ajplung.00129.2004, PMID 15951333.
98. Rehan VK, Torday JS, Peleg S, Gennaro L, Vouros P, Padbury J. 1Alpha, 25-dihydroxy-3-epi-vitamin D3, a natural metabolite of 1alpha, 25-dihydroxy vitamin D3: production and biological activity studies in pulmonary alveolar type II cells. Mol Genet Metab. 2002;76(1):46-56. doi: 10.1016/s1096-7192(02)00022-7, PMID 12175780.
99. Smith EM, Jones JL, Han JE, Alvarez JA, Sloan JH, Konrad RJ. High dose vitamin D3 administration is associated with increases in hemoglobin concentrations in mechanically ventilated critically ill adults: a pilot double blind randomized placebo controlled trial. JPEN J Parenter Enteral Nutr. 2018;42(1):87-94. doi: 10.1177/0148607116678197, PMID 29505145.
100. Han JE, Jones JL, Tangpricha V, Brown MA, Brown LA, Hao L. High dose vitamin d administration in ventilated intensive care unit patients: a pilot double blind randomized controlled trial. J Clin Transl Endocrinol. 2016;4:59-65. doi: 10.1016/j.jcte.2016.04.004, PMID 27419080.
101. Sabetta JR, DePetrillo P, Cipriani RJ, Smardin J, Burns LA, Landry ML. Serum 25-hydroxyvitamin d and the incidence of acute viral respiratory tract infections in healthy adults. PLOS ONE. 2010;5(6):e11088. doi: 10.1371/journal.pone.0011088, PMID 20559424.
102. Schurgers LJ, Vermeer C. Differential lipoprotein transport pathways of K-vitamins in healthy subjects. Biochim Biophys Acta. 2002;1570(1):27-32. doi: 10.1016/s0304-4165(02)00147-2, PMID 11960685.
103. Anastasi E, Ialongo C, Labriola R, Ferraguti G, Lucarelli M, Angeloni A. Vitamin K deficiency and COVID-19. Scand J Clin Lab Invest. 2020;80(7):525-7. doi: 10.1080/00365513.2020.1805122, PMID 32779537.
104. Carr AC, Rosengrave PC, Bayer S, Chambers S, Mehrtens J, Shaw GM. Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. Crit Care. 2017;21(1):300. doi: 10.1186/s13054-017-1891-y, PMID 29228951.
105. DE Grooth HJ, Manubulu Choo WP, Zandvliet AS, Spoelstra DE Man AM, Girbes AR, Swart EL. Vitamin C pharmacokinetics in critically ill patients: a randomized trial of four IV regimens. Chest. 2018;153(6):1368-77. doi: 10.1016/j.chest.2018.02.025, PMID 29522710.
106. Fowler AA, Syed AA, Knowlson S, Sculthorpe R, Farthing D, DeWilde C. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Transl Med. 2014;12:32. doi: 10.1186/1479-5876-12-32, PMID 24484547.
107. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y. Autoantibodies against type I IFNs in patients with life threatening COVID-19. Science. 2020;370(6515):eabd4585. doi: 10.1126/science.abd4585, PMID 32972996.
108. Blanco Melo D, Nilsson Payant BE, Liu WC, Uhl S, Hoagland D, Moller R. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell. 2020;181(5):1036-1045.e9. doi: 10.1016/j.cell.2020.04.026, PMID 32416070.
109. Arvinte C, Singh M, Marik PE. Serum levels of vitamin C and vitamin D in a cohort of critically ill COVID-19 patients of a North American Community Hospital Intensive Care Unit in May 2020: a pilot study. Med Drug Discov. 2020;8:100064. doi: 10.1016/j.medidd.2020.100064, PMID 32964205.
110. Winterbourn CC, Vissers MC. Changes in ascorbate levels on stimulation of human neutrophils. Biochim Biophys Acta. 1983;763(2):175-9. doi: 10.1016/0167-4889(83)90041-1, PMID 6615889.
111. Washko P, Rotrosen D, Levine M. Ascorbic acid transport and accumulation in human neutrophils. J Biol Chem. 1989;264(32):18996-9002. doi: 10.1016/S0021-9258(19)47256-6, PMID 2681206.
112. Manzanares W, Hardy G. Thiamine supplementation in the critically ill. Curr Opin Clin Nutr Metab Care. 2011;14(6):610-7. doi: 10.1097/MCO.0b013e32834b8911, PMID 21912244.
113. Donnino MW, Andersen LW, Chase M, Berg KM, Tidswell M, Giberson T. Randomized double blind placebo controlled trial of thiamine as a metabolic resuscitator in septic shock: a pilot study. Crit Care Med. 2016;44(2):360-7. doi: 10.1097/CCM.0000000000001572, PMID 26771781.
114. Fimognari FL, Loffredo L, Di Simone S, Sampietro F, Pastorelli R, Monaldo M. Hyperhomocysteinaemia and poor vitamin B status in chronic obstructive pulmonary disease. Nutr Metab Cardiovasc Dis. 2009;19(9):654-9. doi: 10.1016/j.numecd.2008.12.006, PMID 19282159.
115. Razeghi Jahromi S, Moradi Tabriz H, Togha M, Ariyanfar S, Ghorbani Z, Naeeni S. The correlation between serum selenium zinc and COVID-19 severity: an observational study. BMC Infect Dis. 2021;21(1):899. doi: 10.1186/s12879-021-06617-3, PMID 34479494.
116. Yan H, Liang X, DU J, HE Z, Wang Y, Lyu M. Proteomic and metabolomic investigation of serum lactate dehydrogenase elevation in COVID-19 patients. Proteomics. 2021;21(15):e2100002. doi: 10.1002/pmic.202100002, PMID 33987944.
117. Shu T, Ning W, WU D, XU J, Han Q, Huang M. Plasma proteomics identify biomarkers and pathogenesis of COVID-19. Immunity. 2020;53(5):1108-1122.e5. doi: 10.1016/j.immuni.2020.10.008, PMID 33128875.