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Review Article

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

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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

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 used to analyze biological samples wholly and usuallv 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.





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 \uparrow , FETUB \uparrow , and KNG1 \uparrow
[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 \uparrow (mild and severe), SAA1, CRP, FGG, and LBP \uparrow (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 1, taurine uracil 1, inosine uracil 1, cyclic adenosine 3', hypoxanthine, cAMP 1. hippurate 1. JMP 1. and abscisic acid 1.
[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	LC-MS	Increasing proinflammatory signal	Severe: IFN-1 \uparrow and TLR \uparrow
[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 \uparrow , AAAs \uparrow , and methionine \downarrow
[9]	Plasma samples were obtained from 44 HC and 6 COVID-19 patients	UPLC-MS/MS	Increasing proteinogenic amino parameters	Mild-severe: AA \uparrow and linoleic acid \uparrow
[27]	Serum in COVID-19 patients to determine the role of LDL serum in COVID-19	ELISA	Increasing lipid	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 natients through a cohort study	ELISA	Increasing lipid	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 \uparrow , IgG \uparrow , and IgM \uparrow , bilirubin \uparrow , hemoglobin \uparrow , and triglycerides \uparrow
[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)

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[33] Serum draw from 95 patients with CVID-19 patients ELISA Decreasing uncronutirent Zanc serum 1 [34] Sorum 100ker of from 60 CVID-19 patients ELISA Decreasing uncronutirent Sorum Vtamin 09 1, 8124, Cl, Di, Magnesiumi, from 1 [36] Sorum fails were obtained from 30 CVID-19 ELISA Decreasing uncronutirent Made and exerct: gG 4 [37] Main was obtained from 3 Suddind 5 MS Decreasing uncronutirent Severe: Neutrophil 1 [38] Serum patients were for bin and from 3 Suddind 5 MS Decreasing uncronutirent Severe: Neutrophil 1 [39] Patients was obtained from 3 Suddind 5 MS Decreasing uncronutirent Severe: Neutrophil 1 [31] Severe CVID-19 patients. MS Decreasing uncronutirent Severe: Neutrophil 1 [31] Severe for more bin bendly patients. MS Decreasing uncronutirent Severe: Neutrophil 1 [32] Severe for more bin bendly patients. NIR Increasing proteinogenic antibus patients (NIR-17) NIR [43] Eblefee EDF Japama Patients were dvalade from soru (NIR-18) NIR Increasing proteinogenic antibus patients (NIR-17) [44] Eblefee EDF Japama Patients were dvalade from soru (NIR-18) NIR Increasing proteinogenic antibus patients (NIR-17) [45] Patients were dvalade from patien		asymptomatic, mild, severe (early), severe (late).		gene	
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[34] Serum Collected from 60 COVID-19 patients with severity ELISA Encoded Decreasing informational formation intermediate int		and 186 HC		serum	
13.1 32 sequence 1 1 1 1 [36] 32 every ment QUUID - 19 pattents with ecompared with healthy pattents. FLSA Partmange Severe: Serum (high and moderate: hgG 1 [37] Plantmass with different severtly who were built healthy pattents. Severe: Serum (high and moderate: hgG 1 [38] Serum (high and moderate: hgG 1 Severe: Serum (high and moderate: hgG 1 [39] Plantmass with different severtly who and the severe severe severe (high and moderate: hgG 1 Severe: Serum (high and moderate: hgG 1 [39] Plantmass match severe taken from head by pattents. NRL Increasing lipid Kynuremine 1, insystemphan 1, HDL 1, triglycerides 1, and triglycerides 1,	[34]	Serum collected from 60 COVID-19 patients	ELISA	Decreasing micronutrient	Serum Vitamin B9↓, B12↓, C↓, D↓, Magnesium↓, Iron
[35] 24 continues (LVIII-19 patients with and modest (g), 1 Mit and modest (g), 1 [36] Server: Neurophil Server: Neurophil [37] Plasma was obtained from 3 study and the state (g), 1 Diversity (g), 1 [38] Server: Neurophil Server: Neurophil [39] Plasma was obtained from 1 all and 5 MS Overexpression of neurophil [39] Plasma was obtained from 1 all and 5 MS Overexpression of neurophil [39] Plasma was obtained from 1 all and 5 MS Overexpression of neurophil [39] Plasma samples were taken from healthy patients. NMR MS and Increasing [ipid] Kynarcmin L, 1997 patients 1, 1D, 1, 1pig/sperifes 1, L24, 1D, 1D, 1, 1D, 1, 1pig/sperifes 1, L24, 1D, 1D, 1, 1D, 1, 1D, 1D, 1D, 1D, 1D,	1051	in hospital.	FI 10 1	serum	
[36] Security of the security who were secure shows on the secure show secure shows on the	[35]	32 confirmed COVID-19 patients with	ELISA	Decreasing	Mild and moderate: IgG↓
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compared with healthy patients.patientspatients[37]Plasma was oblaided from 3 wild and 5 severe (OUD-19 patients.MS neutrophil Increasing immune responseGenere. Neutrophil 7 contents of the patient was oblaided from 3 wild and 5. severe (OUD-19 patients.MS NS contents of the patient was oblaided from 3 wild and 5. severe (OUD-19 patients (n = 17), (IA)MR-M3 and Increasing immune responseCyckines IP-10 1 and MCP-3 1 (DUI, 14) and VLD 1[39]Patients (n = 33) and HC (n = 35), patients (n = 33) and HC (n = 35), Index study of generation metabolomic and High dom in (OUD) - 19 patients, (IA)NMR NMR MR Increasing ipid parameters amino parameters amino parameters amino parameters amino parameters amino parameters amino parameters amino parameters amino parameters index study of generation 3. parameters amino parameters amino parametersCycoprotein concentrations 1, and Amino acid concentrations (Increasing lipid parameters amino parameters amino parametersMIR Increasing lipid parameters[44]Blood plasma samples were obtained from swere parametersBiomedical test tomerasing lipid parametersMild-swere: It is 1, 1, 1, 2, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	[50]	19 patients with different severity who were	115	narameters	glycosylceramides 1
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[38] Serum peptides were obtained from 146 MalDP1-P patients, Tangative and 45 MalDP10F-19 patients, Tangatingative and 45 MalDP10F-19 patients, Tangative and 45 MalDP10F-1		severe COVID-19 patients.		neutrophil	
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[41]Cohor study of serum metabolomic and light duric in CVVD-19 patients.NMRIncreasing proteinogenic and topsMinimo acid (phenylatanite) 1, lectones 1, phospholipholis 1, and trig/series 1, and trig/series 1, and CD8-1[42]Serum was taken from patients of varying serverity.NMRIncreasing (pipid)Vul. 1, HD.1-4 1, LD.4 1, LD.5 1 and CD8-1[43]Ethylene EDTA plasma was collected in 30 biod plasma samples were obtained from serverity.NMRIncreasing (pipid)Vul. 1, HD.1-4 1, LD.4 1, LD.5 1 patients stratified by gender and age. parameters[44]Blood plasma samples were obtained from server (n=217) moderate (n=364), and mild (n=212) patients with COVD-19Biomedical test proinfammatory patients (n= 22)Biomedical test proinfammatory patients (n= 22)Mild-severe: flar-Oblast growth factors 2 1, IFN y 1, mild-severe: RR 1[46]Serum yotes handle from potents with differentiation of severity. Jarcady means with differentiation of severity. Jarcady means obtained from s2 CVUD-19 patients of different serverity patients of different serverity	[-•]	patients ($n = 34$) and HC ($n = 35$)		proinflammatory signal	IL-1α↑
Injeduction in COVID-19 patients.annino parametersannino parametersmild ad moderate glucose 1, glutanate 1, formate 1, annino parameters[4]Riverer, Construction of patients stratified by gender and age.NMRIncreasing protinometersMild admodrate glucose 1, glutanate 1, formate 1, annino parameters[4]Riod plasma samples were obtained from severe (n=217), moderate (n=364), and mild (n=215) patients.NMRIncreasing lipid ad proteinogenic amino proteinogenic amino <td>[41]</td> <td>Cohort study of serum metabolomic and</td> <td>NMR</td> <td>Increasing proteinogenic</td> <td>Amino acid (phenylalanine) ↑, ketones ↑,</td>	[41]	Cohort study of serum metabolomic and	NMR	Increasing proteinogenic	Amino acid (phenylalanine) ↑, ketones ↑,
[42] Serum was taken from patients of varying NMR Increasing proteinogenic anino parameters Mild and moderate: glucose 1, glutamate 1, formate 1, and DPA 4 [43] Ethylene EDTA plasma was collected in 30 NMR Increasing lipid AULD 1, 1, 1DL - 1, LDL - 1, LDL - 5 1 [44] Blood plasma samples were obtained from severe (n=217), moderate (n=04), annulld (n=217), moderate (n=04), annulld (n=10, n=10,		lipidomic in COVID-19 patients.		amino parameters	phospholipids ↑, and triglycerides ↑
amino parametersamino parametersamino parameters[44]Biodo Jaams any sentise were obtained from 251 COVID-19 patients.NMRIncreasing lipid parametersVLDL TAID.31, HDL-41, LDL-41, LDL-51[45]Plasma lipids were obtained from severe (n=217) moderate (n=364), and mild (n=215) patients with COVID-19Biomedical testIncreasing lipid parametersGlycoprotein acetylation 1, Lipoprotein concentrations 1, and Amino acid concentrations proteinogenic amino parameters[46]Samples were obtained from COVID-19Biomedical testIncreasing lipid parametersMild severe: C1 and HDL-C1 marameters[47]Serum protein samples were obtained from severity, already negative patients, and HC patients with differentiation of severity, already negative patients, and HC patients with differentiation of registry studyBiomedical test parametersIncreasing lipid marameters[50]Samples were obtained from 52 COVID-19 patientsMildparametri registry studyMildparametri registry studyMild-severe: HoL-C1, TC 1, ApoA1 1 and LD-C 1 marameters[51]Samples were obtained from 52 COVID-19 patientsMildparametri severe 3, 220 (MI), Thi cells 1, method and the immunoutrividiIncreasing immune responseMild-severe: HoL-C1, TC 1, ApoA1 1 and LD-C 1 cells 4, Louder 4, and 6, 19% severe[52]Plasma taken from a COVID-19 patients coUOID-19 patients.Mildparametri severe 3, 220 (MI), Thi cells 1, method and the 	[42]	Serum was taken from patients of varying	NMR	Increasing proteinogenic	Mild and moderate: glucose \downarrow , glutamate \downarrow , formate \downarrow ,
[43] Ethylene EDTA plasma vas collected in 30 NMK Increasing lipid VLDL [1,RUL-3], RUL-4], LUL-4], LUL-5] [44] Blood plasma samples were obtained from severe (n=217), moderate (n=364), and mild (n=reasing lipid namparameters (n=10, n=16, n=16), n=16, n=	[40]	severity.	NUCD	amino parameters	and CD8+↓
[44]platents strained by genuter and age. Discreption genue and book of parametersplatents protein agely and platents.Glycoprotein acetylation 1, Lipoprotein concentrations 1, and Amino acid concentrations parameters[45]Plasma lipids were obtained from severe (m=217) platents.Biomedical test parametersIncreasing lipid parametersGlycoprotein acetylation 1, Lipoprotein concentrations 1, and Amino acid concentrations (metation and phenylatamine) 1, Triglycrides 1 Mild-severe: TC 1 and HDL C 1[46]Samples were obtained from patients with (module and phenylatamine) 1, Triglycrides 1 parametersMild-severe: TC 1 and HDL C 1[47]Serum was obtained from patients with (module and phenylatamine) 1, Triglycrides 1 parametersMild-severe: Bioblast growth factors 2 prohafammatory signal parameters[48]Serum mortein samples were obtained from from COVID-19 patients of different severity patientsSingle center Flow CytometryIncreasing lipid parametersMild-severe: GR 1 mild/moderate = 4.55 g/di severe: 3.80 g/di), CDs4: [mild/moderate = 4.55 g/di severe: 3.80 g/di), CDs4: [mild/moderate = 4.55 g/di (mild/moderate = 10.05 cell/ul) mild/moderate = 4.55 g/di severe = 50.14 cell/ul)[50]Samples were obtained from 52 COVID-19 patientsMultiparametric Flow Cytometric The direct memoval method and the immunoutribid metric method.[51]Serum was taken from 125 normal patients and 17 COVID-19 patients.Multiparametric Flow Cytometric The direct serological test parametersIncreasing lipid metric method.[52]Plasm at sever and cold test servere.Serological test <b< td=""><td>[43]</td><td>Ethylene EDTA plasma was collected in 30</td><td>NMR</td><td>Increasing lipid</td><td>VLDL T,HDL3 T, HDL-4 T, LDL-4 T, LDL-5 T</td></b<>	[43]	Ethylene EDTA plasma was collected in 30	NMR	Increasing lipid	VLDL T,HDL3 T, HDL-4 T, LDL-4 T, LDL-5 T
[197]Distant a singlet with or bottline from 251 COVID-19 patients.Output of the construction of the constru	[4.4]	Blood plasma samples were obtained from	NMP	Increasing lipid and	Chronrotein acetulation 1 Lipoprotein
Label Control of parametersparameters[Leache and phenylalanine 1, Triglycerides 1[45]Plasma lipids were obtained from severe (n=217) moderate (n=364) and mid (n=215) patients with COVID-19 patients (n=22)Biomedical testIncreasing proinflammatory parametersMid-severe: TC 1 and HDL-C1 Mid-severe: TC 1 and HDL-C1[47]Samples were obtained from patients with COVID-19 and HCBiomedical testIncreasing proinflammatory parametersMid-severe: florbiblat growth factors 1 mid-severe: florbiblat growth factors 2 Mid-severe: GR 1[48]Serum yoot is amples were obtained from COVID-19 patients with differentiation of patients (metric method) patients (metric method)Single center registry studyIncreasing immune resonse in protein resonse and protein[49]Plasma and serum samples were obtained patientsMultiparametric Flow CytometryIncreasing immune resonse and protein resonse in funct parametersMid-severe: GN 1[50]Samples were obtained from 22 COVID-19 patients.Multiparametric Flow CytometryIncreasing immune resonse The direct- surfactant removal method and the immutor/bid metric methodSevere: 368 g/d1), C08+1 (mid/moderate = 4.55 g/d1; severe = 3.80 g/d1), C08+1 (mid/moderate = 4.55 g/d1; moderate = 1.000, Sel/d1; severe = 0.000, Sel/d1; severe =	[44]	251 COVID-19 natients	INMIX	proteinogenic amino	concentrations 1 and Amino acid concentrations
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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 Creactive 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-1 β , 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 survivors. A hyperactive/fatigued immune response to 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 cvtokines. 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 nonhospitalized 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 $(2.6\pm0.49 \text{ vs. } 2.9\pm0.48 \text{ g/dl})$. 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 β 2-m levels of 3.57±1.39 mg/l and severe patients had β 2-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 membranebound 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 proresolving 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 (250HD) 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 bv 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 increase in inflammation through hypersecretion of an 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- α^2 (IFN- α^2), 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 cellderived factor 1 (SDF-1 α)/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.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

Declared none

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