**Review Article**



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# COVID-19: A Systematic Review of Metabolomics Data and Predicting Potential Biomarkers Based on Pathway Analysis

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The COVID-19 pandemic is a worldwide disaster in medicine, public health, and the economy. Many details of COVID-19 are currently unknown. This study aims to offer dysregulated metabolic profiles as potential biomarkers for SARS-CoV-2 infection by analyzing identified COVID-19 metabolites. We searched PubMed, Web of Science, EMBASE, and Scopus for metabolomics studies on COVID-19 patients. Studies investigating COVID-19 metabolite changes and utilizing mass spectrometry-based techniques are included. Two reviewers separately retrieved pertinent data for each selected publication. Differences of opinion among the reviewers were settled via conversation, and a final judgment was obtained. The online MetaboAnalyst 3.0 was used to conduct the pathway analysis of COVID-19. This study comprised 31 investigations with QUADOMICS quality evaluation. We isolated modified metabolites that have been found in at least three other investigations. The metabolomics data in response to SARS-CoV-2 alter at the metabolite expression level, leading to dysregulation of major metabolic pathways, including carbohydrates, amino acids, and lipids associated with COVID-19. The pathway analysis of metabolic reprogramming across different biological samples demonstrated a significant role in amino acid metabolism, including phenylalanine, tyrosine, and tryptophan production, in the severity of COVID-19. This review showed dysregulated metabolic profiling for identifying individuals with high severity of COVID-19. These results provide an understanding of metabolic pathways and how dysregulated metabolic profiling reflects the severity of COVID-19 in the general population. The high frequency of changed metabolites might be used as COVID-19 biomarkers for early detection, and significant metabolic routes could reveal new information about pathogenesis and lead to potential treatment targets.

**Keywords:** SARS-CoV-2; COVID-19; Metabolomics; Potential biomarker; Metabolic pathway

## INTRODUCTION

COVID-19, a pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been proclaimed by the World Health Organization (WHO) (1). The SARS-CoV-2 infection can manifest itself in various ways, ranging from no symptoms to severe forms needing urgent care (2). Around 20% of patients, especially those over 65 and those with chronic illnesses such as hypertension, diabetes, renal disease, and heart disease, may develop interstitial pneumonia and breathing

problems, necessitating oxygen therapy or the use of ventilators (3). COVID-19 has been related to various life-threatening symptoms, including thrombosis, sepsis, organ failure, ARDS, and interstitial pneumonia (4). Patients with the highest risk of morbidity and mortality following SARS-CoV-2 infection have a hyper-inflammatory syndrome, according to the excess production of early response pro-inflammatory cytokines (including L-1, IL-1, IL-6, IL-10, IL-18, and TNF-), the so-called "cytokine storm" (5, 6).

The introduction of current OMICs-based techniques has offered essential tools for a comprehensive knowledge of molecular processes, identifying particular biomarkers, detecting metabolic pathway abnormalities throughout illnesses, and advancing cellular and molecular biology (7-9). In the case of COVID-19, several studies based on OMICS and MS have been recorded, which are very helpful in identifying molecular pathways in the development, progression, and treatment of the disease (10-13). Metabolomics, also known as the global quantitative evaluation of endogenous metabolites in a biological system, is an omics science in system biology. The human metabolome is made up of thousands of tiny molecules (less than 1500 Da) produced by the host organism's genome and the genomes of its microflora, and external effects such as medical treatments (14). As a result, metabolomic analyses of patient samples can assist in understanding biochemical changes in connection to yet-unknown processes (15). Several investigations have recently shown metabolic dysregulations in COVID-19, including assessment of glucose, amino acids, lipids, and nucleotides. COVID-19's metabolite networks have been evaluated using various biological materials, including serum, plasma, urine, and tissue (16). As a result of metabolomics methods, interesting new biomarkers and unique insights into COVID-19 molecular etiology can be identified, leading to innovative preventative and treatment. Using a uniform approach in omics-based research design would improve the data quality and lead to the discovery of more appealing biomarkers for disease monitoring. Figure 1 shows the most frequent metabolomics workflow research. In addition to the existing polymerase chain reaction (PCR) or antibody assessments, metabolomic findings can provide a set of markers that could be useful for rapid tests to determine the SARS-CoV-2 virus, symptom severity, and potential outcomes because they evaluate the effects on the host rather than the presence of the infecting agent (17).

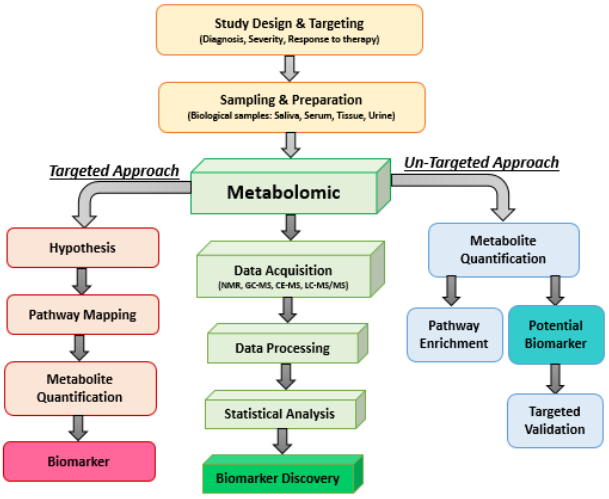


**Figure 1.** The use of metabolomics approach in COVID-19 research

To our knowledge, no review research on this topic has been published so far. To address this knowledge gap, we undertook a systematic review to summarize and evaluate the currently known metabolomic research on COVID-19. This will help us better understand chemical signatures and reduce infection and death rates in this epidemic.

## MATERIALS AND METHODS

### Literature search strategy

Up to September 2022, a systematic analysis is being conducted to discover metabolomics-based research on COVID-19. The literature search was performed using the MeSH keywords "Severe Acute Respiratory Syndrome Coronavirus 2" OR "SARS-CoV-2" OR "COVID-19" AND "Metabolome" OR "Metabolomics" OR "Metabonome" OR "Metabonomics" OR "Metabolite" in PubMed, Web of Sciences, EMBASE, and Scopus databases. In addition, the references of pertinent publications were combed through for any further research that could be relevant. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, http://www.prism a-statement.org/) were used to perform this systematic search.

### Inclusion and exclusion criteria

Duplicate articles across the search databases were eliminated once the papers were imported into EndNote. Two scientists independently examined full-length publications to reduce selection bias. This systematic review covered targeted and untargeted metabolomic investigations or studies with potential biomarker identification for individuals with COVID-19. The research was only allowed to be published in English, with no restrictions on the type of sample used for metabolomics analysis. Reviews, non-metabolomic, irrelevant, and bioinformatics-based papers were also removed. The design of this study, population, region, and publication years were all unrestricted.

### Data extraction

Researchers, publication year, area, sample type, analytical platform, sample size, male and female numbers, study aims, and differential distribution, including up-and down-regulated metabolites across comparison groups, were all collected for all included studies (Tables 1, 2). Two reviewers (N.AD and MK) retrieved pertinent data for each selected publication. To avoid unintended biases, the reviewers separately retrieved the data. Differences of opinion among the reviewers were resolved through conversation, and a final judgment was reached.

**Table 1.** Baseline characteristics of the included studies

| Study | Region | Analytical platform | Sample type | COVID-19 sample size (M/F) | Control Sample size (M/F) | Study Target |
|---|---|---|---|---|---|---|
| Su (Cell;2020) | USA | UHPLC-MS/MS | Plasma | 139 (60/79) | 133 | Identification of metabolites associated with all levels of COVID-19 severity |
| Zheng (ComputStructBiotechnol J;2021) | China | LC-MS, GC-MS | Plasma | 40 (20/20) | - | Identification of sex-specific metabolic changes in discharged survivors, and also analyze correlations between metabolites and clinical parameters |
| Bruzzone (iScience;2020) | Spain | NMR | Serum | 263 (117/146) | 280 (164/116) | Investigation of specific metabolic profiles associated with patients diagnosed with COVID-19 |
| Overmyer (Cell Syst;2021) | USA | AEX-LC-MS/MS, GC-MS | Plasma | 204(128/76) | 52(26/26) | Detection of molecular signatures of COVID-19, and correlate them with disease severity and clinical metadata. |
| Dierckx (medRxiv;2020) | Belgium | NMR | Serum/Plasma | 581 | - | Investigation of blood metabolites to elucidate how infection with SARS-COV-2 can lead to a variety of pathologies |
| Troisi (Preprint;2020) | Italy | GC-MS | Serum | 43(22/21) | 109(40/69) | Comparison of serum metabolomics profiles of asymptomatic SARS-CoV-2 carriers to patients affected by mild and severe symptoms |
| Fraser (Crit Care Explor;2020) | Canada | LC-MS/MS, NMR | Serum/Plasma | 10 | 20<br>Healthy controls:10<br>COVID-19-:10 | The deciphering of COVID-19 underlying pathologic processes and pathways, and identification of potential diagnostic or prognostic biomarkers |
| Shi (MetabClin Exp;2021) | China | LC-MS | Serum | 79(47/32) | 10(49/59)<br>Healthy controls:78(38/40)<br>COVID-19-like patients:30(11/19) | Examination of metabolite alterations in COVID-19 patients and the associations of them with disease development to identify potential biomarkers |
| Marín-Corral (Int J Mol Sci;2021) | Spain | LC-MS/MS | Plasma | Total:49 (24/25)<br>Moderate:13<br>Severe:10<br>Critical:26 | - | Assessing the critical metabolic pathways altered by COVID-19 severity |
| Shen (Cell;2020) | China | RP/ UPLC-MS/MS | Serum | Total:65(82/48)<br>Non-severe:37<br>Severe:28 | Total:53(38/15)<br>Healthy controls:28<br>Non-COVID-19:25 | Comparative metabolomics of sera from COVID-19 patients and control groups |
| Blasco (Sci Rep;2020) | France | LC-HRMS | Plasma | 55(27/28) | 45(23/21) | Exploration of plasma metabolome of patients infected with SARS-CoV-2 to search for diagnostic and prognostic biomarkers |
| Danlos (Cell Death Dis;2021) | France | GC-MS<br>UHPLC-MS | Serum/Plasma | Mild:23<br>Moderate:21<br>Critical:28 | 29 | The revelation of disease- and stage-associated shifts in the metabolome profile of COVID-19 patients |
| Grassin-Delyle | France | PTR-TOF-MS | Exhaled breath | COVID-19 | Non-COVID-19 | Determination of metabolomics breath signature in a |

| | | | | | | |
|---|---|---|---|---|---|---|
| (EBio Medicine;2021) | | | | ARDS:18(12/6) | ARDS:10(5/5) | group of ARDS patients with or without COVID-19 |
| Sindelar (medRxiv;2021) | USA | LC-Q-TOF-MS | Plasma | 274(158/116) | 67(28/39) | Prognostic classification of COVID-19 severity based on untargeted metabolomics profiling |
| Thomas (Clin Med;2020) | USA | UHPLC-MS | Serum | 33 (25/8) | 16 (6/10) | Investigation of metabolic effects of SARS-CoV-2 infection |
| Meoni (PLOS Pathog;2021) | Italy | NMR | Plasma | 30 | 30 | Identification of metabolomics signature of COVID-19 compared with controls. Moreover, evaluation of metabolic effects due to tocilizumab administration |
| Song (Cell Metab;2020) | China | UPLC-TOF-MS/MS | Plasma | 50(30/20) | Total:26 (15/11)<br>Mild:18<br>Moderate:19<br>Severe:13 | Utilization of a combination of targeted and untargeted tandem mass spectrometry to analyze the plasma metabolome in mild, moderate, and severe COVID-19 patients and healthy controls |
| Barberis (Int J Mol Aci;2020) | Italy | GCxGC/TOFMS | Plasma | Total:103<br>Critical:19<br>Non-critical:84 | Total:58<br>Healthy:26<br>Non-COVID critical pneumonia:12<br>Non-COVID non-critical pneumonia:20 | The metabolomic and lipidomic study to capture the host response to SARS-CoV-2 infection |
| Maras (medRxiv;2020) | India | UHPLC-MS/MS | Respiratory specimen | 20 | COVID-19 negative:20<br>H1N1:5 | Characterization of baseline molecular determinants associated with SARS-CoV-2 diagnosis and prognosis using proteomics and metabolomics approach |
| Delafiori (Anal Chem;2021) | Brazil | HESI-Q Exactive Orbitrap-MS | Plasma | 442 (256/186) | Controls: 350<br>COVID-19 suspicious:23 (17/6) | Identification of metabolic information related to the presence and severity of risk for the COVID-19 infection |
| Xu (Clin Infect Dis;2021) | China | LC-ESI-MS/MS | Plasma | Total:103<br>Mild/moderate:34<br>Severe/critical:69 | Healthy:27 | Determination of plasma metabolomics profile from COVID-19 survivors with pulmonary sequelae 3 months after discharge |
| Kimhofer (J Proteome Res;2020) | Australia | NMR, LC-MS | Plasma | 17 | Healthy:25 | Determination of metabolic effects of SARS-CoV-2 infection on human blood and plasma |
| Wu (Natl Sci Rev;2020) | China | LC-ESI-MS/MS | Plasma | Total:34<br>Fatal:9<br>Severe:11<br>Mild:14 | Healthy:10 | Targeted metabolomic and lipidomic analyses of plasma from a cohort of patients with COVID-19 who had experienced different symptoms |
| Xiao (Nat. Commun; 2021) | China | UHPLC-MS/MS & UHPLC-TOF-MS/MS | Serum | Total: 44<br>mild: 21<br>severe: 23 | Healthy controls: 17 | Metabolomics and cytokine/chemokine profiling on serum samples from healthy controls, mild and severe COVID-19 patients, and delineating their global metabolic and immune response landscape |
| Ansone (MedRxiv preprint;2021) | Latvia | LC-MS (targeted metabolomic) | Serum | 32 hospitalized COVID-19 patients at the acute 75 phase | recovery phase (40 ± 14.92 days) of the disease | Description of metabolites list describing the severe, acute phase of the infection and brings evidence of crucial metabolic pathways linked to aggressive immune responses |
| Páez-Franco (Sci Rep;2021) | Mexico | GC-MS | Serum | Total: 65<br>Severe: 46<br>Mild: 19 | Controls: 27<br>(subjects with a negative PCR test for SARS-CoV-2 infection) | Identification of the main changes in serum metabolites associated with severe and mild COVID-19 patients |
| Valdes (Sci Rep; 2022) | Spain | HPLC-QTOF-Ms | Plasma | Positive asymptomatic patients: 28<br>Mild: 27<br>Severe: 36 | Negative COVID-19: 25 | Provide new information about the changed metabolites and with that the altered biological pathways of patients in different stages of SARS-CoV-2 infection. |
| Roberts (Metabolomics; 2022) | UK | UHPLC-Ms/Ms | Serum | Fatal outcome: 29<br>COVID-19 Patients: 120<br>mild:71 severe:49 | COVID-19 patients validation cohort: 90 | Prediction of patient's infection severity and potential outcome. |
| Chen (EMBO J; 2020) | China | UHPLC-Ms/Ms | Serum | COVID-19 Patients: 20 | Healthy control: 20 | Identification of molecular markers in peripheral blood and plasma samples to understand host responses to COVID-19. |
| Lewis (Metabolites; 2022) | UK | LC-MS | Serum | Positive COVID-19: 123 | Negative COVID-19: 41 | Identification of metabolic disturbance changes to obtain a better understanding of its impact on host metabolism and enable better treatments. |

**Table 2.** Changes in metabolites during COVID-19 progression (non-severe to severe) and compared to healthy controls

| Study | Main Results (Metabolites/metabolic pathways) | Outcome |
|---|---|---|
| ***Plasma*** | | |
| Su Y *et al.,* 2020 (18) | ➢ ***Healthy to mild COVID-19***<br>***Amino acid metabolism:*****Up-regulated** (n=58), **Down-regulated** (n=8)<br>***Nucleotide metabolism:*****Up-regulated** (n=14), **Down-regulated**(n=2)<br>***Carbohydrate metabolism:*****Up-regulated** (n=11), **Down-regulated**(None)<br>***Lipid metabolism:*****Up-regulated** (n=61),**Down-regulated** (n=79) | A major immunological shift is seen between mild and moderate infection and represents that moderate disease may provide the most effective setting for therapeutic intervention. |
| Zheng H *et al.,* 2021, (19) | ➢ ***Mild to moderate & moderate to severe COVID-19;*** **Down-regulated:** Lipid and amino acid metabolites<br>➢ ***In male patients***<br>**Up-regulated:** 8-methoxy-13-hydroxy-9,11-octadecadienoic acid, 7,10-hexadecadiynoic acid, ceriporic acid B, 9-10-DHOME, decanoylcarnitine, O-octanoyl-R-carnitine, PGF1a alcohol, PGE1 alcohol, 21-methyl-8Z-pentatriacontene, tetrahydrodeoxycortisol, 4hydroxyproline, methyl beta-d-glucopyranoside, glycerol, kamahine C, 4-hydroxydebrisoquine, 3-7-dimethyl-2E,6E-decadien-1,10-dioic acid<br>**Down-regulated:**22-hydroxydocosanoic acid, 20-hydroxy-eicosanoic acid, (+)-14-methyl palmitic acid and 13,14-dihydroxy-docosanoic acid, 17-hydroxy stearic acid, phytophthora mating hormone alpha1, pristanic acid, 7-alpha-hydroxy-3-oxo-5beta-cholan-24-oic acid, MG(18:1(9Z)/0:0/0:0), indinavir, sphinganine | This study shed light on sex-specific metabolic shifts in non-severe COVID-19 patients during the recovery process, suggesting a sex bias in prognostic and therapeutic evaluations based on metabolic profiling. |
| Overmyer KA *et al.,* 2021 (20) | ➢ ***In female patients***<br>**Up-regulated:** PC, Sphingosine-1-phosphate, anandamide (20:l, n-9), 11-deoxy-PGF1b, tyramine, dehydroascorbic acid, methyl alpha-d-glucopyranoside-hexadecanoate, carbamic acid, coumarin-SAHA;**Down-regulated:**PC(18:3),LysoPC(18:3), 3-heptynoic acid, cortisol, poststerone, leucine and 6,7-dimethyl-4-hydroxy-2-pteridinamine<br>➢ ***dysregulated in COVID-19 patients:*** neutrophil degranulation, vessel damage, platelet activation and degranulation, blood coagulation, and acute phase response<br>➢ ***Top 5 most important predictive features:*** Quinolinic acid, L-Kynurenine, 2-methyl citric acid, Glucosamine 1-phosphate, 3-hydroxyisovaleric acid | Prediction of COVID-19 severity along with proteomic and transcriptomic data |
| Marín-Corral J *et al.,* 2021 (21) | **Up-regulated**: ceramides (C18:0, C16:0, C24:1), LDH, kynurenine, 3-hydroxykynurenine, kynurenine/tryptophan,3-hydroxykynurenine/kynurenine, 3-hydroxykynurenine/tryptophan<br>**Down-regulated**: HexCer C20:0, HexCer C22:0, HexCer C24:0, HexCer C24:1, tryptophan, cortisone/cortisol, lactate/pyruvate | Ceramide metabolism, tryptophan degradation, and reductions in NAD were significantly associated with respiratory severity and correlated with inflammation. |
| Blasco H *et al.,* 2020 (22) | ➢ ***Metabolome profile distinguishes C + and C – patients:*** cytosine, indole-3-acetic acid<br>➢ ***Metabolites associated with COVID-19 prediction:*** L-asparagine, L-leucine, L-isoleucine, 1-NH2-cyclopropane-1-carboxylate, cytosine, 2-aminophenol | Diagnosis from metabotype and COVID-19 disease evolution (Day 7 and Day 15). |
| Sindelar M *et al.,* 2021 (23) | ➢ ***54 statistically significant metabolites (p<0.05, FC>2):*** Striking changes in multiple representatives of lipid classes, including LPCs, PCs, and TGs. Further, several polar metabolites known to be related to COVID-19, including gluconate and dimethylguanosine were also significantly altered | The confirmation of metabolite prognostic markers are directly related to disease progression and that their levels are restored to baseline upon disease recovery |
| Meoni G *et al.,* 2021 (24) | ➢ ***COCID-19 compared to controls***<br>**Up-regulated:** phenylalanine, mannose, pyruvate**,** 3-hydroxybutyrate<br>**Down-regulated**: tyrosine, alanine, glycine, glutamine, histidine, HDL and LDL cholesterol-related parameters<br>➢ ***post-tocilizumab treatment***<br>**Up-regulated:** LDL-5, HDL-4, IDL, VLDL-1, VLDL-2<br>**Down-regulated:** HDL-1 subfractions of cholesterol, phospholipids | The general increment of lipoprotein after treatment by Tocilizumab confirms the metabolic reversion and supports the key role of lipids in the metabolism of COVID-19 patients. |
| Song JW *et al.,* 2020 (25) | ➢ ***Metabolites in COVID-19 patients compared to healthy controls (n=10)***<br>**Up-regulated:** S1P, LysoPC 18:1, LPA 18:1, GM3 d18:1/25:0, SM d18:1/18:1, 5-hydroxy-tryptophan, biliverdin<br>**Down-regulated:** medium-chain TAG 48:1(18:0), long-chain TAG 60:3(18:1), DAG 34:1(16:1/18:0) | This study suggests that GM3-enriched exosomes may partake in pathological processes related to COVID-19 pathogenesis. |
| Barberis E *et al.,* 2020 (26) | ➢ ***metabolic pathways affected by the SARS-CoV-2 infection***<br>Phenylalanine, tyrosine and tryptophan biosynthesis, phenylalanine metabolism, arachidonic acid metabolism, TCA cycle, aminoacyl-tRNA, | Amino acids, fatty acids, and the TCA Cycle are involved in the host response to SARS-CoV-2 infection. |
| Delafiori J *et al.,* 2021 (27) | ➢ **SARS-CoV-2 infected patients versus non-infected individuals**<br>**Up-regulated:** TG, DG, purine**, Down-regulated:** LysoPC, cholesterol species, and unsaturated fatty acids | Detection of infection through metabolites and contextualizing the findings with the disease's pathophysiology. |
| Xu J *et al.,* 2021 (28) | **Up-regulated**: triacylglycerol, phosphatidylcholines, prostaglandin E2, arginine<br>**Down-regulated**: betaine, purine, vitamin D3, guanosine, species of phosphatidylcholines (PCs), stearidonic acid | Distinctive metabolites of COVID-19 survivors compared to the healthy donor, which is associated with severity and involved amino acid and glycerophospholipid metabolic pathways. |
| Valdes A *et al.* 2022 (29) | **Up-regulated**: 3-Hydroxyphenylacetic acid, 3-hydroxybutyric acid, xanthine, alpha-linolenic acid, **Down-regulated:** hippuric acid, urea | Findings suggest metabolites such as 3-hydroxibutirate, linoleic acid, LPC, LPE, kynurenic acid and tryptophan as potential biomarkers of the clinical severity of COVID-19. |
| Kimhofer T *et al.,* 2020 (30) | **Up-regulated:** kynurenine/tryptophan ratio, LDL and VLDL triglycerides, glutamine/glutamate and Fischer's ratios, α-1-acid glycoprotein**; Down-regulated:** HDL Apolipoprotein A1, HDL triglycerides | Differentiate SARS-CoV-2 infected patients from controls. |
| Wu D *et al.,* 2020 (31) | **Up-regulated:** Diglycerides, free fatty acids, triglycerides**; down-regulated:** L-aspartic acid, malic acid, carbamoyl phosphate, GMP | Show many of the metabolite and lipid alterations, particularly those associated with hepatic functions. |
| *Serum* | | |
| Bruzzone C *et al.,* 2020 (32) | **Up-regulated:** TG, TG-VLDL, TG-IDL, TG-LDL, TG-HDL, acetoacetic acid, 3-hydroxybutyric acid**,** acetone, glucose, succinic acid, citric acid, glutamic acid, pyruvic acid, phenylalanine, 2 hydroxybutiryc acid**, Down-regulated:** Apo-A1, Apo-A2, methionine, isoleucine, histidine, lysine | The impact that the infection has on overall metabolism and SARS-CoV-2 infection induces liver damage associated with dyslipidemia and oxidative stress |
| Troisi J *et al.,* 2020 (33) | ➢ ***MI compared to both CTRL and AS subjects;*** **Up-regulated:** mandelic acid, methionine, oxoleucine, **Down-regulated:** Tyrosine, phenylalanine, acetoacetate, fumarate<br>➢ ***MI & SE subjects;*** **Up-regulated**: lauric acid, myristic acid, phosphatidylmyo-inositol, lyso-phosphatidyl inositol, histamine<br>➢ ***MI subjects;*** **Down-regulated:** Aspartic acid, alanine, isoleucine, valine, proline | Identify mechanisms underlying the predisposition towards the different disease forms and increased production of L-DOPA possibly led to imbalance levels of metabolites |
| Shi D *et al.,* 2021 (34) | ➢ ***COVID-19 and COVID-19-like patients versus HCs;*** **Up-regulated:** butyric acid, 2-hydroxybutyric acid, L-glutamic acid, L-phenylalanine, L-serine, L-lactic acid, Cholesterol<br>➢ ***COVID-19 patients compared to COVID-19-like patients and HCs;*** **Up-regulated:** D-fructose and succinic acid, **Down-regulated**: Citric acid, 2-palmitoyl-glycerol<br>➢ ***COVID-19 patients compared to HCs;*** **Up-regulated:** 4-deoxythreonic acid, **Down-regulated:** 1,5 anhydroglucitol | Prediction of patients who progressed from mild to severe COVID-19 using the combination of 2-hydroxy-3-methylbutyric acid, 3-hydroxybutyric acid, cholesterol, succinic acid, L-ornithine, oleic acid and palmitelaidic acid. |

| | | |
|---|---|---|
| | ➢ ***COVID-19 patients compared to COVID-19* like; Up-regulated:** oxalic acid, **Down-regulated:** phosphoric acid | |
| Shen B *et al.*, 2020 (35) | **Up-regulated:** 21-hydroxypregnenolone, kynurenate, kynurenine, 8 methoxykynurenate, phosphocholine**; Down-regulated**: Sphingolipids, glycerophospholipids, choline, glutamate, arginine, citrulline, ornithine, glutamine, 2-oxoglutarate, N-acetyl-L-glutamate, urea, fumarate, argininate, asymmetric dimethylarginine, symmetric dimethylarginine, homoarginine, N-acetyl-arginine | Differences in proteomic and metabolomics profiles of COVID-19 vs healthy controls. |
| Thomas T *et al.*, 2020 (36) | **Up-regulated:** Kynurenine, kynurenic acid, picolinic and nicotinic acid, arginine, methionine sulfoxide, cystine, creatine, creatinine, spermidine, acetyl-spermidine, glycolysis and pentose phosphate intermediates**,Down-regulated**: Tryptophan, serotonin, indole pyruvate, alanine, glycine, serine, glutamine, histidine, cysteine, taurine, ornithine, citrulline | This study identified amino acid and fatty acid metabolism as correlates of COVID-19, providing mechanistic insights, potential markers of clinical severity, and potential therapeutic targets. |
| Ansone L *et al.*, 2021 (37) | **Up-regulated:**3-Hydroxy-DL-Kynurenine, L-Phenylalanine, L-Methionine, Isovalerylcarnitine, Kynurenine, L-Asparagine, L-Glutamic acid, L-Valine, Carnitine, L-Tyrosine, L-Threonine, Taurine, Ornithine, L-Lysine, L-Isoleucine, L-Acetylcarnitine**; Down-regulated:** L-Glutamine, citrulline, 4-Hydroxyproline, L-Tryptophan, L-Proline, L-Octanoylcarnitine | Results suggested that the tryptophan and arginine metabolism as contributing pathways in the immune response to SARS-CoV-2 with a potential link to the clinical severity of the disease. |
| Páez-Franco JC *et al.*, 2021 (38) | **Up-regulated:** α-Ketoglutarate, phenylalanine, glutamic acid, 3-Hydroxyisovaleric, 3-Hydroxybutyric acid, α-Hydroxybutyricnacid, α-Hydroxyisovaleric, 2,3-Dihydroxybutanoic acid, malic acid, glutamic acid, phenylalanine**; Down-regulated:** Threonine, citrate, cysteine, isoleucine, glutamine, glyceric acid, citric acid | The modified metabolic were associated with an altered amino acid catabolism. |
| Xiao N *et al.*, 2021 (39) | ➢ **healthy controls vs. mild patients:** 89 (50 up and 39 down) & healthy controls vs. severe patients: 88 (37 up and 51 down)<br>**Up-regulated: In COVID-19 patients:** LPCs**; During disease severity:** glutamate, aspartic acid, succinate, kynurenine**; Down-regulated: During disease severity:** glutamine, citrulline, tryptophan, serotonin, nicotinamide mononucleotide (NMN) | Correlation analyses show associations between metabolites and cytokines such as IL-6, M-CSF, IL-1α, IL-1β, and imply a potential regulatory crosstalk between arginine, tryptophan, purine metabolism and hyperinflammation. |
| Roberts I *et al.*, 2022 (17) | **Up-regulated:** ureidopropionate, cytosine, N1-acetylspermidine<br>**Down-regulated:** uracil, arginine, tryptophan | Prognostic markers identified in this study could allow improvement in the planning of COVID-19 patient treatment. |
| Chen Y *et al.*, 2020 (40) | **Up-regulated:** linolenate, choline, glycerol-3-phosphate, glycerophosphocholine, di-homolinoleate | Identification of potential biomarkers that might assist in predicting the prognosis of SARS-CoV-2 infection |
| Lewis HM *et al.*, 2022 (41) | **Up-regulated:** TG (22:1_32:5), TG (18:0_36:3), glutamic acid<br>**Down-regulated:** glycolithocholic acid, aspartic acid | This study demonstrated that metabolic dysregulation has partially changed over the course of the pandemic, reflecting changes in variants, clinical presentation and treatment regimes. |
| ***Serum/plasma*** | | |
| Dierckx T *et al.*, 2020 (42) | **Up-regulated:** inflammatory markers, leucine, phenylalanine, lipoprotein particle (except VLDL), triglyceride, mono-unsaturated fatty acid**; Down-regulated:** cholesterol levels (except in large HDL and VLDL), poly-unsaturated fatty acid, Choline | The results of this study point to systemic metabolic biomarkers for COVID-19 severity. |
| Fraser D *et al.*, 2020 (43) | **Up-regulated:** Kynurenine**; Down-regulated:** sarcosine, lysophosphatidylcholines | COVID-19 diagnosis by arginine/kynurenine, and COVID-19-related death by creatinine/arginine ratio. |
| Danlos FX *et al.*, 2021 (16) | **Up-regulated**: arabinose, ribose and its reduction product ribitol, arabitol, erythritol, xylitol, disaccharide maltose, trisaccharide raffinose, arginine, aspartic acid, glutamic acid, phenylalanine, tyrosine, trimethyl-lysine, the methionine derivative (S-adenosylmethionine), dipeptide leucylproline, ornithine, spermine, spermidine, and their mono- or diacetylated derivatives, kynurenine, anthranilic acid ,3-hydroxy-DL-kynurenine, 5-hydroxy-DL-tryptophan, 3-methylhistidine, creatine, urea, O-phosphoethanolamine; **Down-regulated:** desaminotyrosine, arginine, tryptophan, indole-acetamide, indole-3-acrylic acid, methyl-3-indole-acetate, valine, hypotaurine, Dimethylglycine**,** carnitine esters, phospholipids, immunomodulator sphingosine-1-phosphate, deoxycholic acid, niacin metabolite trigonelline**,**ß-hydroxypyruvate, N1-acetylspermidine | The high levels of anthranilic acid predict the maintenance of high levels of IL10 and IL18, suggesting that the kynurenine pathway has an immunomodulatory impact on COVID-19 pathogenesis. |
| ***Breath*** | | |
| Grassin-Delyle S *et al.*, 2021 (44) | **Up-regulated:** methylpent-2-enal, 2,4-octadiene 1-chloroheptane, nonanal | detection of methylpent-2-enal, 2, 4-octadiene 1-chloroheptane, and nonanal in exhaled breath. |
| Maras JS *et al.*, 2020 (45) | **Total:** 106; **Up-regulated:** 53metabolites enriched in **the** biosynthesis of unsaturated fatty acids, glycerophospholipid metabolism, phenylalanine, tyrosine and tryptophan biosynthesis<br>**Down-regulated:** 53 metabolites enriched in thiamine metabolism, vitamin B6 and riboflavin metabolism, steroid biosynthesis | Rapidly diagnosis of SARS-CoV-2 infection and identification of asymptomatic and mild disease using MX1 and WARS proteins. |

### Quality assessment

The quality of the papers included in this systematic review was assessed using QUADOMICS. QUADOMICS is a set of 16 criteria for assessing the methodological quality of studies involving "-omic" technology. Two researchers evaluated each publication independently using the QUADOMICS approach, and disagreements were addressed by consensus.

### Pathway enrichment analysis

We collected differentially expressed metabolites as possible biomarkers from the publications listed. The metabolites obtained in greater than or equivalent to three experiments were then selected for pathway enrichment analyses. Before the pathway analysis, the chemical standard name was obtained from the Human Metabolome Database version. The pathway enrichment analysis was performed using the MetaboAnalyst online platform version 5.0 (http://www.metaboanalyst.ca). An over-representation test was run for this analysis, and the pathways with P-value< 0.05 were considered significantly enriched pathways.

## RESULTS

Figure 2 shows a flowchart depicting the study selection process. We initially did a comprehensive literature search to detect changed metabolites associated with COVID-19 pathogenic processes and address possible biomarkers. After deleting duplicates, 69 studies were

selected for abstract and full-text reading from 211 entries (including 55, 73, 35, and 48 from PubMed, Web of Science, EMBASE, and Scopus, respectively). The analysis was then excluded 38 papers; they were reviews unrelated to the study issue, were done on animals, were non-metabolomic, irrelevant publications, or were based on bioinformatics. Finally, the current systematic review was applied to the final list of selected research, which included 31 papers based on the stated criteria.

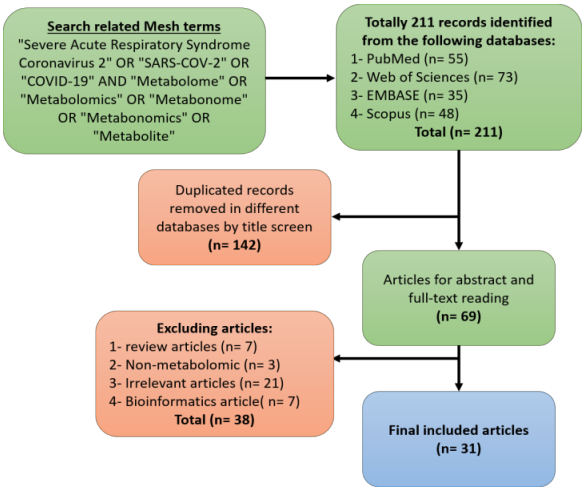


**Figure 2**. Flow chart of literature identification and the selection process

## Characteristics of included studies

Table 1 lists the essential features of the studies that were considered. The publications were divided into two groups according to their study objectives: studies that compared the metabolic profiles of COVID-19 patients to healthy controls and studies that identified important metabolites in various clinical presentations of the disease (including mild, moderate, and severe outcomes). Some investigations have identified possible biomarkers as well as severity-related metabolites. During the years 2020 and 2022, all of the selected research was published. The included research used serum/plasma (29 studies) and breath samples (two studies) for metabolomics analysis. Healthy people were used as control groups in the majority of investigations. Furthermore, several experiments used COVID-19-negative and COVID-19-like illnesses as controls. NMR (n = 5), LC-MS/MS (n = 23), GC-MS (n = 5), PTR-MS (n = 1), and HESI-Q Orbitrap-MS (n = 1) were among the analytical platforms used to identify metabolites. In addition, five research used several analytical platforms to undertake metabolomics analysis. Table 2 shows the differentially expressed metabolites retrieved from the included studies.

## Methodological quality assessment

Figure 3 and the Supplementary File provide the QUADOMICS quality evaluation findings and items. According to the QUADOMICS tool, 28 out of 31 studies (90.32%) reported at least 10 out of 16 items accurately (Figure 3). Furthermore, Items 2 and 14, covering the application of metabolomics testing in practice, do not apply to all investigations and, as a result, are not included in quality reporting.

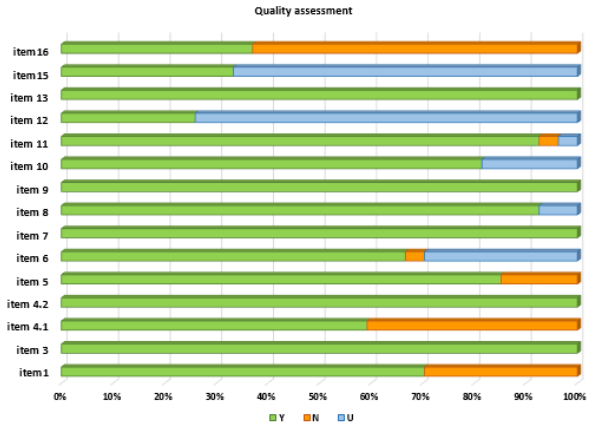


**Figure 3.** The quality assessment results of the included studies by the QUADOMICS tool. Items 2 and 14 regarding the use of metabolomics testing in practice are not applicable to all of the studies and are not presented in the figure

## Carbohydrate metabolism and derivatives

Carbohydrates are the primary energy source in the biological system, and disruptions or dysregulation of carbohydrate metabolic pathways result in disease. Table 2 shows changes in metabolite levels associated with carbohydrate metabolism and tricarboxylic acid (TCA) cycle disturbances discovered in metabolomics-based investigations of COVID-19. Several carbohydrate-related metabolites, such as glucose, pyruvate, fumarate, and succinic acid, have been described in the majority of the studies reviewed in this study. Two investigations found that people with COVID-19 had considerably lower glucose levels; however, the results were inconsistent. In two investigations, succinic acid was found to be up-regulated, and in one research, it was shown to be downregulated. Citric acid, another major TCA cycle

metabolite, was both up-and down-regulated in two investigations. Previously, several studies have linked carbohydrate metabolism metabolites to various disorders.

### Lipid metabolism and derivatives

As seen in Table 2, phosphatidylcholines, triglycerides, fatty acids, and lipoproteins were the most often identified dysregulated metabolites in lipid metabolism. Unfortunately, not all investigations revealed consistent outcomes for these lipid metabolites. In addition, several lipid metabolites have been observed in many investigations and are removed and presented separately as repeated metabolites. Some of these metabolites were found to be consistent across multiple studies (3 studies), such as up-regulated butyric acid ad derivatives (4 studies), down-regulated LysoPCs (3 studies), up-regulated TGs (5 studies), down- (2 studies), up-regulated unsaturated fatty acids, and down-regulated cholesterol Ceramides, LDL, and HDL metabolites have previously been linked to respiratory severity, dyslipidemia, and liver damage.

COVID-19 changes from mild to moderate and moderate to severe are linked to lipid metabolism. Su et al. discovered that COVID-19 patients had a marked preference for lipid downregulation (18). In summary, there is a significant variability of metabolites in lipid metabolism in COVID-19 patients, and disruption of fatty acid and lipid metabolism across COVID-19 progression supports lipids' key involvement in COVID-19 patients' metabolism.

### Amino acid metabolism and derivatives

Most of the research considered conflicting results observed for amino acids. The reduced arginine level was seen in most COVID-19 metabolomics experiments (six out of eight). Furthermore, most research indicated a rise in phenylalanine levels, whereas just one study on serum samples reported a drop in this amino acid's level. In COVID-19 individuals, levels of primary amino acid derivatives were dysregulated in several investigations. Based on plasma and serum samples from COVID-19 patients, increased kynurenine was consistently documented in 10 trials. According to Thomas et al., COVID-19 causes tryptophan metabolism to shift towards the kynurenine pathway, which controls inflammation and immunity. In addition, two investigations found that nicotinic acid was altered (36). Roberts et al. used metabolomics profiling to predict the severity of a patient's infection and likely prognosis, and nicotinic acid (energy metabolism) was identified as a predictor of COVID-19 severity (46).

Even though a few pieces of research briefly mentioned possible amino acid-related biological processes, none of them used statistical approaches to assess the pathways or profiles of amino acids linked to SARS-CoV-2 infection.

### Pathway enrichment analysis of frequent metabolites

We did a pathway enrichment analysis of the most common metabolites (Table 3), significantly changed in at least three independent trials, to obtain insight into the molecular processes of metabolites implicated in COVID-19 pathogenesis. The functional KEGG pathways of the relevant metabolites were elicited using MetabAnalyst v5. 0 (P=0.05). Pathway analysis showed several significantly changed pathways, as shown in Figure 4. The substantially changed pathways in COVID-19 were phenylalanine, tyrosine, tryptophan biosynthesis, Alanine, aspartate, glutamate metabolism, D-glutamine, D-glutamate Arginine biosynthesis, and Arginine and proline metabolism.

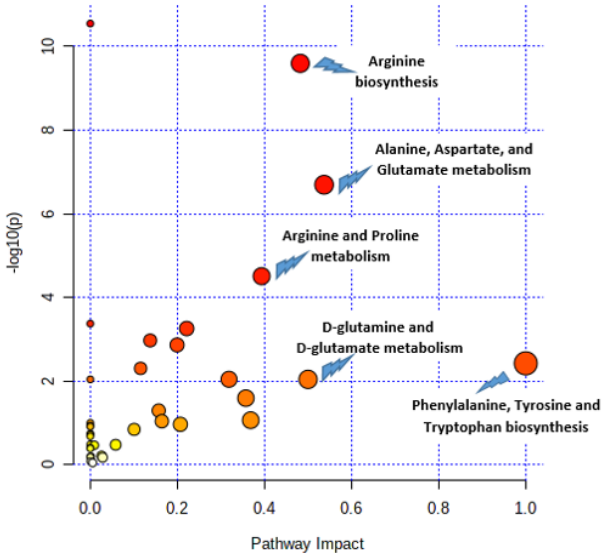


**Figure 4.** Pathway analysis results for repeated metabolites. The pathway impact versus –log(p-value) is plotted. The most important involved pathways (with p-val<0.05 and higher impacts) include phenylalanine, tyrosine and tryptophan biosynthesis, alanine, aspartate and glutamate metabolism, D-glutamine and D-glutamate metabolism, arginine biosynthesis, and Arginine and proline metabolism

### Other studies

Several studies reported metabolites of nucleotides associated with COVID-19. When compared with healthy individuals, purine and guanosine levels in COVID-19 patients' serum were shown to be lower. Blasco et al. identified cytosine as a metabolite that may be used to identify COVID-19-positive patients from COVID-19-negative patients, as well as a metabolite linked to COVID-19 prediction (22). In addition, Roberts et al. identified pyrimidine metabolism as a metabolic route connected to COVID-19 severity and prognosis. Although COVID-19 has been shown to alter nucleotide metabolism-related pathways, still insufficient data (46).

Other types of molecules that studies detected include vitamins. Patients with COVID-19 have lower vitamin D3 levels than healthy controls. Furthermore, when COVID-19-positive patients were compared to COVID-19-negative patients, vitamin B6 and thiamine metabolism were shown to be enriched pathways of downregulated metabolites (28).

**Table 3.** List of metabolites that were repeated in at least three independent studies

| ***A)*** ***List of amino acid metabolites that were repeated in at least three independent studies*** | | | |
|---|---|---|---|
| **Metabolite and its derivatives** | **Compound name (regulation)** | **Regulation** | **Source** |
| • **Proline (Pro)** | Oxoproline | Down | Zheng et al. |
| | 4-hydroxyproline | Up | Zheng et al. |
| | Pro | Down | Troisi et al. |
| | Leucylproline | Up | Danlos et al. |
| • **Aspartic acid (Asp)** | Asp | Down | Troisi et al. |
| | Asp | Up | Danlos et al. |
| | L-aspartic acid | Down | Wu et al. |
| • **Arginine (Arg)** | Arginine, Arginate, Dimethylarginine, Homoarginine, N-acetyl arginine | Down | Shen et al. |
| | Arg | Up | Danlos et al.&Thomas et al. |
| | Arg | Down | Xu et al. |
| • **Citrulline** | Citrulline | Down | Shen et al.&Thomas et al.&Ansone et al.&Xiao et al. |
| • **Ornithine** | Ornithine, Ornithine | Down | Shen et al.&Thomas et al. |
| | Ornithine | Up | Ansone et al.&Danlos et al. |
| • **Tryptophan (Trp)** | Trp | Down | Marín-Corral et al. &Danlos et al.&Thomas et al. |
| | 5-hydroxy-DL-tryptophan | Up | Danlos et al. |
| | 5-hydroxy-tryptophan | Up | Song et al. |
| • **Glycine (Gly)** | Gly, Gly | Down | Thomas et al.&Meoni et al. |
| | Dimethylglycine | Down | Danlos et al. |
| • **Tyrosine (Tyr)** | Desaminotyrosine | Down | Danlos et al. |
| | Tyr | Up | Danlos et al. |
| | Tyr | Down | Troisi et al.&Meoni et al. |
| • **Glutamine (Gln)** | Gln | Down | Shen et al. &Thomas et al.&Meoni et al. |
| • **Histidine (His)** | His | Down | Meoni et al.&Bruzzone et al.&Thomas et al. |
| | 3-methylhistidine | Up | Danlos et al. |
| • **Methionine (Met)** | Met | Up | Troisi et al. |
| | S-adenosylmethionine | Up | Danlos et al. |
| | methionine sulfoxide | Up | Thomas et al. |
| | Met | Down | Bruzzone et al. |
| • **Leucine (Leu)** | Oxoleucine | Up | Troisi et al. |
| | Leu | Down | Zheng et al. |
| | Leu | Up | Dierckx et al. |
| • **Phenylalanine (Phe)** | Phe | Down | Troisi et al. |
| | phe | Up | Shi et al.&Danlos et al.&Meoni et al.&Dierckx et al. &Bruzzone et al. |
| • **Alanine (Ala)** | Ala | Down | Meoni et al.&Troisi et al.&Thomas et al. |
| • **Glutamic acid** | Glu | Up | Bruzzone et al. |

| | | | |
|---|---|---|---|
| | L-glu | Up | Shi et al.&Danlos et al. |
| | Glu, N-acetyl-L-glutamate | Down | Shen et al |
| • **Kynurenine** | Kynurenine, Kynurenate | Up | Shen et al. |
| | Kynurenine, 3-hydroxykynurenine | Up | Marín-Corral et al. |
| | Kynurenine, 3-hydroxy-DL-kynurenine | Up | Danlos et al. |
| | Kynurenine, Kynurenic acid | Up | Thomas et al. |
| | Kynurenine/Trp | Up | Kimhofer et al. |
| | Kynurenine | Up | Fraser et al. |

***B) List of carbohydrate metabolism and TCA cycle metabolites that were repeated in at least three independent studies***

| Metabolite and its derivatives | Compound name | Regulation | Source |
|---|---|---|---|
| • **Glycolysis** | ß-hydroxypyruvate | Down | Danlos et al. |
| | Indole pyruvate | Down | Thomas et al. |
| | Pyruvate | Up | Meoni et al. |
| | Pyruvate, LDH | UP | Marín-Corral et al. |
| | Glucose | Down | Zheng et al. |
| | Glucose, Succinic acid, Citric acid | Up | Bruzzone et al. |
| • **TCA cycle** | Fumarate, Succinate | Down | Shen et al. |
| | Fumarate | Down | Troisi et al. |
| | Succinic acid | Up | Shi et al. |
| | Citric acid | Down | Shi et al. |

***C) List of fatty acid/lipid metabolites that were repeated in at least three independent studies***

| | | | |
|---|---|---|---|
| • **Butyric acid** | 3-hydroxybutyric acid, 2-hydroxybutyric acid | Up | Bruzzone et al. |
| | 2-hydroxybutyric acid, Butyric acid | Up | Shi et al. |
| • **Phosphatidylcholine** | PC (O-8:0/O-8:0), PC (O-16:1(9E)/0:0), PC (O-18:1(9Z)/0:0), PC (O-16:0/3:0), PC (P-15:0/0:0), PC (O-16:0/4:0) | Up | Zheng et al. |
| | PC (18:3(9Z,12Z,15Z)/0:0), PC (18:3(6Z,9Z,12Z)/0:0), LysoPC (18:3(9Z,12Z,15Z)), LysoPC | Down | Zheng et al. |
| | PCs | Down | Delafiori et al. |
| | LysoPCs | Up | Xu et al.&Shen et al. |
| | LysoPC 18:1 | Down | Fraser et al. |
| | Choline | Up | Song et al. |
| | | Down | Dierckx et al. |
| • **Fatty acids** | Unsaturated fatty acids | Up | Maras et al. |
| | Free fatty acids | Up | Wu et al. |
| | Mono-unsaturated fatty acid | Up | Dierckx et al. |
| | poly-unsaturated fatty acid, Unsaturated fatty acids | Down | Dierckx et al. |
| • **Phospholipid** | PLs | Down | Danlos et al.&Meoni et al. |
| | Glycerol-PLs | Down | Shen et al. |
| • **Lipoproteins** | TG-VLDL, TG-IDL, TG-LDL, TG-HDL | Up | Bruzzone et al. |
| | HDL, LDL | Down | Meoni et al. |
| | HDL-TG | Down | Kimhofer et al. |
| | LDL-TG, VLDL-TG | Up | Kimhofer et al. |
| | LPs (except VLDLD) | Up | Dierckx et al. |
| • **Lipids** | Triglycerides (TG), Diglycerides (DG) | Up | Wu et al. |
| | TG, DG | Up | Delafiori et al. |
| | TG | Down | Xu et al.&Dierckx et al.&Bruzzone et al. |
| | TAG 48:1(18:0), TAG 60:3(18:1), DAG 34:1(16:1/18:0) | | Song et al. |
| • **Cholesterol** | cholesterol (except in HDL and VLDL) | Down | Dierckx et al. |
| | Cholesterol | Up | Shi et al. |
| | Cholesterol | Down | Meoni et al. |

## DISCUSSION

Due to the urgent need to provide efficient diagnostic and therapeutic methods against COVID-19, investigations based on omics technologies, such as metabolomics, offer much promise in this area (47). In COVID-19, metabolomic profiling is utilized to characterize metabolic dysregulation in depth. In this context, metabolomic profiles of serum/plasma, saliva, and tissue samples from COVID-19 patients offer novel potential biomarkers for predicting disease severity and patient outcomes and enabling the creation of customized therapy to target the altered pathways (16, 18, 39, 46).

Viruses snatch the metabolism framework of their hosts to redirect the host resources for their proliferation and survival. How SARS-CoV-2 affects the host metabolism is still unclear (48). The entire dependence of viruses on the host cells for their replication and survival may have involved a variety of ways to modify the host metabolism to achieve their objectives (49). It is known that the metabolic pathways in the host, including carbohydrate, fatty acid, and nucleotide metabolism, dysregulate during different viral infections. Very viral species may trigger specific metabolic reprogramming of the host cell (50). Therefore, the host metabolomics profile data in response to SARS-CoV-2 is helping to discover metabolite expression changes.

We comprehensively reviewed 31 published papers on metabolomic profiling in COVID-19 patients and summarized the fundamental results on metabolic pathway dysregulation in COVID-19 patients, including carbohydrates, amino acids, and lipids. However, we discovered some discrepancies in the levels of several of the provided metabolites among the various study groups. In a study by Bruzzone et al., the serum level of phenylalanine increased as illness severity increased (32). On the other hand, it was reported that patients had lower phenylalanine levels than asymptomatic patients and control groups (33). The inconsistency of research results can be explained by the heterogeneity of study design, which includes varied sample kinds, small sample sizes, different types of individuals, and a variety of analytical platforms. Despite differences in COVID-19 metabolomics analysis, virtually all studies found substantial differences between patient and control groups. COVID-19 seems to influence the body's metabolic pathways. Metabolites that are described here were discovered by more than one group.

### Carbohydrate metabolism pathways and COVID-19

In several of the trials examined, there was a change in carbohydrate metabolism. Several investigations on COVID-19 have found dysregulated glycolysis intermediates such as glucose and pyruvate (24). Two studies detected dysregulated glucose levels in COVID-19 patients (19, 32). During COVID-19, highly concentrated immune cells in the lungs, such as monocytes and macrophages, boost glycolysis to aid viral multiplication. These cells also respond to infection by releasing more pro-inflammatory cytokines, which worsens COVID-19 severity (51). According to Codo et al., the elevated glucose levels and high glycolytic pathways raise SARS-CoV-2 replication and cytokine production in monocytes through a mitochondrial ROS/hypoxia-inducible factor-1a dependent pathway, resulting in T cell dysfunction and epithelial cell death (52). Similarly, in Caco-2 cells infected with SARS-CoV-2, the enhanced glycolytic process as a beneficial carbon source was seen (52, 53). Furthermore, transcriptome evidence suggests that glycolysis increased during COVID-19. Delays in the production of type 1 interferon (IFNI) have been observed in recent years, resulting in an insufficient inflammatory response to the virus and the formation of a favorable breeding environment for its replication. COVID-19 has recently revealed a reduction in antiviral response as well as a significant inflammatory response by interleukin-6. As a result, it appears that modulating glycolysis in the early phases of the IFN I response might be an effective method for increasing host defense in the early stages of infection (54, 55).

SARS-CoV-2 does not rely on mitochondrial metabolism for replication or survival. According to

Moolamalla et al., the mitochondria have been proven to function in the host's innate immunity and be a potential target for invading pathogens (48). Furthermore, Meoni et al. and Marín-Corral et al. study groups observed elevation of the pyruvate end product of glycolysis in COVID-19 patients compared to controls and throughout disease severity (21, 24). According to studies, patients with high glucose levels were also shown to be 58 percent more likely to advance and 3.22 times more likely to die from COVID-19 (56). As a result, those with obesity and diabetes who have uncontrolled blood glucose levels are more likely to acquire COVID-19's severe variant (57). Elevated glucose levels have been linked to not just COVID-19 severity but also death in individuals with the severe form of the disease (58). Surprisingly, these findings align with research on Influenza, SARS-COV, and MERS. Hyperglycemia and COVID-19 have been linked through many molecular processes, including controlling receptor expression for viral entrance into host cells, a dysregulated immunological response, and hyperinflammation.

Furthermore, high glucose levels have been demonstrated to affect the ACE2 receptor, facilitating and increasing viral entry and reproduction in vivo. Indeed, elevated glucose levels may exacerbate viral infection severity by suppressing the antiviral immune response. Increased glucose levels have several effects on the innate and adaptive immune systems, including decreased neutrophil degranulation, chemotaxis, phagocytic activity, complement activation impairment, and lymphocyte proliferative response suppression (59). A study reported that hyperglycemia in diabetes causes dysfunction of the immune response that leads to pathogens spreading in diabetic patients (60).

Govender et al. demonstrated that diabetic subjects are significantly susceptible to advanced COVID-19 and worse outcomes (61). Furthermore, during SARS-CoV-2 infection, ACE2 is overexpressed, resulting in increased angiotensin II (AngII) activity, which leads to the development of insulin resistance (IR), oxidative stress, inflammation, hypertension, and cardiac dysfunction (62). Also, the elevated IR leads to increased pancreatic expression of ACE2 receptors, causing more affinity for the spike protein of the virus to bind, thereby predisposing those with IR to increased vulnerability to COVID-19 infections (63). On the other hand, IR is a crucial player in activating the inflammatory response, which helps prevent hyperinflammation (cytokine storm), hyperinsulinemia, and lung injury (64, 65). In addition, individuals with preexisting IR have various comorbidities such as hypertension, hyperglycemia, and diabetes, resulting in severe pathophysiological symptoms during COVID-19 and, as a result, death (66). To summarize, glycemic management is critical for improving illness prognosis during SARS-CoV-2 infection.

Furthermore, it has been established that COVID-19 affects and damages many organs in the body, including acute kidney injury (AKI). The kidney is one of the essential organs in humans for controlling glucose metabolism throughout the body. Because the ACE2 receptor is also present in the kidney, it is one of the SARS targets; SARS-CoV-2 and any changes in renal metabolism might activate pathways that lead to AKI and aggravate patients' conditions. Along with alterations in lipid metabolism, problems in glucose metabolism develop during AKI, which might have negative consequences (67). In contrast to a reduction in gluconeogenesis, an increase in glycolysis was detected during renal failure, and the same thing occurred in ischemia-reperfusion damage (68). Hypoglycemia under stress and a crisis of systemic metabolism might occur from a reduction in gluconeogenesis, resulting in a deterioration of the patient's state. Following this, Legouis et al. found that glucose metabolism reprogramming during AKI was linked to mortality (68). Patients with metabolic problems in COVID-19 show a deterioration of the clinical condition associated with acute kidney injury, suggesting that dysregulation of systemic metabolism may play a role in COVID-19 renal injury (50).

The metabolic intermediates of the TCA cycle, such as citric acid, fumarate, citrate, malate, aconitate, and

succinate, have also been discovered in COVID-19 concerning carbohydrate metabolism (34, 35). Wu et al. also introduced the malic acid of the TCA cycle as a significantly reduced energy metabolism-related metabolite between healthy individuals and dead cases of COVID-19 (31). Malic acid joins the TCA cycle and participates directly in human energy metabolism, performing critical physiological activities in the body. It also protects the liver from harm by speeding up the ammonia transformation process and lowering the ammonia levels. As a result, the researchers conclude that the considerable downregulation of malic acid is consistent with the liver damage associated with COVID-19. According to a recent study, the virus directly influences the expression of genes that regulate oxidative phosphorylation and the electron transport chain. Another study found that lower citrate levels in the peripheral blood of people with COVID-19 are linked to poorer outcomes (20). As a result, considerably lower TCA metabolite levels in COVID-19 patients might be used as indicators for dysregulated cellular metabolism following SARS-CoV-2 infection.

Increased levels of metabolites linked with dysregulated glucose metabolism in COVID-19 individuals can contribute to a shift in the intensity of immunologic responses to the virus. As a result, targeting glucose metabolism intermediates in the glycolysis and TCA pathways might lead to new antiviral and organ-supportive techniques for COVID-19 therapy, particularly in those with metabolic illnesses.

### Lipid metabolism and COVID-19

Although lipid metabolism is thought to have a role in the development and course of acute disease, there is little information on the lipid metabolism of SARS-CoV-2 patients. Recent research has shown the involvement of lipids in viral infection, including manipulating host cell metabolism to weaken the protective immune response (69). Several investigations on COVID-19 patients found that their levels of diglycerides, free fatty acids, and triglycerides had altered, with exceptionally high levels in the fatal group(31). Lipids are known to have a role in the innate and adaptive immune responses to various respiratory disorders, including influenza, pneumonia, asthma, and acute lung injury (ALI)(70). Previous research has shown that cells with excessive lipid buildup have increased viral multiplication (71). Furthermore, during lung infection and hyperinflammation, high-density lipoprotein cholesterol (HDL-C) and apolipoprotein AI (Apo-AI), low-density lipoprotein cholesterol (LDL-C), and other lipid parameters exhibited substantial changes.

The cytokine storm and hyperinflammation that occur during COVID-19 are severe and crucial, and this inflammatory state has been linked to disease severity and prognosis (72). As a result, elevated pro-inflammatory cytokines may change COVID-19 patients' lipid profiles. The effects of COVID-19 on lipid profiles and their correlation with acute phase reactants were investigated in a recent study, which found that LDL-C, HDL, TG, and TC levels were significantly lower in COVID-19 patients when compared to the control group and that all parameters decreased gradually with the severity of COVID-19 disease (73). The metabolic implications of SARS-CoV-2 infection were investigated in another study by Thomas et al., who compared blood metabolites from patients with COVID-19 to COVID-19-negative controls. The findings revealed an increase in free fatty acids in circulation, particularly in individuals with high levels of inflammatory cytokines (36). Low HDL and high triglycerides also predicted COVID-19 severity (74). As a result, measuring low HDL cholesterol and high triglyceride levels in patients during their hospitalization is a potent and sensitive biomarker for predicting inflammation and a severe form of COVID-19. Patients with a history of dyslipidemia are more likely to develop severe COVID-19 infections, while cholesterol levels upon hospitalization showed the opposite. According to the findings, dyslipidemia may have a role in the severity of COVID-19 (75). In this context, Atmosudigdo et al. suggested a link between dyslipidemia and higher mortality and COVID-19 severity in a systematic study. The link was more significant in older,

male individuals who had hypertension (76). However, the paucity of information on comorbidities and medication use among the patients limits this association. Drugs like statins have been found to minimize the risk of death or severe illness in COVID-19 individuals (77). A dysregulated lipid profile raises the likelihood of severe COVID-19, as well as the risk of acute cardiovascular events following the pandemic (78).

Wu et al. discovered a significant decrease in malic acid and glycerol 3-phosphate in COVID-19 patients in the moderate, severe, and fatal groups (31). These two metabolites are aided by energy metabolism (malic acid and glycerol 3-phosphate). Glycerol 3-phosphate is an intermediary metabolite in the glycolysis route, and malic acid enters the TCA cycle in mitochondria, demonstrating the dysregulations in metabolites involved in human energy metabolism (31). A recent study has also found that lipids, particularly cholesterol, may play an essential role in viral replication, internalization, and immunity activation in COVID-19 patients (79). Furthermore, lipid abnormalities seen during and after the infection might be utilized to assess the response to treatment measures indirectly. These data suggest that abnormalities in host systemic and cell lipid metabolism may be essential events in the course and severity of COVID-19 from SARS-CoV-2 infection.

### Amino acid metabolism and COVID-19

Several metabolomics studies have also reported dysregulations in amino acid metabolism, such as tryptophan and kynurenine in COVID-19 (37), indicating that metabolic alterations of the tryptophan/kynurenine catabolism pathway are associated with the development of SARS-CoV-2 infection. The kynurenine (Kyn) system is the primary mechanism for tryptophan (Trp) metabolism, and it is involved in a variety of critical biological processes, such as neurodegenerative disorders (80), infection (81), and cardiovascular diseases (82). The Kyn pathway has recently received much attention as a key dysregulated route in COVID-19 development. Previous research has also shown that the serum kynurenine-to-tryptophan ratio increases with progressive viral infections such as HIV-1 (83) and hepatitis C virus (HCV) (84). Because hyperinflammation, oxidative stress, and innate immune activation have been implicated in the pathogenesis of several respiratory viral infections, including COVID-19, it is crucial to investigate the Kyn pathway's potential role in COVID-19 pathogenesis(85).

In hepatocytes, the tryptophan 2, 3-dioxygenase enzyme oxidizes Trp. It is mediated by indoleamine-pyrrole 2, 3-dioxygenase (IDO) in other cell types, increasing Kyn metabolite synthesis (86). In addition, IDO is up-regulated by several viral, microbial, and parasitic pathogens. Besides, IDO and the IDO-related pathway are the main mediators of the inflammatory responses in diseases such as atherosclerosis (87). In addition, Kyn, 3-hydroxykynurenine is associated with inflammation, oxidative stress, endothelial dysfunction, and carotid artery intima-media thickness values in patients with renal disease (82). Moreover, IDO is a potential novel contributor to metabolize in systemic infections. Therefore, the Kyn pathway can play an important role in the increased prevalence of COVID-19 by regulating inflammation, oxidative stress, and immune activation.

According to a recent metabolomics study, L-tryptophan, kynurenine, and 3-hydroxy-DL-kynurenine, which are involved in the Trp-Kyn pathway, have also been reported as significantly changed metabolites between acute function and recovery phase of COVID-19 (37). It can be concluded that the reduced level of Trp and increased level of Kyn and 3-hydroxy-DL- Kyn in the acute stage indicate that the Trp-Kyn pathway plays an important role in COVID-19 progression. It is also demonstrated that deprivation of tryptophan leads to T cell apoptosis, no proliferation of T cells, and suppression of CD8 T-cells in cancer (88). According to Thomas et al., COVID-19 severity in aged individuals can be explained by the deregulation of Trp metabolism, which is a crucial regulator of inflammation and immunity (36).

On the other hand, some persistent viral infections have been linked to neurological and cognitive

impairment, which has been linked to the activation of the Kyn pathway and the creation of neuroactive metabolites in some circumstances (89). Surprisingly, Torii et al. found that individuals with influenza-associated encephalopathy had higher blood L-Kyn levels than those without encephalopathy (90). Patients with COVID-19 also have brain abnormalities, suggesting that activation of the Kyn pathway may play a role in COVID-19-related cognitive problems (91). These findings suggest that activation of the Kyn pathway in the peripheral response to immune system stimulation by viral infections may play a role in cognitive impairment.

This study found glutamine to be the most frequently altered amino acid, with consistently downregulated (24, 35). It has been discovered that glutamine deprivation inhibits M2 macrophage polarization and reduces glutaminolysis, which may help to explain the hyperinflammation seen in people with severe COVID-19 (92). Furthermore, it is believed that glutamine has a favorable influence on improving hospitalized patients' circumstances (93). In COVID-19, two more amino acids, phenylalanine, and tyrosine, were observed to be altered. Phenylalanine and tyrosine were identified as metabolic hot spots in COVID-19 based on a recent meta-analysis of COVID-19 global metabolomics datasets (94). Increased phenylalanine levels in the blood have been related to immunological activation and an increased risk of cardiovascular disease in other conditions, including sepsis and HIV-1 (95). In severe COVID-19, this occurrence is consistent with microvascular endothelial damage and increased coagulation (96). Epinephrine, created by the catabolism of phenylalanine and tyrosine, had a role in cardiac arrest caused by hyperinflammation, which is typical of COVID-19's severe form (97).

COVID-19 showed changes in citrulline and ornithine, which are implicated in the urea cycle and arginine catabolism. Citrulline levels are lower in COVID-19 patients (36), but low citrulline levels have been linked to ARDS in severe sepsis patients (98). One of the treatment strategies utilized in cancer therapy is amino acid restriction, which disrupts the host-virus connection (99). Among different amino acids, arginine is presented as an essential nutrient factor in the life cycle of several families of viruses (including Herpesviridae and Adenoviridae) that also established in vitro studies (100). Therefore, therapeutic depletion of arginine may stop SARS-CoV-2 replication.

Arginine is a substrate of NO signaling molecules. NO is a critical mediator of hyperinflammatory responses in viral infectious diseases (101). A limitation on arginine to make NO is advised to minimize the hyperinflammatory response (cytokine storm) in COVID-19. These investigations showed that SARS-CoV-2 causes host cell metabolic reprogramming in immune cells, including amino acid changes dependent on the host (102). In addition, NO is a signaling molecule that plays an important role in the pathogenesis of inflammation. It plays an anti-inflammatory role under normal physiological conditions. Furthermore, NO is a pro-inflammatory mediator that induces inflammation due to overproduction in abnormal conditions. NO is synthesized and released into the endothelial cells with the help of NOSs that convert arginine into citrulline, producing NO. It is involved in the pathogenesis of joint, gut, and lung inflammatory disorders. Therefore, NO inhibitors represent an important therapeutic advance in managing inflammatory diseases (103). Arginine-citrulline-NO metabolism during inflammatory conditions is as follows: Essential in developing multiple organ failure is the competition for arginine between the microcirculation and the inflammatory response. NOS3 is downregulated, while NOS2 is upregulated in response to pro-inflammatory cytokines. This will lead to more NOS2-induced NO production, which is essential in the immune responses. Similarly, arginase, mainly arginase I, is up-regulated by anti-inflammatory cytokines but is expressed in a later phase of infection and will therefore prevent NO overproduction by NOS2 (104).

Notably, most metabolic disorders are associated with amino acids and their metabolites. Hartnup disease is a

rare inherited disorder along with mutations in the SLC6A19 gene, resulting in defective neutral amino acid (tryptophan, alanine, asparagine, glutamine, histidine, isoleucine, leucine, phenylalanine, serine, threonine, tyrosine, and valine) transport in the kidney and small intestine. In addition to the characteristic neutral aminoaciduria, patients may develop pellagra-like skin rash, neurologic manifestations (e.g., cerebellar ataxia, dysarthria, seizures, headache, dizziness), or psychiatric symptoms (e.g., anxiety, rapid mood changes, delirium). The mental and neurological symptoms of Hartnup patients elicit the most prevalent neuropsychiatric symptoms of COVID-19. As a result, amino acid-related metabolites may be critical in determining the degree of problems in COVID-19 individuals.

Finally, pathway analysis of frequently repeated metabolites revealed phenylalanine, tyrosine, tryptophan biosynthesis, alanine, aspartate, glutamate metabolism, D-glutamine and D-glutamate metabolism, arginine biosynthesis, arginine, and proline metabolism were the most critical pathways involved in the pathogenesis of COVID-19. Overall, our data imply that SARS–CoV–2–induced metabolic reprogramming in several organs may play a role in COVID-19's widespread toxicity and fatality. Furthermore, metabolomics is valuable for identifying altered metabolic pathways linked to COVID-19-related organ damage.

The present study has several limitations. The sample size of several of the included studies is small, which may substantially impact the current study's conclusions. Hence, the findings should be considered with caution. The included populations were diverse regarding ethnic, geographic, and socioeconomic status. Furthermore, the date of sample collection differed among the included studies. However, the research did not record the precise moment of sample collection. Another limitation of the research included in this systematic review is that we cannot distinguish between metabolite changes and COVID-19 severity. However, in the current analysis, we looked at the differences in metabolites between COVID-19 patients and healthy controls, as there were no asymptomatic COVID-19 patients in the included trials. Finally, a more extensive patient group with mild to severe COVID-19 should be studied further.

## CONCLUSION

SARS-CoV-2, a new coronavirus, has raised health concerns throughout the world. Despite extensive efforts to identify the various components of SARS-CoV-2 and COVID-19, many concerns remain unexplained, including metabolic pathway reprogramming during COVID-19. MS-based metabolomics can provide new insights into prognostic biomarkers and aid in identifying potential treatment targets by providing vital information about disease progression. Several metabolites and metabolic pathways linked with COVID-19 were discovered in this research. The high frequency of changed metabolites suggests that they might be used as COVID-19 biomarkers for early detection. The significant metabolic route could reveal new information about pathogenesis and lead to new treatment targets. More research with more significant sample numbers is needed to confirm the findings and interpret the potential overlap between various biofluids. Our research reveals that metabolomic profiling might give new insights into molecular pathogenesis mechanisms and can help identify possible diagnostic biomarkers and therapeutic targets in COVID-19. These findings might help develop new treatment techniques and speed up the healing process following infection.

### Availability of data and materials

Data from this study are included in the article, and the corresponding author can provide the primary data.

### Conflict of interest

The authors declare that they have no conflict of interest.

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