

REVIEW ARTICLE

Hyperhomocysteinemia and MTHFR C677T polymorphism in SARS-CoV-2 infection severity

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Abstract

COVID-19 virus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) has imposed a huge burden of mortality, morbidity, and socio-economic issues worldwide. Dominating transmission efficacy and the surge in instant genetic mutations pose challenges to the overwhelmed healthcare system. In this study, we aim to explore the role of homocysteine (Hcy) as a biomarker in COVID-19 and to develop strategies to mitigate the severity of SARS-CoV-2 infection. We reviewed the biochemical, physiological, and genetic implications of COVID-19. Upon SARS-CoV-2 exposure, Hcy metabolism is disrupted, leading to hyperhomocysteinemia (HHcy) and inducing inflammatory markers, e.g., interleukins (IL-6 and IL-7), tumor necrosis factor, interferon- γ , and C-reactive protein, which are characterized as a cytokine storm. HHcy develops numerous complications, including cardiovascular disorders, neural problems, and musculoskeletal disorders. However, nutritional deficiencies, e.g., folic acid, vitamin B6, and vitamin B12, and elevated serum creatinine are the important determinants of Hcy concentrations in the body. Additionally, the MTHFR C677T polymorphism is also a key factor that modulates Hcy levels and increases the risk of viral incidence. Overall, the identification of biochemical, metabolic, and genetic biomarkers may improve risk stratification, inform COVID-19 management, and help identify potential therapeutic targets.

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1. Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a highly infectious, single-stranded, positive-sense RNA-enveloped virus. It shares 79% genomic similarity with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and 50% genomic similarity with the Middle East Respiratory Syndrome Coronavirus (MERS-CoV).¹ Both groups (SARS-CoV and MERS-CoV) were observed in 2002 and 2012, respectively. SARS-CoV-2 genomic organization also shared similarity with the family of β coronaviruses. Moreover, glycosylated spike proteins cover the surface of SARS-CoV-2, facilitating binding to host cell angiotensin-converting enzyme-2 (ACE2) receptors and mediating viral entry into host cells. Glycosylated spike proteins utilize ACE2 as the receptor and human serine proteases as entry factors at the target site, inducing fusion between the virus and the host cell membrane and playing a vital role in viral invasion. Once SARS-CoV-2 invades the cells (host), the viral genome (RNA) is discharged, and polyproteins are synthesized.^{2,3}

The COVID-19 pandemic was caused by the transmission and multiplication of a

virus that originated in Wuhan, China, and quickly spread worldwide. Several countries were severely affected by the virus's transmission from 2020 to 2022. SARS-CoV-2 efficiently generates multiple genetic variants that exhibit high infectivity, rapid spread, immune evasion, severe respiratory consequences, and resistance to targeted drugs, vaccines, or other therapeutic measures. This virus is transmitted in the community through direct and indirect pathways, including close contact with infected individuals and through contaminated secretions.^{4,5}

SARS-CoV-2 enters host cells by binding to ACE2 receptors, which are predominantly expressed in tissues such as the liver, lungs, kidneys, and heart.⁶ It induces endothelial dysfunction and systemic thrombosis.⁷ Importantly, India is concerned about its pediatric transmission, as few child fatalities have been reported. Children usually respond significantly to respiratory viruses; however, the COVID-19 response is the opposite. The possibility of getting infections is minimal for the newborn, and no relevant data are available regarding the transmission of SARS-CoV-2 from an infected mother to the newborn or fetus. For more profound insight, an immediate, high-quality, well-controlled study is necessary to elucidate potential routes of transmission in the community.^{8,9}

Homocysteine (Hcy) has been identified as a potential marker of COVID-19 severity for stratification, preventive measures, and supplementation. A significant association was observed between Hcy levels and COVID-19 cases and mortality.¹⁰ In humans, Hcy is an intermediary substrate formed through the methionine (Met) cycle and metabolized through trans-sulfuration and/or remethylation.¹¹

As shown in Table 1, Hcy concentrations of 5–15 μ M are considered normal, whereas concentrations >15 μ M are elevated and may increase the risk of vascular coagulopathy, cognitive decline, and neural defects, e.g., Alzheimer's disease and dementia. Lowering Hcy levels through adequate supplementation of vitamin (vit) B and folic acids significantly reduces cognitive decline and brain atrophy. Evidence suggests that increased Hcy levels are associated with "brain fog" observed in COVID-19 cases and cognitive deficits.¹⁶ In clinical practice, preventive measures focus on the daily intake of Met, vit B6, vit B12, and folic acid, along with other effective dietary plans. This dietary strategy empowers the population to fight COVID-19.^{17,18} Vit C and vit D deficiencies in COVID-19 cases induce coagulopathy, suppress the immune system, cause lymphocytopenia, and are associated with higher mortality.¹⁹ Similarly, vit B deficiency also impairs cellular defense mechanisms and promotes inflammation

due to the accumulation of Hcy and other intermediate metabolites.²⁰ In a study, 17 hospitalized COVID-19 patients receiving daily supplementations of vit D (1,000 IU), magnesium (150 mg), and vit B12 (500 μ g) reported significant improvement compared with 26 non-supplemented patients.²¹

2. SARS-CoV-2: Genomic lineages

SARS-CoV-2 can generate multiple genetic variants with specific mutations. While some viral mutations weaken the virus, others make it more efficient, enabling it to proliferate rapidly and cause more severe infections. The World Health Organization (WHO) has designated certain genetically mutated forms of SARS-CoV-2 as variants of concern (VOCs). These variants possess characteristics that increase transmissibility, COVID-19 severity, immune escape, diagnostic failure, community transmission, and mortality. Numerous VOCs have been identified in different countries, including B.1.1.7 (United Kingdom), B.1.351 and B.1.1.529 (South Africa), B.1.1.28.1/P.1 (Brazil), and B.1.617 mutants E484Q and L452R (India). Besides VOCs, the WHO has also identified variants of interest (VOIs). Examples include B.1.525 (December 2020), B.1.427/B.1.429 (March 2020), B.1.1.28.2/P.2 (April 2020), B.1.1.28.3/P.3 (January 2021), B.1.526 (November 2020), B.1.616 (February 2021), C.37 (December 2020), and B.1.621 (January 2021).^{22,23}

2.1. Physiological and biochemical complications of SARS-CoV-2 exposure

Based on disease severity, the clinical course of COVID-19 can be divided into three phases: early infection, pulmonary phase, and hyperinflammation phase, each characterized by distinct biochemical alterations. In the early infection phase, patients exhibit nonspecific symptoms such as dry cough, body aches, and fever. These manifestations are associated with the primary inflammatory response, which involves the innate immune system and often results in lymphocytopenia. The pulmonary phase is characterized by respiratory involvement, most commonly pneumonia, which disrupts normal lung function. In the hyperinflammation phase, the disease becomes severe and may trigger a cytokine storm. During this stage, numerous inflammatory biomarkers are elevated, and patients can experience multi-organ injury, affecting the lungs, heart, and kidneys, and alterations in the central nervous system (Figure 1).^{24–26}

2.2. Hyperhomocysteinemia and SARS-CoV-2 transmission

Hyperhomocysteinemia (HHcy) is a metabolic abnormality characterized by elevated Hcy concentrations

Table 1. Homocysteine risk categories and primary determinants

Homocysteine risk categories	Homocysteine concentrations (μM)	Homocysteine modulators	Reference
Normal	≤ 15	Lifestyle, age, and gender	12
Moderate	15–30	Disruption to the methylation pathway, deficiencies of folate and vitamin (vit) B12, medication, pregnancy, and alcoholism	13
Intermediate	31–100	Genetic polymorphism of <i>MTHFR</i> (C677T and A1298C), nutritional deficiencies (e.g., folate, vit B6, and vit B12), and chronic diseases	14
Severe	>100	Mutations in <i>CBS</i> and <i>MTHFR</i>	15

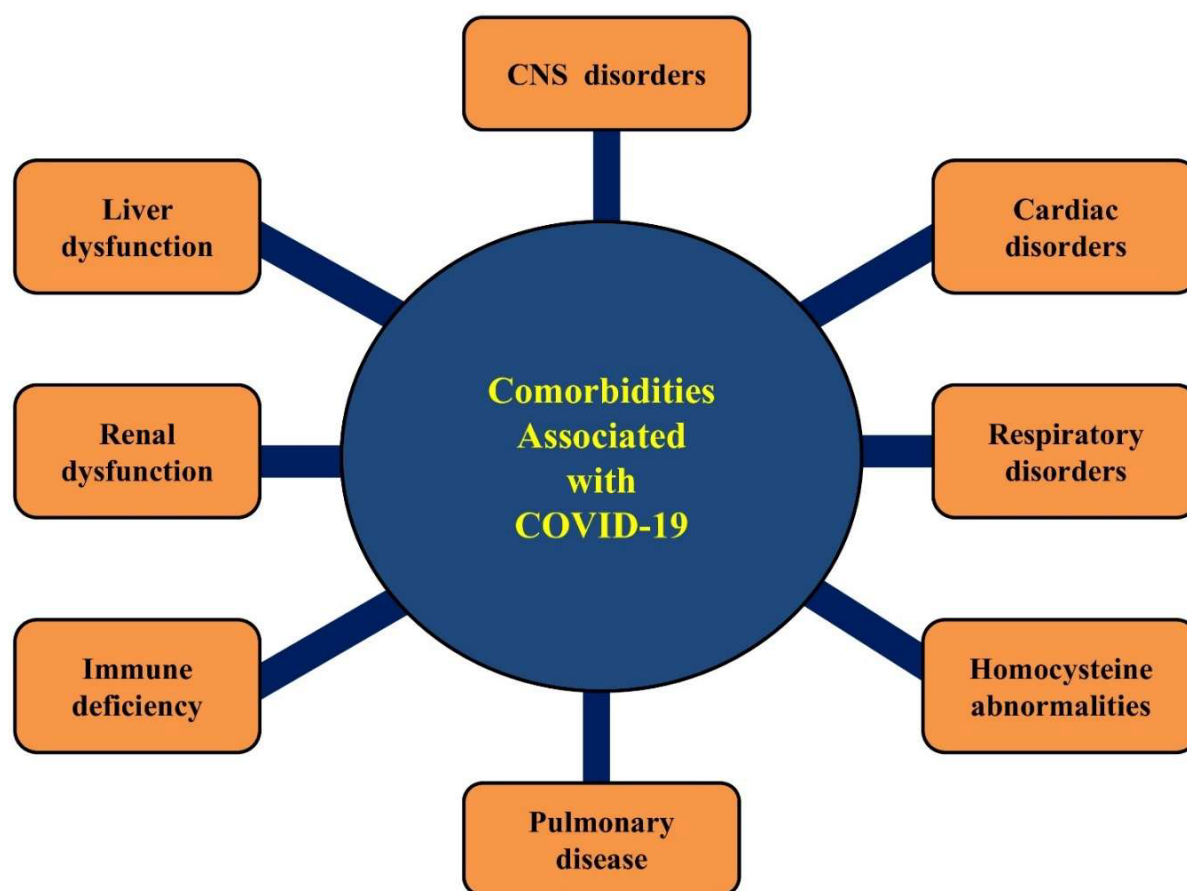


Figure 1. Physiological and biochemical alterations in COVID-19 patients. Image created by the author using Microsoft Office 2019.

in body fluids, such as blood and urine, increasing the risk of cellular and tissue damage. Multiple factors are associated with elevated Hcy levels, including impaired Met metabolism, genetic mutations in *MTHFR*, *MTR*, and *CBS*, nutritional deficiencies in folate, vit B6, and vit B12, viral infections, and chronic disorders.²⁷ In healthy individuals, the optimal Hcy levels are $<15 \mu\text{M}$, whereas

in mild to severe disease conditions, levels may range from $50 \mu\text{M}$ to $500 \mu\text{M}$.²⁸ Elevated Hcy levels can contribute to immunodeficiency and promote susceptibility to viral infections, including papillomavirus, adenovirus, and hepatitis viruses, as well as increased COVID-19 severity.²⁹ In a recent study, Hcy was identified as a key marker in hospitalized COVID-19 patients, with plasma Hcy

concentrations correlating with an optimal value of 16 μM .³⁰ HHcy has also been reported as a prognostic marker of lung disease progression and shows a pathogenic association with SARS-CoV-2.³¹ Furthermore, *MTHFR* polymorphisms in individuals have been correlated with COVID-19 incidence.¹⁰ Supplementation with vit B can reduce Hcy levels and mitigate the effects of the *MTHFR* C677T allelic mutation in the population.³² Specifically, vit B complex is associated with enhanced immunity.³³ Hence, routine assessment of Hcy levels and *MTHFR* polymorphism is crucial for implementing effective management strategies against SARS-CoV-2.³⁴

2.3. Hyperhomocysteinemia and COVID-19 severity

Hyperhomocysteinemia exerts detrimental effects on the neural system, causing prothrombotic, proatherogenic, cardiovascular, cerebrovascular, pro-oxidative, and osteoporotic complications.³⁵ Genetic mutations in *MTHFR* (C677T and A1298C), *MTR*, and *CBS* are major contributors to HHcy.¹⁴ Comorbidities, including thrombosis and coagulopathy, are frequently observed in viral infections, as evidenced by elevated D-dimer and Hcy levels. Both D-dimer and plasma Hcy are independent risk factors for the progression of atherosclerotic vascular disease and thrombosis.^{36,37} Measurement of plasma Hcy levels is therefore useful for assessing COVID-19 severity and cardiovascular risk.³⁸ In a study of 313 hospitalized COVID-19 patients admitted between April and September 2020, plasma Hcy levels were higher in non-survivors than in survivors. Mild cases had Hcy levels of $9.3 \pm 0.2 \mu\text{M}$, whereas severe cases had $10.7 \pm 0.5 \mu\text{M}$.³⁹ Another study reported Hcy values of $8.17 \pm 0.30 \mu\text{M}$ in controls, $12.73 \pm 0.54 \mu\text{M}$ in mild cases, and $15.62 \pm 1.37 \mu\text{M}$ in severely infected patients.³⁸ Increased Hcy levels are associated with increased disease severity and correlate with monocyte-to-lymphocyte ratios, which are significantly higher during COVID-19 progression.⁴⁰ However, a study has reported inconsistent associations between viral infection and Hcy levels.⁴¹ While many studies reported higher Hcy levels in COVID-19 patients compared to healthy individuals,^{39,40,42} several studies reported no significant relationship between Hcy levels and infection status.^{43–45}

MTHFR C677T allelic polymorphism efficiently modulates Hcy levels and influences the severity of viral infections.⁴⁶ The C677T variant has been significantly associated with COVID-19 incidence, mortality, and morbidity. This nucleotide polymorphism is considered a significant marker for stratifying SARS-CoV-2 severity and guiding the development of targeted therapeutic strategies. Several studies have clarified the close association between Hcy metabolism and pathogenic mechanisms in infected patients.^{39,41,47}

2.4. COVID-19 and susceptibility to co-infections

Mucormycosis symptoms have been reported in hospitalized COVID-19 patients.⁴⁸ SARS-CoV-2 infection has been shown to suppress cell-mediated immune responses, as evidenced by reduced CD4+ and CD8+ lymphocyte counts.⁴⁹ This immunosuppression increases susceptibility to bacterial, fungal, and viral co-infections. Mucormycosis is a fungal infection caused by the invasion of tissues and blood vessels by Mucorales (mucor mold), causing ischemic infarction, mycotic thrombosis, and ultimately cell necrosis.⁵⁰ Factors predisposing COVID-19 patients to fungal co-infections include acute respiratory distress syndrome, trauma, diabetes mellitus, corticosteroid use, prolonged neutropenia, and the use of broad-spectrum antibiotics. *Black fungi* (*Mucor*, *Rhizopus*, and *Absidia*), *white fungi* (*Candida*), and others (*Aspergillus* and *Cryptococcus*) may exacerbate disease severity and cause life-threatening complications in severely infected cases.⁵¹ More importantly, severe COVID-19 cases complicated by bacterial and/or fungal co-infections often experience longer hospital stays and higher mortality risk compared with general cases. Furthermore, co-infections increase the burden of disease in patients with underlying comorbidities.⁵² Thus, early detection of bacterial and fungal co-infections is critical for risk stratification and the initiation of appropriate interventions to reduce mortality.⁵⁰

2.5. Hyperhomocysteinemia and associated comorbidities

Increased Hcy levels have been linked to the development of numerous comorbidities in COVID-19 cases.⁵³ In one study, ACE2 receptors were found to be highly expressed in the lungs of COVID-19 patients with comorbidities.⁵⁴ Common comorbidities in COVID-19 include autoimmune diseases, hypertension, cardiovascular disorders, and renal disease. A study has reported mortality among COVID-19 patients with one or more comorbidities: hypertension (55.4%), diabetes (37.3%), high lipid profile (18.5%), cardiovascular disorders (12.4%), renal disease (11%), chronic obstructive pulmonary disease/bronchial asthma (8.3%), and heart failure (7.1%).⁵⁵ Patients with comorbidities were more likely to develop severe symptoms compared with those without comorbidities, and they exhibited longer disease recovery times and higher mortality rates.⁵⁶

2.6. Homocysteine metabolism

Homocysteine is a non-proteinogenic, toxic amino acid synthesized during Met and cysteine metabolism. Hcy levels fluctuate with age, sex (higher in males than in females), and disease conditions.⁵⁷ As shown in Figure 2, Hcy metabolism occurs via two primary pathways: remethylation and

trans-sulfuration. When cellular Met levels are elevated, trans-sulfuration is crucial to maintain metabolic balance. In this pathway, Hcy is converted to cystathionine by cystathionine- β -synthase and subsequently to cysteine via cystathionine- γ -lyase. Conversely, when cellular Met levels are low, Hcy undergoes remethylation to regenerate Met. Hcy remethylation occurs via two mechanisms: the folate-dependent pathway and the betaine-dependent pathway.⁵⁸

In the folate-dependent pathway, Hcy is converted to Met with the addition of a methyl group from N-5-methylenetetrahydrofolate, catalyzed by 5-methyltetrahydrofolate-Hcy methyltransferase. This reaction requires vit B12 as a cofactor. Dietary folic acid

is first converted to 5,10-methylenetetrahydrofolate, which is then reduced by methyltetrahydrofolate reductase to 5-methyltetrahydrofolate, serving as the methyl donor. Tetrahydrofolate generated in this process is recycled and is essential for nucleotide biosynthesis. In the betaine-dependent pathway, Hcy is methylated to form Met by accepting a methyl group from betaine, catalyzed by betaine-Hcy S-methyltransferase.^{59,60}

2.7. Implications of serine and glutathione in COVID-19

Biochemical implications, such as elevated Hcy and depletion of serine and glutathione (GSH), have a distinct

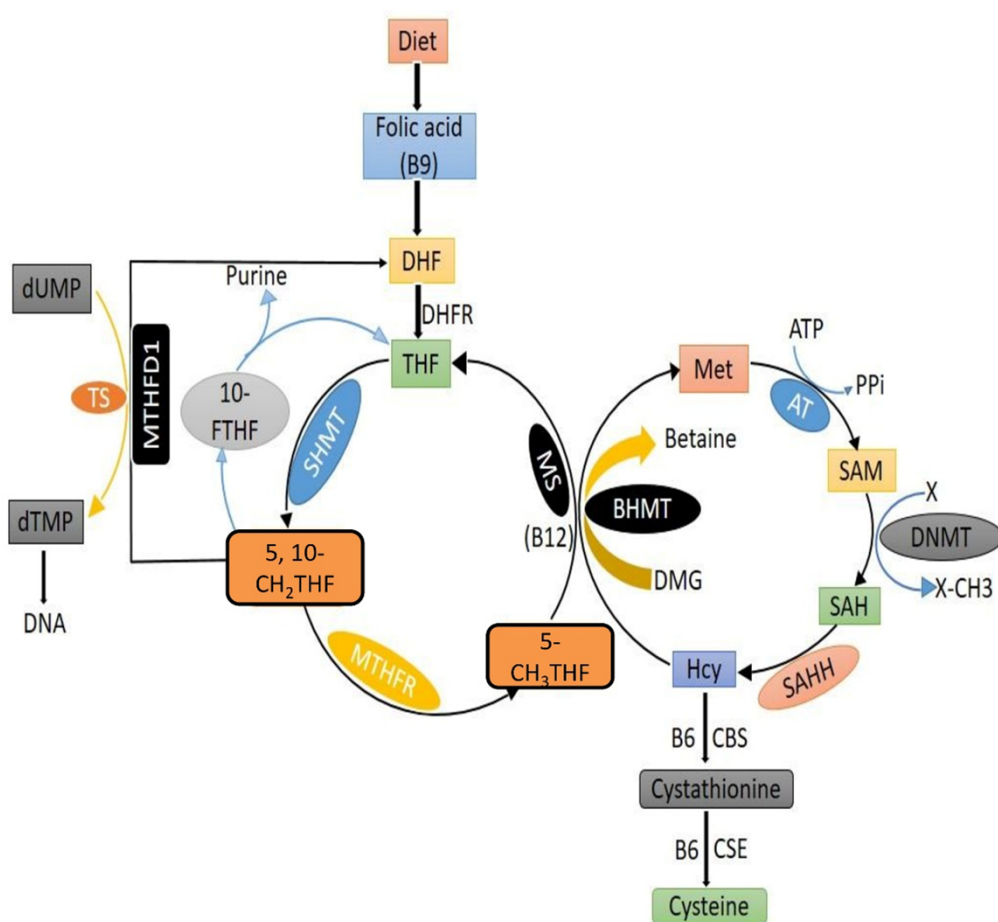


Figure 2. Methionine (Met) synthase (MS) is a vitamin B12-dependent enzyme that synthesizes Met from homocysteine (Hcy) and is linked with the folate cycle. Image created by the author using Microsoft Office 2019.

Abbreviations: AT: Adenosyl transferase; BHMT: Betaine-homocysteine S-methyltransferase; CBS: Cystathionine- β -synthase; CH₂THF: Methylene tetrahydrofolate; CH₃THF: Methyl tetrahydrofolate; CSE: Cystathionine- γ -lyase; DHF: Dihydrofolate; DHFR: Dihydrofolate reductase; DMG: Dimethyl glycine; DNMT: DNA methyltransferase; dTMP: Deoxy thymidine monophosphate; dUMP: Deoxy uridine monophosphate; FTHF: Formyl tetrahydrofolate; MTHFD1: Methylene tetrahydrofolate dehydrogenase 1; MTHFR: Methylene tetrahydrofolate reductase; PPi: Inorganic pyrophosphate; SAH: S-adenosylhomocysteine; SAHH: S-adenosyl-homocysteine hydrolase; SAM: S-adenosylmethionine; SHMT: Serine hydroxymethyl transferase; THF: Tetrahydrofolate; TS: Thymidine synthetase.

impact on symptoms during long-term COVID-19 exposure.⁶¹ In COVID-19, the demand for single-carbon units exceeded that reflected in serine levels in the cells. However, the serine metabolic pathway operates in the kidney; glycine is taken up from the blood and converted to serine. Patients suffering from kidney problems or undergoing renal transplants are more susceptible to COVID-19. Serine is an essential component in the SARS-CoV-2-induced T-cell response.^{62,63} Furthermore, GSH is crucial for metabolizing formaldehyde and vit B12 in the cells. GSH is an efficient antioxidant that reduces oxidative stress in COVID-19 patients. Both GSH and N-acetylcysteine have shown antiviral activity against viruses such as dengue, influenza, herpes simplex, and rotavirus.^{64–66} In two recent studies, mild COVID-19 patients have been found to have a normal GSH/glutathione disulfide ratio, whereas severe COVID-19 patients have been found to have a low GSH/glutathione disulfide ratio.^{67,68} The levels of antioxidant activity of GSH, superoxide dismutase, and catalase were depleted in COVID-19 cases, indicating severe oxidative damage.

2.8. Disturbance in biochemical markers in COVID-19

Recently, various clinical, hematological, and biochemical markers have been investigated in COVID-19 cases.⁶⁹ As presented in Table 2, alterations in levels of specific biomarkers direct the severity of SARS-CoV-2.⁴¹ Certain inflammatory markers, including interleukin (IL)-2, IL-6, IL-7, tumor necrosis factor, interferon- γ -induced protein-10, macrophage inflammatory protein, granulocyte-colony stimulating factor, monocyte-chemoattractant protein, C-protein, and ferritin, are all linked directly with viral diseases, causing mortality and morbidity.^{25,70} A study of 84 COVID-19 cases found that levels of cardiac enzymes and electrocardiographic findings were positively associated with inflammation, particularly procalcitonin and C-reactive protein.⁷¹ List of markers has been identified in severe cases of COVID-19 presenting multi-organ damage, including systemic vasculitis, erythrocyte sedimentation rate, cytokine-mediated coagulation, hematological status (neutrophils, lymphocytes, and neutrophil-lymphocyte value), Hcy, aspartate aminotransferase, creatine, troponin, and angiotensin II.^{72–74}

2.9. Impact of one-carbon and vitamin B12

One-carbon (C) metabolism facilitates various biochemical processes, including nucleotide synthesis, maintenance of glycine, serine, and Met concentrations, and energy generation via mitochondrial ATP. Additionally, it also serves as an antioxidant via GSH. A one-C metabolic

pathway is centered throughout folate's metabolism. The three oxidation states of folates: (i) 5-methyltetrahydrofolate, (ii) 5, 10-methylenetetrahydrofolate, and (iii) 10-formyltetrahydrofolate serve as single carbon donors. 5-methyltetrahydrofolate (CH_3THF) converts Hcy into Met, methylates DNA, and donates a methyl group for various biochemical processes. Vit B regulates proper activation and response of the immune system (innate & adaptive), depletes pro-inflammatory cytokines, prevents coagulopathy, maintains endothelial integrity, and improves the respiratory system. Poor nutritional status predisposes individuals to a wide range of infections. Therefore, adequate intake of vits promotes physiological processes and strengthens the immune system.^{92–94} Vits B, such as folic acid, mitigate COVID-19 severity and SARS-CoV-2 prevalence.⁹⁵ They also empower immune response by downregulating pro-inflammatory cytokines, suppress breathing impairment and digestive disorders, and protect against hypercoagulopathy in COVID-19 cases.⁹⁶ Vit B12 (active form hydroxo-adenosyl-methyl-cobalamin) is essential for the proper growth and development of erythrocytes, myelin synthesis, nervous system potential, and DNA synthesis. It causes pernicious anemia when methylation status is compromised, a condition that shares symptoms with long COVID-19. A reduced vit B12 level elevates methylmalonic acid, Hcy, reactive oxygen species, and inflammation.^{41,97,98} HHcy suppresses the immune response, causes endothelial dysfunction, disrupts myelin sheath integrity, platelet activation, and coagulation cascades, and causes megaloblastic anemia.^{96,99,100} SARS-CoV-2 infection disrupts vit B12 status, exacerbates gut microflora proliferation, and induces digestive issues. Moreover, vit B12 dysregulation leads to certain abnormalities, such as Hcy elevation, oxidative stress, vasoconstriction, coagulation cascade activation, and pulmonary and renal vasculopathy.^{101,102} Additionally, vit B12 deficiency leads to respiratory, central nervous system, and gastrointestinal disorders.⁹⁹ Interestingly, in a recent study, methylcobalamin supplementation significantly reduces COVID-19-related organ dysfunction.¹⁰³ Furthermore, another study found that vit B12 (500 μg), vit D (1000 IU), and Mg administration in severely infected COVID-19 cases reduced oxygen dependency and facilitated a faster recovery in the intensive care unit.²¹

2.10. Smoking and COVID-19 risk

Smoking reduces SARS-CoV-2-related infection, whereas it accelerates the development of other chronic illnesses. However, in a recent study, few cases of smoking were observed among the hospitalized COVID-19 patients.¹⁰⁴ The exact impact of smoking on COVID-19 cases is not fully explored clinically.

Table 2. Disturbance in biological markers in SARS-CoV-2 infection

Marker categories	Biological/Biochemical markers	Status in the human body (increased [+]/decreased [-])	Reference
Electrolytes	Sodium (Na ⁺)	–	75
	Potassium (K ⁺)	–	
	Calcium (Ca ⁺)	–	
Hematological	Homocysteine in blood	+	38, 76, 77, 78
	Serine in blood	–	
	Lymphocyte counts (CD4 ⁺ and CD8 ⁺)	–	
	Neutrophil count	+	
	Platelet count	–	
	NLR	+	
Coagulation	D-dimer	+	79, 80, 81
	Fibrinogen	+	
	FDP	+	
	PT	+	
	aPTT	+	
Inflammatory	CRP	+	82, 83
	ERS	+	
	PCT	+	
	Ferritin	+	
	LDH	+	
	Interleukins (IL-1, IL-2, IL-6, and IL-7)	+	
	Tumor necrosis factor- α	+	
	Tumor necrosis factor- β	+	
	Interferon- γ	–	
	MCP-1	+	
	MDW	+	
	MIP-1 α	+	
	G-CSF	+	
Hepatic	ALT	+	84, 85
	AST	+	
	ASP	+	
	Albumin	–	
	Bilirubin	+	
Cardiac	cTn	+	86, 87
	BNP	+	
Renal	Creatinine	+	88
	ACR	+	
	α 1MGCR	+	

(Cont'd...)

Table 2. (Continued)

Marker categories	Biological/Biochemical markers	Status in the human body (increased [+]/decreased [-])	Reference
Muscular	CK	+	89, 73
	Myoglobin	+	
Antioxidant activity	Superoxide dismutase	–	90, 91
	Catalase	–	
	Glutathione	–	

Abbreviations: α 1MGCR: α 1-microglobulin-creatinine ratio; ACR: Albumin-creatinine ratio; ALT: Alanine aminotransferase; aPTT: Activated partial thromboplastin time; ASP: Acylation-stimulating protein; AST: Aspartate aminotransferase; BNP: Brain natriuretic peptide; CK: Creatine kinase; CRP: C-reactive protein; cTn: Cardiac troponin; ERS: Erythrocyte sedimentation rate; FDP: fFbrin degradation products; G-CSF: Granulocyte-colony-stimulating factor; LDH: Lactate dehydrogenase; MCP-1: Monocyte chemoattractant protein; MDW: Monocyte distribution width; MIP-1 α : Macrophage inflammatory protein-1 α ; NLR: Neutrophils-to-lymphocytes ratio; PCT: Procalcitonin; PT: Prothrombin time.

2.11. COVID-19 and therapeutics

Fortunately, a few antiviral drugs have shown efficacy in the management of SARS-CoV-2, including Veklury (remdesivir), lopinavir/ritonavir, favipiravir, and oseltamivir. These agents have shown effectiveness primarily in mild-to-moderate COVID-19 cases.^{105–107} However, their administration in critical COVID-19 patients has often been associated with poor outcomes. This highlights the need for novel antiviral combinations and additional therapeutic approaches to improve clinical efficacy.¹⁰⁸ Researchers and pharmaceutical companies are advancing the development and design of new antiviral drugs targeting the emerging SARS-CoV-2 variants.¹⁰⁹ In parallel, vaccination remains a cornerstone of SARS-CoV-2 management. Several vaccines, such as Covishield, Covaxin, Sputnik-V, ZyCoV-D, and Covovax, have shown varying efficacy against multiple SARS-CoV-2 variants. Additionally, the WHO has approved several vaccines for emergency use globally to counter future COVID-19 outbreaks, including Pfizer-BioNTech's Comirnaty, Covishield/Vaxzevria, Johnson & Johnson's Janssen, Sinopharm BBIBP-CorV, and Sputnik V.^{110–112}

3. Discussion

COVID-19 has created a global health crisis, with confirmed cases and mortality rising tremendously. In many countries, rising COVID-19 cases have imposed huge burdens on overstretched and unsettled healthcare systems, causing unprecedented havoc.¹¹³ The emergence of multiple SARS-CoV-2 variants presents major public health challenges worldwide.¹¹⁴ Monitoring viral mutations through genome sequencing is crucial for establishing a genetic repository and an open-source genetic database for global researchers and healthcare providers.¹¹⁵ Early detection enables the implementation of effective health interventions, including anti-transmission strategies,

decontamination planning, and identification of high-risk areas. To mitigate future outbreaks, appropriate administrative interventions, aggressive vaccination campaigns, public compliance, and safety precautions, such as social distancing, masking, sanitizing, and quarantines, will be essential. Additionally, emphasis should be placed on personal protective measures and maintaining adequate stockpiles of essential supplies.^{116,117}

In addition to serological, clinical, and biochemical markers, Hcy has emerged as a potential diagnostic marker in COVID-19.¹⁰ Its effects are highly diverse and concentration-dependent.¹¹⁸ Increased plasma Hcy concentration significantly increases the incidence of vascular damage or injury.¹¹⁹ Clinically, Hcy promotes thromboembolism, platelet reactivity,¹²⁰ oxidative stress, endothelial dysfunction, neural defects, and atherosclerotic processes.¹²¹ Studies have reported increased Hcy concentrations in several viral infections, including hepatitis viruses, human immunodeficiency virus, and human papillomavirus.^{122,123} Furthermore, HHcy leads to atherosclerosis independently. Specifically, Hcy upregulates endothelin receptors, which are involved in atherosclerosis and may influence individual COVID-19 outcomes.^{124,125} HHcy also exhibits neurotoxic, neurodegenerative, neuroinflammatory, prothrombotic, proatherogenic, and pro-oxidative effects.²⁹ Besides, disease progression and severity are closely associated with Hcy concentrations.⁷² In a study of 117 COVID-19 patients, significant findings included HHcy, disrupted D-dimer, monocyte-lymphocyte ratios, and lymphopenia.¹²⁶ Now, Hcy is considered in the prediction, prevention, and personalization of medical approaches. In the COVID-19 management plan, a study reported that pomegranate peel extract polyphenols potentially inhibit SARS-CoV-2 virus entry; however, more efficient and highly effective therapeutic strategies need to be investigated for future perspectives.¹²⁷

4. Conclusion

Homocysteine concentration is emerging as a prognostic biomarker for SARS-CoV-2 severity. Upon SARS-CoV-2 exposure, host cells modulate Hcy metabolism to meet the increased demand for viral RNA synthesis, involving folic acids and one-C metabolism. Therefore, disruption of Hcy metabolism affects a wide range of biological processes. Increased levels of Hcy cause HHcy, which induces inflammatory markers, such as IL-6, IL-7, TNF, interferon- γ , and C-reactive protein, characterized by a “cytokine storm.” Moreover, deficiencies in folate, vit B6, and vit B12, along with elevated serum creatinine, are important determinants of Hcy concentrations in SARS-CoV-2 cases. *MTHFR* C677T mutation also modulates Hcy levels and increases susceptibility to COVID-19. This study has discussed the close association between elevated Hcy concentration, SARS-CoV-2 infection, COVID-19 exacerbation, nutritional deficiencies, co-infections, comorbidities, and *MTHFR* C677T polymorphism. Therefore, it is reasonable to conclude that the identification of biomarkers through biochemical, metabolic, and genetic detection influences the management of COVID-19 and helps identify therapeutic targets. This study will be accessible for further work between Hcy and SARS-CoV-2-related exploration.

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Conflict of interest

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