

# Pathophysiology of COVID-19: SARS-CoV-2 mimics neoplastic cells, and long COVID-19 syndrome can be a Warburg effect and ACE-2 internalization consequence

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## Article

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# Abstract

This article develops a theory involving SARS-CoV-2 pathophysiological mechanisms based on an extensive literature review and is reinforced by two years of dealing with COVID-19 patients in different footage of the natural history of the disease. SARS-CoV-2 mimics the Warburg effect (W.E. ), a well-described mechanism in neoplastic cells to obtain energy and substrates to enable cell growth. The W.E. is responsible for characteristic clinical and laboratory findings such as elevated lactic dehydrogenase (LDH), lactate, uraemia, and acidosis, in addition to explaining why a specific profile of patients evolves into severe forms of the disease. This article also exposes a hypothesis for maintaining the inflammatory status after acute SARS-COV-2 infection, "The Long COVID-19 Syndrome". Assessment of the PubMed platform followed by evaluation of articles that supported issues regarding COVID-19/SARS-CoV-2 AND AEROBIC GLYCOLISIS/WARBURG EFFECT. COVID-19 is a biphasic infectious disease (such as yellow fever) that causes tenacious immune-metabolic changes that impact the inflammatory status. The hyperlactatemia (type B) in COVID-19 is due to the metabolic shift to aerobic glycolysis (W.E. ), and it can differentiate chronic or acute COVID-19 inflammatory status from septic shock hyperlactatemia, especially when associated with negative cultures. This article sheds light on the pathophysiology of SARS-CoV-2 and possibilities for treatment and improvement in the clinical management of patients affected by this severe and catastrophic disease. The COVID-19 signature is the Warburg effect + ACE-2 + innate response + hypoxia + phenylalanine (Phe) and tryptophan (Try) metabolism. The disease's magnitude is directly proportional to the patient's exposure to hypoxia.

## Introduction

SARS-CoV-2 is a beta coronavirus responsible for a systemic infectious disease with an inflammatory characteristic, with the lungs being just another target affected by this disease. It has a bimodal characteristic, with a viraemic phase, defervescence interphase, and a third, toxæmic (immune-mediated) phase. Most patients progress to convalescence after the defervescence phase, and the minor part progresses to the toxæmic phase. Other diseases have the characteristic of being bimodal: yellow fever, leptospirosis, and the severe forms of dengue(1,2).

SARS-COV-2 uses the Warburg effect to obtain energy and substrate for its replication. Other viruses also use this exact mechanism, usually via viral proteins that shift metabolism to aerobic glycolysis, to the detriment of oxidative phosphorylation (OXPHOS), which remains active but is of lesser importance for the maintenance of viral replication mechanisms. EW is also used physiologically by some human body cells, such as the myocardium and cells of innate and adaptive immunity.

The variation between the aerobic mechanisms of cellular respiration and aerobic glycolysis impacts the differentiation of immune system cells and the possibility of neoplastic cells developing and causing metastasis(3–6).

The profile of patients who evolve to the most severe forms of COVID-19 (severe and critical) are those who have inflammatory comorbidities with some degree of hypoxia so that their cells already have their metabolic pathways diverted to perform W.E., and hyperlactatemia is due to metabolic deviation, although mixed situations, that is, increased lactate associated with shock conditions (septic shock, for example) can occur due to immunosuppression secondary to COVID-19(7,8).

COVID-19 presents a very variable chronic form, presenting itself in a pleomorphic form, making its diagnosis difficult. Although the chronic inflammatory status (called "Long COVID-19 Syndrome) has multiple faces, some signs and symptoms, such as gastrointestinal, airway, and neuropsychiatric symptoms, are prevalent. Inflammatory shock (IS) is the most severe outcome in COVID-19, which can occur immediately after the acute phase of the disease or later (weeks or months after acute disease). Inflammatory shock, often confused with septic shock and rarely diagnosed, causes great underreporting of deaths from COVID-19.

This article brings the possibility of facing COVID-19 from a structured look at possible and plausible pathophysiology. Much necessary information is in the APPENDIX of this article and is necessary for a global understanding of the presented content. This article is supported by an extensive review of the scientific literature by the author's clinical experience, two years ago dealing with COVID-19 patients in multiple settings, in addition to having carried out other reviews on the subject in the last two years. It follows the theory about the pathophysiology of COVID-19, being aware that they are hypotheses, but based on the primary evidence on the subject (Figure 1).

## Results

### ACE-2 and Inflammation

For SARS-CoV-2 to infect human cells, binding the viral surface protein (S protein) with the angiotensin-converting enzyme 2 (ACE-2) protein, which is expressed in numerous human body tissues, is required.

ACE-2 expression is prevalent in microvilli of the intestinal tract, proximal renal tubules, membranes of gallbladder epithelium, epididymis epithelium, testicular Sertoli cells and Leydig cells.

ACE-2 is also expressed in the cornea and conjunctiva of the eye, interlobular pancreatic ducts, and placental villi (in cytotrophoblasts, syncytiotrophoblasts, and extravillous trophoblasts) but not in the placental decidua. Moreover, ACE-2 is expressed at the base of the ciliated fallopian tube epithelium, endothelial cells and pericytes in several tissues, including the thyroid, parathyroid, adrenal gland, pancreas, and heart(14–17).

The ACE-2 enzyme is associated with the endothelial surface, and ACE2 activity shifts the ACE/Ang II/AT1R axis to ACE-2/Ang (1–7)/MasR by converting the vasoconstrictor Ang II to Ang (1–7). ACE-2 converts angiotensin I to angiotensin (Ang) (1–9), which yields Ang (1–7). Ang (1–7) exerts potent vasodilatory, anti-inflammatory, and antiproliferative effects when binding to MasR and angiotensin type 2 receptor (AT2R). MasR is ubiquitously expressed in neurons, microglia and endothelial cells of the cortex, basal ganglia, thalamus, hypothalamus, hippocampus, and striatum.

The ACE2 gene is located on Xp22.2 and undergoes X inactivation, resulting in phenotypic differences between sexes, and in females, ACE-2 can recognize the SARS-CoV-2 receptor-binding domain (RBD) on either of the two X. In children, the ACE2 gene is hypermethylated and silenced. Elderly individuals show increased expression of ACE2(14,15,18,19).

ACE-2 cleavage occurs by ADAM17 (Disintegrin and Metalloproteinase Domain-Containing Protein 17 or TACE) processing. ADAM17 is an ACE-2 sheddase that requires arginine and lysine residues and competes with TMPRSS2 for ACE-2 processing.

TMPRSS2 is a human transmembrane serine protease II (TMPRSS2) expressed on the cell surface of several target cells that allows activation of S proteins bound to the ACE-2 receptor on the surface of the viral host cell, inducing fusion of the viral envelope plasma membrane and direct entry of SARS-CoV-2 into cells. Upon binding to ACE-2, SARS-CoV-2 virions are taken up into endosomes and are cleaved and activated by the pH-dependent cysteine protease cathepsin L.

There are two possible routes in SARS-CoV-2 infection: the S protein of some coronaviruses is cleaved into S1 and S2 subunits during their biosynthesis in the infected cells. The S protein is cleaved by proprotein convertases such as Furin in virus-producing cells. The S1 subunit binds ACE2, and the S2 subunit anchors the S protein to the membrane. The S2 subunit also includes a peptide fusion and other machinery necessary to mediate membrane fusion upon infection of a new cell. ACE2 engagement by the virus exposes the S2' site. S2' site cleavage – by transmembrane protease serine 2

(TMPRSS2) at the cell surface or by cathepsin L in the endosomal compartment following ACE2-mediated endocytosis. When TMPRSS2 is scarce or the virus does not encounter TMPRSS2, the virus–ACE2 complex is internalized via clathrin-mediated endocytosis into endolysosomes, where S2' cleavage is performed by cathepsins, which require an acidic environment for their activity. When Ace-2 and TMPRSS2 are expressed together, fusion occurs between viral and cellular membranes, forming a fusion pore, and viral RNA is released into the host cell cytoplasm.

Furin is ubiquitously expressed in the Golgi apparatus of all cells. It is known for its role in viral pathogenesis by cleaving polybasic or multibasic sites in the COVID-19 glycoprotein. This cleavage capacity could explain COVID-19's ability to bind to tissue with relatively lower ACE2 expression. Since furin is a widely expressed protease in the respiratory tract, COVID-19 uses it to increase its infectiveness and transmissibility(20–23).

SARS-CoV-2 entry into the cell by endocytosis results in downregulation of ACE-2 in the lungs by activating A disintegrin and metalloproteinase-17 (ADAM17), cleaving the ACE2 N-terminal.

The decreased expression of ACE-2 prevents the degradation of des-Arg9 bradykinin (DABK) by epithelial cells in the lungs. Increased DABK results in the activation of DABK/bradykinin receptor B1, resulting in the release of proinflammatory chemokines by the lung epithelium. Specifically, C-X-C motif chemokine ligand 5 (CXCL5), macrophage inflammatory protein 2 (MIP2), C-X-C motif ligand 1 (CXCL1) and tumour necrosis factor-alpha (TNF)-α are released, leading to an exaggerated neutrophilic response, thereby worsening lung injury.

Additionally, overexpression of ACE2 via genetic therapy increased the production of Ang-(1–7), upregulation of the MAS pathway, inhibition of the extracellular signal-regulated kinase (ERK)/nuclear factor kappa B (NF-κB) pathway, and hence prevention of exaggerated inflammatory response seen in acute respiratory distress syndrome (ARDS). Decreased ERK/NF-κB activation via MAS has been shown to reduce transforming growth factor-beta (TGF-β) and interleukin (IL)-6(24,25).

While the effects of Ang II are rapid, the effects of aldosterone are retarded due to slower effects on downstream targeted gene transcription. The overall physiological net effects of RAS activation are an increase in total body sodium, total body water, and increased vascular tone. Furthermore, the binding of Ang II to AT receptors results in vasoconstriction, endothelial injury, endovascular thrombosis and increased blood volume. Increased Ang II is associated with hypertension and accelerated thrombosis in arterioles by activating the coagulation cascade (both thrombin and platelets). Interestingly, the thrombogenic effects of AngII on platelets were not reversible by the application of aspirin.

At the cellular level, AngII induces various signalling pathways, including serine/threonine kinase, ERK, JNK/MAPK, and PKC. Studies have shown that Ang II effectively induces IL-6 and TNF-α, possibly through serine tyrosine kinases, ERK/JNK MAPK activation, G protein-coupled receptor activation, or interaction with mineralocorticoid receptors. Ang II is a potent activator of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and hence an inducer of reactive oxygen species (ROS) production.

Ang II stimulates the expression of proinflammatory mediators such as interleukin-8/cytokine-induced neutrophil chemoattractant-3 and interleukin-6 via both receptor subtypes.

MasR expression is in line with the reduction in proinflammatory cytokines and the induction of IL-10, an anti-inflammatory cytokine. These anti-inflammatory effects of ARBs were associated with the downregulation of multiple signalling pathway-related proteins, such as PI3K, phospho-Akt, phospho-p38 MAPK, phospho-JNK, phospho-ERK, and phospho-MAPK-2

Cells expressing pattern recognition receptors that can detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) trigger the activation of the cytoplasmic NOD-like receptor family and pyrin domain-containing 3 protein (NLRP3) inflammasome pathway. Inflammasome activation in macrophages, epithelial cells, and endothelial cells releases the proinflammatory cytokines interleukin (IL)-1 $\beta$  and IL-18, which produce neutrophilia and leukopenia, contributing to the pathogenic inflammation responsible for the severity of symptoms of COVID-19

Toll-like receptor (TLR) 3, TLR7, TLR8, and TLR9 sense viral RNA and activate the nuclear factor kappa B (NF- $\kappa$ B) pathway and a high number of proinflammatory cytokines with a significant role in initiating virus-induced inflammation

The increased secretion of the proinflammatory cytokines and chemokines IL-6, interferon-gamma (IFN- $\gamma$ ), monocyte chemoattractant protein-1 (MCP-1), and IFN- $\gamma$ -induced protein 10 (IP-10) attracts immune cells, notably monocytes and T lymphocytes, but not neutrophils(19,24,26–28).

## **The Warburg effect/SARS-CoV-2 relationship and the presented phenomena in clinical and laboratory evaluation**

The interference of SARS-CoV-2 in the human immunometabolic pathways seems to be the cause of the severity of the disease, especially in those who have inflammatory comorbidities and divert cellular metabolism to the glycolytic pathway and the immune system to create a tolerant environment in the presence of an inflammatory state. These changes are even more intensified and directly proportional to the lung injury caused by the coronavirus.

The immune axis influences the metabolic axis and vice versa. These relationships are described in a simplistic way below and, in more detail, in the Appendix.

Regarding the immunometabolic axis in COVID-19

SARS-CoV-2 infects cells through the ACE-2 protein, internalizing it and promoting its downregulation. It infects II pneumocytes (highly expressing ACE-2), dendritic cells, macrophages, and other cells and tissues that express this protein. With the internalization of ACE-2, there will be less availability of its soluble fraction, mediated by ADAM17, generating an ACE/ACE-2 imbalance, creating a positive trend of inflammatory stimulus. In addition, ACE-2 is part of the intestinal protein complex responsible for the absorption of the neutral amino acids tryptophan (Try) and phenylalanine (Phe), simulating Hartnup's disease(16,24,29) hypothesis.

Inside the infected cells, the virus launches mechanisms mediated by viral proteins and glycosylation that delay the immune system's identification of the viral RNA, allowing its replication more peacefully, mainly in the first two days of infection.

By initiating the immune response mainly via the production of interferon-gamma (IFN- $\gamma$ ), the axis of Try metabolism is diverted to the production of kynurenine, negatively interfering with the serotonin and NAD/NADH<sup>+</sup> pathways, which are usually in a state of homeostasis. Try is processed by the enzyme tryptophan hydroxylase (TDO) when in homeostasis; however, in the inflammatory state, the liver stops producing TDO, and the processing of Try starts to be mediated by the indoleamine 2,3-dioxygenase (IDO) enzyme produced mainly by dendritic cells (DCs), macrophages (MOs) and monocytes. It remains controversial how IDO-1 influences the tendency towards the kynurenine pathway. KYNA produces some toxic metabolites that bind to GABA receptors. These metabolites are found in diseases such as Alzheimer's and Parkinson's. These metabolites appear to exert significant neuropsychiatric symptoms in COVID-19 patients, whose

symptoms are prevalent. In addition, they hinder the action of anaesthetics in sedation and intubation processes and activate pain mechanisms, especially peripheral ones(30–32).

The deviation of the Try axis promotes lower production of NAD/NADH due to low production of the B complex (mainly B3), causing Pellagra signs in patients and an enzymatic deficit in intracellular aerobic respiration. 5-HT is also compromised, producing less melatonin and causing acute depressive symptoms, even in patients with no previously reported psychiatric illness history(33–35).

Kynurenine mainly influences AhR receptors present in T lymphocytes, whose activation by this receptor activates mTOR, shifting the immune system to Treg and tolerance and promoting the activation of the innate immune system enhanced by the hypoxemic environment due to lung injury. The magnitude of the tolerant environment and the activation of the innate over the adaptive immune system appears to also be proportional to the time of exposure to hypoxia; thus, timed intubation appears to be part of the treatment for patients with severity predictors for COVID-19(36–39).

Phe is mainly inhibited by neopterin produced mainly by monocytes and DCs by IFN- $\gamma$  stimulation. In monocyte-derived macrophages and dendritic cells, IFN- $\gamma$  triggers GTP-cyclohydrolase-I, the key enzyme for the biosynthesis of pteridine derivatives such as neopterin 5,6,7,8-tetrahydrobiopterin (BH4).

Neopterin has been linked to the mortality outcome in cardiovascular and other inflammatory diseases; in addition, it influences the increase in the Phe/Tyr and Kin/Tryp ratio PAH, which may be due to an increased output of reactive oxygen species (ROS), which is produced by macrophages upon stimulation by IFN- $\gamma$  in parallel to neopterin production(40–42).

The decrease in Tyr due to the increase in Phe/Tyr influences the decreased production of melatonin, affecting sleep-wake dynamics, with insomnia being a prevalent symptom in COVID-19 patients.

The decrease in Tyr due to the increase in Phe/Tyr influences the decreased production of melatonin, affecting sleep-wake dynamics, with insomnia being a prevalent symptom in acute COVID-19 and the "Long COVID-19 Syndrome". Melatonin is synthesized from serotonin in a two-step process by the sequential action of the key enzymes aralkylamine N-acetyltransferase (AANAT) and acetylserotonin O-methyltransferase (ASMT)(36,43–46).

Melatonin acts in the human body as a sleep-inducing hormone and preserves the evolutionary characteristic of interacting with various ROS to produce cyclic 3-hydroxymelatonin and other melatonin metabolites, e.g., N1-acetyl-N2-formyl-5-methoxykynuramine and N-acetyl-5-methoxykynuramine. These metabolites function as radical scavengers, sometimes even more aggressively than melatonin, regarding their capacity to neutralize ROS. Melatonin stimulates the antioxidant enzyme superoxide dismutase (SOD2), an action that involves elevated levels of sirtuin 3 (SIRT3). Melatonin enters mitochondria through the oligopeptide transporters PEPT1/2 and influences mitochondrial membrane potential by uncoupling protein (UCP); finally, melatonin from the matrix may leak out of the mitochondria to interact with the melatonin receptors MT1 and MT2 to control the release of cytochrome c(47–49).

Most 5-HT originates outside the central nervous system, with only approximately 3 to 5% of the total produced represented by this system. Most are produced peripherally, and most are produced by enterochromaffin cells in the intestine. 5-HT, increasingly recognized as a hormone and neurotransmitter, plays an essential role in glycemic control. Patients with insulin resistance have elevated serum 5-HT concentrations. Adipocyte-derived 5-HT inhibits adaptive thermogenesis in brown and subcutaneous adipose tissues. In contrast, gut-derived 5-HT regulates hepatic lipid accumulation through the gut–liver axis but activates lipolysis specifically in visceral adipocytes under obese conditions via HTR2B signalling at the 5-HT receptor that couples to G proteins(33,50–53).

In adipose tissue, 5-HT, when in deficit, promotes lipolysis in yellow fat, promoting an important event called thermogenesis. Initially, an adaptive mechanism to cold exposure that becomes harmful in pathological conditions, as in obese patients and with insulin resistance in COVID-19, promotes hyperthermia and tissue damage. This state can be alleviated by using an insulin pump that reverses the lipolysis mechanism. Nevertheless, during oxidative stress, the stimulus to greater adrenaline production promotes intensification of thermogenesis, constituting a severe cycle if maintained in critically ill COVID-19 patients. Central 5-HT exerts an opposite effect of peripheral 5-HT on adipocytes, and the central serotonergic neurons may be master regulators of whole-body energy homeostasis. This fact may be associated with an acute situation of exposure to cold in patients with normoglycemia and a situation in which there is chronic hyperuricemia. Peripheral 5-HT is increased under hyperglycaemic conditions, and adipocyte-derived serotonin may increase energy storage and adipogenesis in WAT through HTR2A and inhibit adaptive thermogenesis in BAT through HTR3. Paracrine and central serotonin act on the pancreas to stimulate insulin production, while peripheral serotonin induces hypoglycemia and stimulates obesity. This antagonistic action is essential in the homeostatic control of glucose, which is altered in critically ill COVID-19 patients and in patients with insulin resistance and 2TDM(54–57).

Chronic inflammatory status causes deficiency in peripheral and central amounts of serotonin. In COVID-19, the production mechanism is reduced by Try deficiency and consumption due to inflammatory control for Treg induction. Patients with high serum 5-HT start a consumption process due to the a priori issues reported in the inflammatory environment resulting from SARS-CoV-2 infection. Due to the lack of 5-HT, the prevalent phenomena of hyperglycaemia and hyperthermia secondary to thermogenesis or even hypothermia events occur in normoglycaemic patients without previous insulin resistance.

The insulin resistance status favors the polarization of M2 macrophages, whose characteristic is an anti-inflammatory action. 5-HT promotes the inhibition of IL-12 and TNF- $\alpha$  release, but it increases IL-10, NO, and PGE2 production via 5HT2 receptors. 5HT stimulates macrophage polarization to an M2-like phenotype, and this effect is mediated by 5HT2B and 5HT7, which are preferentially expressed by anti-inflammatory M2 macrophages(58–62).

The hypothalamic pituitary adrenal (HPA) axis is responsible for mediating various changes in the body in homeostasis and at the time of stress, as it exerts glycemic control, sleep-wake control (through the action of the melatonin pathway), in the metabolic axis with peripheral impact and neuropsychiatric, and in the immune system trigger multiple changes, usually anti-inflammatory. Dissociated dynamics between ACTH and glucocorticoids are observed when inflammatory stress is present. The hypothalamic release of corticotropin-releasing factor (CRF) binds to CRF receptors on the anterior pituitary gland, and adrenocorticotrophic hormone (ACTH) is released. Because of ACTH, the adrenal cortex produces and releases cortisol. Cortisol exerts negative feedback on the hypothalamus. This hypothalamic cortisol sensitivity decreases with ageing. The hypothalamus responds positively to the catecholaminergic input, representing a major excitatory drive on the HPA axis and inducing CRF expression and protein. Vasopressin also has a positive effect on the activation of the HPA axis.(63–65)

The Warburg effect is the metabolic signature in COVID-19, as SARS-CoV-2 expresses proteins that favour metabolic modification for anaerobic glycolysis at the expense of oxidative phosphorylation, similar to other viruses. However, the hypoxia caused by lung lesions by the action of the coronavirus further intensifies the expression of proteins that facilitate the metabolic mechanism of the Warburg effect (Appendix).

The Warburg effect, also called aerobic glycolysis, is a mechanism in which the cell obtains energy (ATP) through the glycolytic pathway at the expense of oxidative phosphorylation and was initially described for neoplastic hypoxic environments with and without hyperglycaemia(3,4,66–69).

The hyperglycaemic environment favours the development of the Warburg effect, as hypoxia and inflammation intensify this effect. That is why inflammatory and neoplastic diseases, obesity, 2MDD and advanced heart failure (diseases now

considered inflammatory because they promote tissue hypoxia and, consequently, inflammation) are predictors of severity in COVID-19.

The Warburg effect is essential in favoring the pentose pathway to provide nitrogenous bases as a source for viral replication. Furthermore, it causes the displacement of pyruvate to form lactate, which is mediated by lactic dehydrogenase (LDH). Thus, oxidative phosphorylation can occur at a lower intensity than what occurs in physiological normality. Lactate travels to the liver to form glucose via the Cori cycle(7,70).

COVID-19 patients have elevated LDH and lactate, a hallmark of the disease, in addition to significant lymphopenia. DHL is stimulated due to the high accumulation of pyruvate. The citric acid cycle is under-functioning. Thus, the investigation of LDH and lactate can help diagnose the disease, both in the acute and chronic phases (the long COVID-19 syndrome), being good tests to differentiate, for example, inflammatory syndrome or inflammatory shock from sepsis or septic shock. Although the events may overlap, there is a need to use antimicrobials since systemic inflammation allows bacterial translocation through the skin and intestine in a tolerant and tumorigenic environment, as in COVID-19(7,71).

The activated pentose pathway (PPP) supports purine formation, and NADPH generated by the pentose phosphate pathway (PPP) is necessary for glutathione recycling for antioxidant protection and lipid synthesis. Glutamate also plays an essential role in W.E., as this amino acid is required to provide substrate. Glutamate is formed from the breakdown of skeletal tissue, contributing significantly to the wasting syndrome in COVID-19. Glutamine produces oxaloacetate during anaplerotic reactions in various cell types in many c-Myc transformed cells. It is a prevalent condition in the elderly and can be confused due to some neoplasms.

What differentiates neoplastic wasting syndrome from "The long COVID-19 syndrome" is the fact that the latter has acute weight loss, in addition to acute delirium with acute loss of functionality, elevated LDH and lactate and no previous history of neoplasia. Although COVID-19 may open the door to the rapid development of neoplastic cells due to cellular changes brought about by oxidative stress and W.E. (6,69,72,73)

W.E. favours dyslipidaemia, as it favours the formation of fatty acids to be used for ATP production via beta-oxidation. This status is also favoured by oxidative stress with the intensification of hyperglycaemia. This explains recent studies that find alterations in the metabolism of lipids, branched-chain amino acids (BCAAs), Try, Phe and citric acid cycle metabolites(74–77).

Host lipid metabolism occurs via peroxisome proliferator receptor gamma (PPAR- $\gamma$ ) signaling, one of the central regulators of lipid homeostasis that controls fatty acid uptake, storage and lipogenesis. Many viral and parasitic intracellular pathogens utilize host lipid droplets during their life cycle, as in the dengue virus.

The W.E. de novo increased lipid synthesis, elevated anabolic processes, decreased/altered TCA cycle metabolism, and high glucose usage as an energy and carbon source for cell growth and division. Oncogenes such as myc and ras and suppressor genes such as p53 are transcriptional factors or signalling molecules that are typically present in cells with W.E.pento(77,78).

PPP operates in the oxidative or the nonoxidative mode depending on the relative contribution of G6PDH and transketolase/transaldolase action, substrate inputs (G6P, F6P, Triose-P (3C)), NADH/NAD ratio and the removal of F6P by the formation of F1,6 diP, and triose-P by pyruvate kinase The PPP intermediates are parts of the sugar-phosphate system consisting of ketoses, aldoses and sugar alcohols, which oxidation of these promotes amino acid precursors.

Energy metabolism in cells comprises a spectrum of anabolic and catabolic activities driven by a hybrid system, one generating predominantly NADH (anabolic) and the other ATP (catabolic). Reducing equivalents are best used for

anabolic processes such as fatty acid synthesis and nucleic acid pentose synthesis, while ATP is used for macromolecular synthesis, substrate transport, and electrical and mechanical energy generation(78–81).

Many of the enzymes in this glycolysis/pentose cycle compartment are inducible by hypoxia-induced factor 1 (HIF-1). In addition, viral proteins favour the shift of metabolism to anaerobic glycolysis, NAD/NADH<sup>+</sup> (which is lacking, for example, by the altered Try pathway). Growth factor stimulation results in signalling through RTKs to activate PI3K/Akt and Ras. Akt promotes glucose transporter activity and stimulates glycolysis by activating several glycolytic enzymes, including hexokinase and phosphofruktokinase (PFK). Akt phosphorylation of apoptotic proteins such as Bax makes cancer cells resistant to apoptosis and helps stabilize the outer mitochondrial membrane (OMM) by promoting attachment of mitochondrial hexokinase (mtHK) to the VDAC channel complex. RTK signalling to c-Myc results in transcriptional activation of numerous genes involved in glycolysis and lactate production. The p53 oncogene transactivates TP-53-induced glycolysis and apoptosis regulator (TIGAR) and increases NADPH production by PPS. Signals impacting levels of hypoxia-inducible factor (HIF) can increase the expression of enzymes such as LDHA to promote lactate production and pyruvate dehydrogenase kinase to inhibit the action of pyruvate dehydrogenase and limit the entry of pyruvate into the Krebs cycle.

Another important consequence of the breakdown of muscle tissue in search of amino acids and glutamine is the elevation of uraemia, often not associated with renal dysfunction.

W.E. also acts on the immune system, favouring a more tolerant environment than the inflammatory one, being responsible, for example, in the occurrence of metastases, considering its effect on neoplastic cells. The detailed mechanisms of EW are covered in the "APPENDIX" of this article(3,81–86).

W.E. acts on the immune system in several ways, tending the immune system towards tolerance. Negative signalling induced by ligand binding causes a downregulation of the immune response to avoid overactivation of immune activities, and some of the immune checkpoints have been identified, such as PD-1, CTLA4, and TIM3. W.E. stimulates macrophage polarization to M2 induces apoptosis of NK and T-cells of the inflammatory spectrum while favoring innate immunity and the Treg pole.

Myeloid and lymphoid cells of both the innate and adaptive immune systems, ranging from lymphocytes and NK cells to DCs and macrophages, undergo Warburg-like metabolic reprogramming in response to inflammatory stimuli. The balance between EW and OXPHOS is responsible for the differentiation of immune system cells. Upregulation of glycolysis in T cells is a coordinated response to immune activation, with CD28 costimulation producing increased glucose transporter expression, glucose uptake, and glycolysis via phosphatidylinositol 3-kinase (PI3K). Glycolysis is necessary for the survival/proliferation, differentiation, and effector functions of CD4. It is suggested that glycolytic reprogramming in lymphocytes presents regulators such as Myc and hypoxia-inducible factor 1 $\alpha$ , increased expression of the glucose transporter GLUT1, and activation pyruvate dehydrogenase kinase isoform 1(87–90).

For example, Tcm cells use energy mainly via the oxidation of fatty acids, and with W.E. inhibition, these lymphocytes are inhibited via OXPHOS activation. This existing balance may perhaps suggest the range of phenotypes presented by COVID-19 patients regarding antibody production, NK cell action and the tendency to Treg cells in addition to apoptosis of immune system cells in general, which may also corroborate the explanation of the immunoparalysis presented in the period after acute infection by SARS-CoV-2.

The acidification of intra- and extracellular environments promoted by W.E. contributes to tolerance. Cytosolic lactate is transported out of cells via monocarboxylate transporters (MCTs), while protons (H<sup>+</sup>) are secreted through membrane-bound transporters, leading to extracellular acidification. Vacuole ATPases (V-ATPase) allow H<sup>+</sup> into the extracellular

space, contributing to its acidification by consuming ATP. This acidification mechanism is beneficial for cancer cells in their proliferation, survival, metastasis, and signal transduction(91–93).

Acidification of intra- and extracellular media can benefit SARS-CoV-2 by providing an optimal environment for the performance of cathepsins, especially cathepsin L, used by the coronavirus in the processing of viral proteins, enabling their replication. This fact corroborates the difficulty in raising the pH in many critically ill patients using the permissive hypercapnia approach. When thinking about the viral mechanisms of action on the human host, it would be a mistake to allow high CO<sub>2</sub> pressures, as it contributes to the maintenance of the low pH stimulated by W.E. activation of cathepsins, syncytium formation and a tendency to immunosuppression (Figures 2 and Figure 3).(93,94)

## Discussion

COVID-19 is a multisystem infectious disease since the ACE-2 receptor, for a viral infection to occur, is disseminated to almost all human body tissues.

The most recent proteomics studies show alterations in the metabolism of lipids, branched-chain amino acids (BCAAs), tryptophan, phenylalanine, and components of the citric acid cycle, probably related to the shift from oxidative metabolism mediated by OXPHOS to aerobic glycolysis metabolism called the Warburg effect(72,78).

Many viruses use W.E. to carry out replication more effectively within cells, as aerobic glycolysis provides substrate (nitrogenous bases and ATP) for producing genetic material and molecules that make up the viral organization. W.E. is used by neoplastic cells for growth and metastasis and usually occurs in a hyperglycaemic and hypoxemic environment. Although OXPHOS continues to occur, it is less used as the metabolic changes that occur trigger a truncated citric acid cycle.

W.E. cause significant acidosis since there is a large lactate production from pyruvate, which is prevented from going to TCA. The increase in pyruvate is a stimulus for LDH expression. In this way, W.E. explains the laboratory alterations prevalent in COVID-19 patients, especially in severe and critical patients. The lactate produced acidifies the intra- and extracellular environments and is the basis for glucose production by the liver (Figure 2 and Figure 3).

Uraemia, often present with preserved renal function, is justified by the large consumption of skeletal tissue to obtain amino acids, especially glutamate, which serves as an energy substrate, together with the activation of the pentose pathway (PPP).

Acidaemia allows an optimal environment for activating lysosomal enzymes, for example, cathepsin L, which is widely used by SARS-CoV-2 for its replicative process to occur in the host cell. In addition, cathepsin L is 6 times higher in syncytiotrophoblasts, and intense cathepsin activation may explain the formation of syncytial structures in critically ill patients. That is, permissive hypercapnia without pH correction, which must be performed with 8.4% sodium bicarbonate, provides an optimal environment for the activation of cathepsins, positively contributing to viral replication, in addition to causing a shift in the immune axis to the tolerant pole. and tumorigenic(116).

COVID-19 patients, to a greater or lesser extent, undergo a process of immunosuppression resulting from W.E., although they remain, at the same time, with a tendency to activate the TH17 immune response. This inflammatory environment concomitant with the shift from the pole to Treg is conducive to the emergence of autoantibodies. In addition, lymphocytic apoptosis contributes to the development of neoplasms since the death of N.K. and TCD8+ in an environment where cells are under the significant influence of oxidative stress, altering all cellular control mechanisms. Many prevalence studies are still needed, but the development of neoplastic diseases (mainly breast and gastrointestinal diseases) linked to previous SARS-CoV-2 infection is already being noticed.

The hypoxia resulting from lung injury caused by the coronavirus is an excellent ally for intensifying the metabolic and immunological mechanisms that lead the patient to severe and critical forms of the disease. HIF is responsible for stimulating inflammation; moreover, HIF is expressed in inflammatory processes. Hypoxia intensifies oxidative stress, causing an increase in cortisol and insulin resistance and contributing to an optimal environment for aerobic glycolysis to occur. This chronic process can cause adrenal insufficiency and be another cause of shock in COVID-19(82,84).

The magnitude of COVID-19 is influenced by multiple factors, such as the parasite-host relationship, the host's genetic issues, and the amount of inoculum to which the patient was exposed. However, factors of great importance for the patient to progress to severity are mainly the time of exposure to hypoxia and inflammatory comorbidities that produce some degree of hypoxia in the patient. All these conditions can corroborate the clinical and laboratory symptoms in COVID-19 patients (Figure 4).

## Conclusions

SARS-CoV-2 infection is a catastrophe that continues to claim many victims, especially the elderly, but remains underreported or even unreported. This fact occurs because the patient is admitted to hospitals after the viraemic phase or in "The Long COVID-19 Syndrome", periods in which RT-PCR is negative for the virus (with rare exceptions in acute disease, viremia may be more prolonged).

This review and theory show that some tests, such as lactate and LDH, can contribute to the diagnosis of COVID-19 when associated with the clinical history of the disease, blood gas analysis, hypoglycaemia events and neuropsychiatric changes.

The content of this article also seeks to contribute to improving the clinical management of critically ill patients by identifying important relationships in the host-parasite relationship that impact the metabolic changes found in patients.

COVID-19 is a challenge for doctors, and more studies are necessary to elucidate the mechanisms that remain unexplained in the disease so that more deaths are avoided.

## FINAL CONSIDERATIONS

We should not consider serology (IgM or IgG), not even RT-PCR for SARS-CoV-2 to close the diagnosis of COVID-19, as they can be negative on many occasions (RT-PCR is negative, most of the time, because the patient is late admitted to the hospital or is on chronic COVID-19).

One should consider the laboratory tests suggested in this article, natural history of the disease, and epidemiological period.

As a suggestion, blood counts containing significant lymphopenia associated with tomographic imaging are very useful for making the diagnosis.

## Methods

For this review, articles in English were included. The PubMed and Google academic databases were used, the second being for theoretical complementation when necessary. Thus, it was a database used throughout the production of the manuscript. There was no characterization of the minimum date for the articles. From the descriptors: "COVID-19" AND "WARBURG EFFECT"; "COVID-19" AND "AEROBIC GLYCOLYSIS", "SARS-CoV-2" AND "WARBURG EFFECT" AND "SARS-CoV-2" AND "AEROBIC GLYCOLYSIS". Only five articles referring to "metabolic alterations", "Warburg effect" and aerobic

glycolysis" in the abstract were found and considered for this review. There were no articles discarded using the search descriptors. The criteria used were adapted from the PRISMA protocol, at <https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2015-41/ccdr-volume-41-04-april-2-2015/ccdr-volume-41-04-april-2-2015-3.html> Accessed on 02/09/2021 Another 119 articles were added during the writing to support the research. The articles are shown in Table 1.

**Table 1. Articles regarding SAR-CoV-2 and the Warburg effect published between 2020 and May 2022**

AUTHOR	WARBURG EFFECT, AEROBIC GLYCOLYSIS OR METABOLIC CHANGES (ABSTRACT)	DOI
Icard P. et al.(9)	Yes	10.1016/j.biochi.2020.11.010
Icard P. et al. (10)	Yes	10.1016/j.biochi.2021.09.009
Ferraro E. et al. (11)	Yes	10.1155/2021/8841911
Tan D.(12)	Yes	10.3390/molecules25194410
Zhuhua R. et.al(13)	Yes	10.3389/fmicb.2021.807737

## Declarations

## ACKNOWLEDGMENTS

I dedicate this work to all COVID-19 patients who have died or who remain with sequelae.

I dedicate this work to my mother, who was strong and overcame severe COVID-19.

I dedicate this work to my professor Esper G. Kallás, to my colleagues from the Laboratory of Immunopathology and Allergy and to colleagues from the Research Centre II of the University of São Paulo - Medicine School.

I dedicate this work to my colleagues at the Emergency Room of the University Hospital of the University of São Paulo.

## LIMITATIONS OF THE ARTICLE

This article requires studies to be carried out to assess the altered metabolic pathways in COVID-19; moreover, there is a necessity in performing trials that reinforce the medicines cited in this article.

## AUTHOR'S CONTRIBUTION

Luiz Zanella wrote this article and created all the figures presented using Biorender.com.

## CONFLICTS OF INTEREST

The author has no conflicts of interest.

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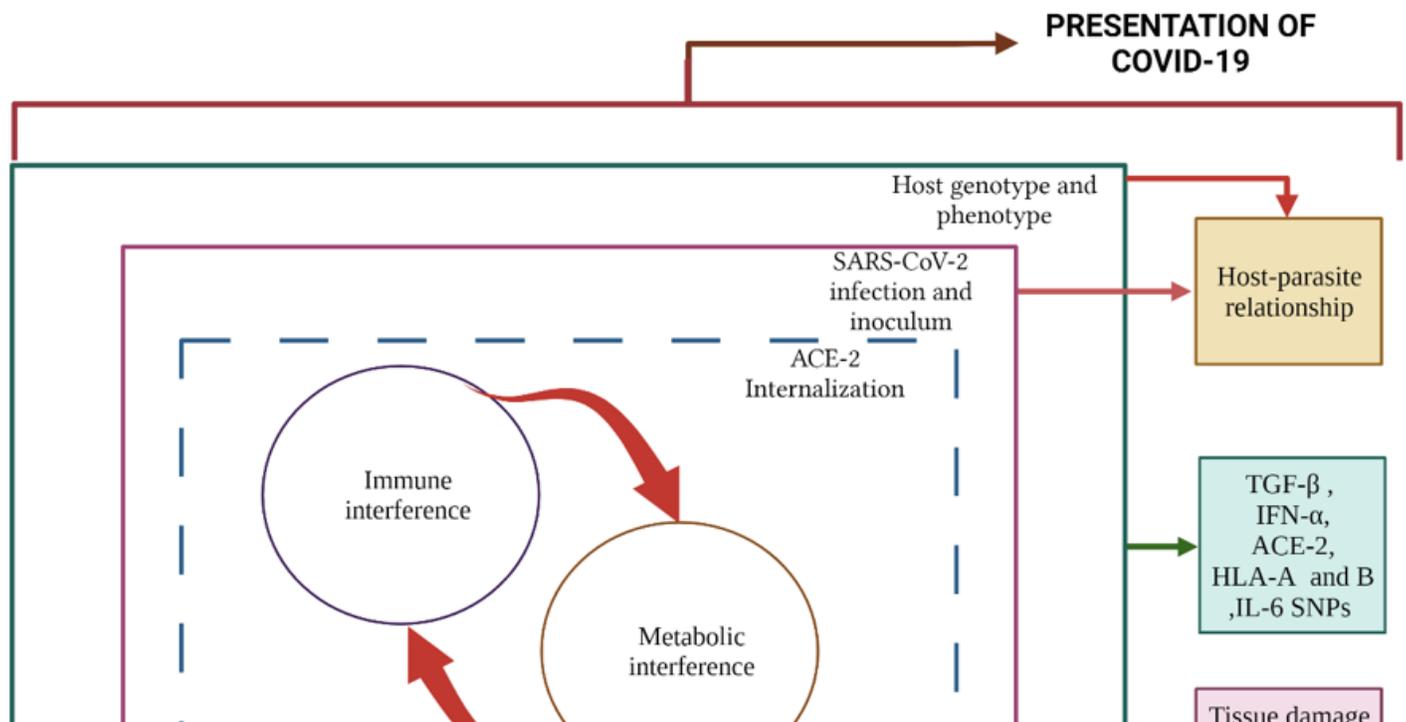
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## Figures



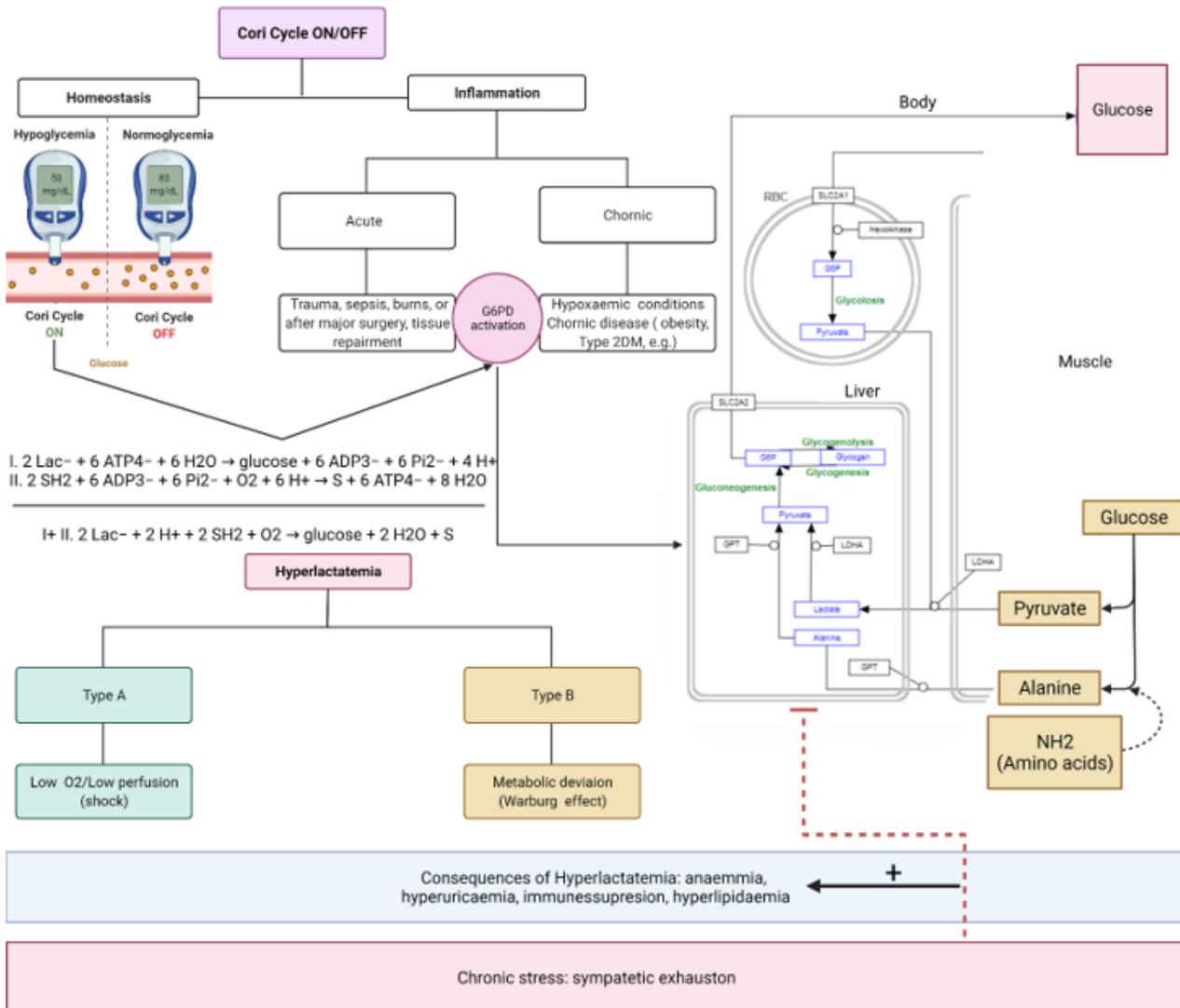
## Figure 1

The figure displays a panel of interactions that reflects the clinical expression of COVID-19, which can be interpreted with a 3-dimensional view. Although the parasite-host relationship and the amount of inoculum are essential for the onset of the disease, once established, all other factors are of double importance, especially the physiological changes triggered by the internalization of ACE-2 and the immunometabolic changes caused by the lower absorption of tryptophan and phenylalanine. Hypoxia is perhaps the most critical factor that can be managed to decrease the severity of the disease since the magnitude of the severity of COVID-19 appears to be directly proportional to the time of exposure to hypoxia. This ample sample space formed by the sets shows possible determinants of the clinical phenomenon present in COVID-19. Created with BioRender.com.

## Figure 2

**Warburg effect deviation.** A. Glycolysis is augmented with the formation of pyruvate, which is diverted to lactate formation, contributing to hyperlactatemia in COVID-19. B and C. Hypoxia activates transcription factors (Appendix), contributing to the shift of the metabolic axis to aerobic glycolysis (W.E.) with activation of the pentose cycle for the formation of nitrogenous bases, contributing to an increase in uraemia, even without worsening renal function. D. Shows the W.E. in the mitochondria with a metabolic shift for lipid formation, substrate for the formation of the capsule of many viruses and the formation of the cell membrane. Skeletal muscle tissue myolysis is activated to obtain BCAAs and glutamine, which enter metabolism for ATP generation. TKT: transketolase, TALDO: transaldolase, RPE: ribulose 5-phosphate 3-epimerase; RPI: ribose 5-phosphate isomerase, 6GDP: glucose-6-phosphate dehydrogenase, GSSG: glutathione disulfide. Created with BioRender.com.

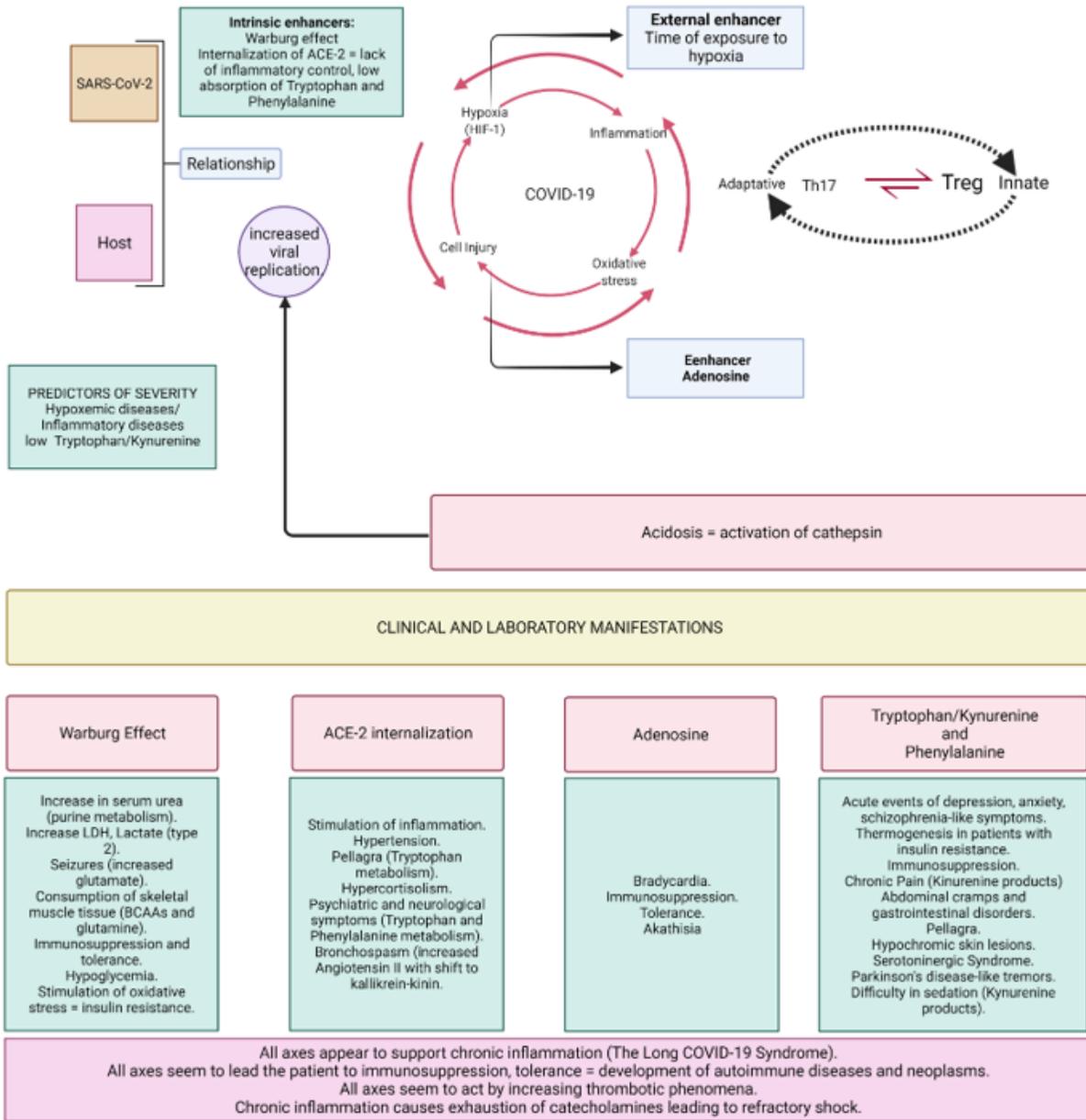
### CORI CYCLE AND LACTATE



**Figure 3**

**Hyperlactatemia in COVID-19.** Hyperlactatemia occurs due to metabolic deviation from the Warburg effect, characterizing type B hyperlactatemia (B1 types related to a process of failure of clearance such as hepatic insufficiency; B2 related to drugs or toxins; B3 related to inborn errors of metabolism). Type A hyperlactatemia occurs secondary to tissue hypoxia caused by shock. A mixed component may occur, with the patient presenting an increase in lactate due to metabolism deviation and shock. The difference is in the presence or absence of acidosis. Type B hyperlactatemia occurs without acidosis, as evidenced by blood gas analysis. In acidaemia, types A and B of hyperlactatemia can occur. The exaggerated increase in LDH contributes to thinking about COVID-19 with metabolic deviation. Lactate/pyruvate (L/P) can help differentiate between A and B hyperlactatemia. The higher this ratio is, the more the oxidative metabolism is defective with an important mitochondrial dysfunction. In nonhypoxic circumstances, lactate elevation occurs without elevation of the L/P ratio. The hyperlactatemia of patients with sepsis is not associated with L/P ratio elevation, and hyperlactatemia with L/P ratio elevation and lactic acidosis is likely to be associated with inadequate tissue perfusion. Explanations for laboratory findings in COVID-19. The shift of metabolism to the W.E. promotes an increase in lactate and LDH due to exacerbation of glycolysis and truncation of the citric acid cycle, although the aerobic pathway remains underactivated (Appendix).

The increased demand for glucose can trigger a hypoglycemic event, even in a patient with hyperglycemia due to inflammation stimulating oxidative stress with hypercortisol production. Elevated uraemia is promoted by increased purine synthesis; dyslipidaemia is motivated by increased lipid synthesis. Hyperlactatemia enters the Cori cycle when the body is deprived of glucose; however, in hyperglycaemia, the cycle is not activated, contributing to the maintenance of high lactate. Created with BioRender.com.



**Figure 4**

Clinical and laboratory events performed by the scientific literature and their possible explanations. SARS-CoV-2 establishes a very peculiar parasite-host relationship with humans, which is polymorphic due to the patient's different profiles of inflammatory comorbidities or lack of comorbidity in healthy patients. Obesity, insulin resistance, heart failure, and neoplasms have a hypoxemic inflammatory profile or metabolic shift to the pop Warburg effect. Aging naturally promotes increased oxidative stress. All these factors are predictors of severity. The inflammation generated by the presence of the virus in the body can be intensified by the time of exposure to hypoxia, contributing to increased inflammation and increased W.E. taking the patient with predictors to the critical patient situation. The immune system

signs COVID-19 with a tendency toward immunosuppression, tolerance, and deviation from the innate immune system. Maintenance of inflammatory states - "The Long COVID-19 Syndrome" - can be maintained or reactivated by cellular changes that facilitate W.E. reactivation by the tendency to become inflammatory due to ACE-2 internalization, unmet oxygen demand, and autoantibodies produced during illness. The main clinical and laboratory manifestations are due to W.E., internalization of ACE-2, cell injury with adenosine production, lack of tryptophan and phenylalanine, with a marked deviation of the immune metabolism for life kynurenine (immunosuppressant) and its toxic metabolites to the central and peripheral nervous system. Created with BioRender.com.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [APPENDIX.docx](#)