SARS-CoV-2 vaccinations have greatly reduced COVID-19 cases, but we must continue to develop our understanding of the nature of the disease and its effects on human immunity. Previously, we suggested that a dysregulated STAT3 pathway following SARS-CoV-2 infection ultimately leads to PAI-1 activation and cascades of pathologies. The major COVID-19-associated metabolic risks (old age, hypertension, cardiovascular diseases, diabetes, and obesity) share high PAI-1 levels and could predispose certain groups to severe COVID-19 complications. In this review article, we describe the common metabolic profile that is shared between all of these high-risk groups and COVID-19. This profile not only involves high levels of PAI-1 and STAT3 as previously described, but also includes low levels of glutamine and NAD⁺, coupled with overproduction of hyaluronan (HA). SARS-CoV-2 infection exacerbates this metabolic imbalance and predisposes these patients to the severe pathophysiology of COVID-19, including the involvement of NETs (neutrophil extracellular traps) and HA overproduction in the lung. While hyperinflammation due to proinflammatory cytokine overproduction has been frequently documented, it is recently recognized that the immune response is markedly suppressed in some cases by the expansion and activity of MDSCs (myeloid-derived suppressor cells) and FoxP3⁺ Tregs (regulatory T cells). The metabolomics profiles of severe COVID-19 patients and patients with advanced cancer are similar, and in high-risk patients, SARS-CoV-2 infection leads to aberrant STAT3 activation, which promotes a cancer-like metabolism. We propose that glutamine deficiency and overproduced HA is the central metabolic characteristic of COVID-19 and its high-risk groups. We suggest the usage of glutamine supplementation and the repurposing of cancer drugs to prevent the development of severe COVID-19 pneumonia.
biochemical commonalities of dysfunction with SARS-CoV-2 infection?

We previously described the involvement of dysregulated STAT1 and STAT3 pathways in COVID-19, which leads to a cascade of pathologies [2]. Subsequently, groups have observed activated STAT3 in biopsied lung specimens [3], and detected the expression of STAT3 downstream genes like PAI-1, HA52 (hyaluronan synthase 2), and MMP9 in BALF (broncho alveolar lavage fluid) samples from severe COVID-19 patients [4]. Furthermore, increased serum PAI-1 levels were found in COVID-19 patients, as compared to those in healthy controls [5, 6].

Table 1 shows the relevant metabolic profile of COVID-19 high-risk groups. Since PAI-1 expression levels are also increased in the major COVID-19 high-risk conditions of old age, hypertension, cardiovascular disease, diabetes, and obesity [2], PAI-1 may be critical to severe COVID-19. In addition, COVID-19 associated comorbidities share not only high PAI-1 levels, but also high hyaluronan (HA: extracellular matrix glycosaminoglycan polymers) levels, and low NAD+ (nicotinamide adenine dinucleotide) and glutamine levels (Table 1).

The low glutamine levels are particularly compelling, as seminal work by Cheng et al. identified that plasma glutamine and the glutamine:glutamate ratio are inversely associated with metabolic risks [7]. Indeed, metabolic analyses of COVID-19 patients have shown low levels of glutamine [8–15], and Lee et al. reported that glutamine was negatively correlated with disease severity [15]. Furthermore, Paez-Franco et al. observed that the reduced levels of glutamine in severe and mild COVID-19 patients were negatively correlated with LDH (lactate dehydrogenase), CRP (C-reactive protein), and pCO2 levels. Conversely, glutamine levels positively correlated with pO2 [10], revealing the previously underdetermined consequences of low levels of glutamine in the severe COVID-19 pathophysiologies. Consistently, Kim et al. reported that glutamine was the top candidate amongst 26,288 FDA-approved drugs tested for reversing SARS-CoV-1 associated changes in murine gene expression [16].

This review discusses the possibility that glutamine deficiency predisposes high-risk patients to severe COVID-19. Other major factors, such as low NAD+, high HA, and high PAI-1, may be related to low glutamine levels in the high-risk groups. SARS-CoV-2 infection affects these same conditions, potentially magnifying the severe pathologies of COVID-19.

PATHOPHYSIOLOGIES

COVID-19 is characterized by a variety of clinical manifestations, including impaired type I interferon (IFN-I) production and, in severe cases, ARDS (acute respiratory distress syndrome) and extensive coagulopathy [2]. Here, we principally focus on the less characterized aspects of COVID-19 pathophysiologies: the hyaluronan storm, NETs, and immune suppression.

CT scans of severe SARS-CoV-2 patients revealed characteristic multiple round white patches called “ground-glass opacities,” containing fluid in the lungs [17]. In almost all cases of SARS-CoV-2, the main pathological finding is diffuse alveolar damage (DAD) [18]. DAD is characterized by damage to the alveolar lining and endothelial cells, leading to pulmonary edema and hyaline membrane formation (the exudative phase), and later by proliferative changes involving alveolar and bronchial lining cells and interstitial cells (the proliferative phase) [19]. To analyze the nature of hyaline membranes in COVID-19, Hellman et al. performed hyaluronan (HA) histochemistry using a direct and specific HA staining method [20] as overproduced HA was suggested to be a fatal cause of COVID-19 [17]. They reported that HA-positive-exudate and alveolar plugs filled the alveolar spaces [20]. They also showed that in the proliferative phase, HA is localized in the thickened perialveolar interstitium. Similar findings were reported by Kaber et al., in which COVID-19 autopsies revealed the extensive occlusion of airway spaces filled with poorly organized polymeric material that stained robustly for HA [21]. They also observed that sputum HA, particularly low-molecular weight HA (LMW-HA), was increased ~20-fold in COVID-19 samples as compared to healthy control samples. Consistently, the critical group of COVID-19 cases had significantly higher serum levels of HA [22] and patients infected with SARS-CoV-2 had higher levels of HA in plasma and lung tissue [23]. One systematic study of COVID-19 autopsies revealed that the average lung weight was ~3.2 times normal and, in an extreme case, 4.6 times normal [24]. These “heavy lungs” may be a direct result of the overproduction of HA and its ability to absorb 1000 times its molecular weight in water [17]. Mechanistically, over-produced HA may quickly induce an accumulation of water in the airspace and perivascular interstitium, causing sudden fatal hypoxia and death in critical COVID-19 [24]. Together, the over-production of HA and subsequent absorption of water are referred to as an induced-hyaluronan storm [24]. We will hereafter use the term hyaluronan storm to describe this phenomenon.

Another significant pathologic change of ARDS in COVID-19 is the formation of dysregulated neutrophil extracellular traps (NETs) in the blood and lower respiratory tract of critically ill patients [25]. NETs are a recently identified neutrophil effector mechanism in which neutrophils contain and kill microbial organisms through the externalization of a meshwork of chromatin fibers, together with granule-derived antimicrobial proteins [26]. In severe COVID-19, neutrophil infiltration of the lungs leads to increased NET formation and contributes to microthrombosis/coagulopathy and COVID-19-related ARDS [18, 27].

A prevailing concept is that a primary cause of death from COVID-19 is due to a hyperactive inflammatory response, characterized by the overproduction of proinflammatory cytokines such as TNF, IL-6, IL-1β, IL-1β, IL-12/IL-23p40, IL-10, and IL-8 [28]. A presumed cytokine storm evokes the consideration of anti-cytokine therapy; specifically, IL-6 receptor (IL-6R) antagonists, in clinical trials for COVID-19. However, a comparison of COVID-19 with other severe diseases demonstrated that the levels of IL-6 were far less than those seen in other inflammatory syndromes, such as sepsis [29]. The nature of the immune dysfunction in severe COVID-19 does not resemble a standard cytokine storm response, as compared to other diseases [29]. Recent reports have indicated that the levels of proinflammatory cytokines seen in COVID-19 are usually no higher, and often lower, than those in other inflammatory syndromes [30, 31]. Finally, the lack of convincing clinical benefits from COVID-19 clinical trials of anti-IL6R inhibitor monoclonal antibodies [32, 33] indicated a minor role for IL-6, a critical cytokine typically associated with a cytokine storm. However, IL-6, together with IL-8, and TNF-α are good biomarkers for severe COVID-19 [28, 34]. In particular, IL-8 seems to serve as a more accurate COVID-19 disease biomarker than IL-6 [28, 35]. While it is not as high as in sepsis [30], the levels of IL-8 are significantly higher in the sera of COVID-19 patients, as compared to sera from healthy people [36–39] or those infected with influenza [28]. Furthermore, the prognostic value of IL-8 for COVID-19 fatalities was suggested by two different groups [40, 41]. Finally, IL-8 is a major chemoattractant for neutrophils and seems to be involved in NETs formation as described later.

On the other hand, indications of immunosuppression are becoming evident in COVID-19 patients. Remy et al. performed ELISPOT functional assays to evaluate the innate and acquired immunities in COVID-19 cases and found that the major immunologic abnormality in COVID-19 is a profound defect in host immunity. They detected a decrease in the number of functional T-cells and the lower expression of critical cytokines from mononuclear cells, thus indicating a decrease in both the quality and quantity of the immune response in severe COVID-19 [42]. Moreover, poor outcomes in COVID-19 patients are correlated with increases in both Treg proportions and intracellular levels of...
Glutamine is the most abundant amino acid in the blood, and is released mainly from skeletal muscles and transported to a variety of tissues [48]. Although most tissues can synthesize glutamine, during periods of stress the demand outpaces the supply, and the expression levels of glutamine transporters on plasma membranes become critical [48]. Two principal enzymes regulate intracellular glutamine metabolism. Glutamine synthetase (GS) catalyzes the synthesis of glutamine from glutamate, while glutaminase (GLS) catalyzes the synthesis of glutamine from glutamate, during periods of stress the demand outpaces the supply, and the expression levels of glutamine transporters on plasma membranes become critical [48]. Two principal enzymes regulating intracellular glutamine metabolism. Glutamine synthetase (GS) catalyzes the synthesis of glutamine from glutamate, while glutaminase (GLS) catalyzes glutaminolysis. In the following sections, we describe how a comorbidity-associated glutamine deficiency worsens these conditions in severe COVID-19.

**PLEIOTROPIC ACTIVITIES OF GLUTAMINE**

**Glutamine**

- L-Glutamine is the most abundant amino acid in the blood, and is released mainly from skeletal muscles and transported to a variety of tissues [48]. Although most tissues can synthesize glutamine, during periods of stress the demand outpaces the supply, and the expression levels of glutamine transporters on plasma membranes become critical [48]. Two principal enzymes regulate intracellular glutamine metabolism. Glutamine synthetase (GS) catalyzes the synthesis of glutamine from glutamate, while glutaminase (GLS) catalyzes glutaminolysis. In the following sections, we describe how a comorbidity-associated glutamine deficiency worsens these conditions in severe COVID-19.

**Aging**

- Opposing results [65–68] have been the result of changes in the mitochondrial status, and migration markers [44]. Agrati et al. reported another type of immunosuppression in severe COVID-19 [38]. They found the expansion of MDSCs (myeloid-derived suppressor cells) in the blood, associated with disease severity, as well as suppressed T-cell functions. Of the three subsets of MDSCs, increased proportions of G-MDSCs [37, 38], M-MDSCs [45], or both [46, 47] were closely associated with the disease severity.

COVID-19 appears to be a combination of a hyperinflammatory response due to the overproduction of inflammatory cytokines, immunosuppression due to the increased levels of Tregs and MDSCs, and respiratory distress produced by a hyaluronic storm and NETs. In the following sections, we describe how a comorbidity-associated glutamine deficiency worsens these conditions in severe COVID-19.

Glutamine is also used for the synthesis of glutathione (GSH), the major endogenous antioxidant molecule in mitochondria [52] and the nucleus [53], which consists of glutamine-derived glutamate, cysteine, and glycine (Fig. 1). Cells are exposed to oxidative stress not only during nutrient starvation and catabolic stresses after trauma, surgery, sepsis, or infection, but also during active cell proliferation [54]. As glutamate represents the first important step in the synthesis of GSH intermediate compounds, intracellular glutamine availability is the key to GSH synthesis.
In turn, glutamine deprivation results in increased reactive oxygen species (ROS) levels through decreased GSH [55].

**NAD⁺**

Glutamine is an important nitrogen donor for the production of NAD⁺, in the last steps of both the de novo (from dietary tryptophan) and Preiss-Handler (from dietary niacin) pathways [56] (Fig. 2). NAD⁺ is an essential coenzyme and substrate for metabolism. Although NAD⁺ is also produced through salvage pathways from nicotinamide (NAM) and nicotinamide riboside (NR) precursors [56], people with ultra-rare inborn errors in the glutamine synthetase gene exhibit severe secondary NAD⁺ deficiency [57], indicating that the glutamine supply for both the de novo synthesis and Preiss-Handler pathways is indispensable for NAD⁺ synthesis (Fig. 2).

In addition, the age-associated dysfunction of enzymes in NAD⁺ production, such as QPRT (quinolinate phosphoribosyl transferase) [58] in the de novo pathway, may be a reason why elderly persons are more susceptible to severe COVID-19. Minhas et al. reported that aged human macrophages had lower QPRT expression that was associated with an induction of upstream KP (kynurenine pathway) metabolites culminating in the accumulation of QA (quinolinic acid), but decreased production of the downstream metabolites NAMN (nicotinic acid mononucleotide), NAAD (nicotinic acid dinucleotide), and NAD⁺ [58] (Fig. 2). Reduced expression of QPRT was found in several lung cell lines infected with SARS-CoV-2 [59], suggesting that the dysfunction of QPRT expression and reduction of NAD⁺ may be exacerbated in COVID-19. Other mechanisms for the age-related reduction of NAD⁺ could result from increases in NAD⁺-consuming enzymes (NADases). NADases include SIRTs (sirtuins) and CD38, and in particular, CD38 is activated in the elderly population [60]. NAD⁺ deficiency is shared amongst the comorbidities of COVID-19 (Table 1) and thus potentially represents a critical component of the disease.

**HBP AND HYALURONAN**

HA is a glycosaminoglycan component of the ECM and presents at high concentrations in the lung. It has important roles in water homeostasis, cell-matrix signaling, tissue healing, inflammation, angiogenesis, and cell migration [61]. As HA is exclusively produced through the hexosamine biosynthetic pathway (HBP) [62] (Fig. 3), understanding this pathway is crucial for treating the hyaluronan storm in severe COVID-19. The HBP utilizes 2–5% of the glucose that enters cells, and after the first two steps of glycolysis, the resultant fructose-6-phosphate (F6P) is catabolized with the rate-limiting enzyme glutamine-fructose-6-phosphate amidotransferase (GFAT), which transfers the amino group from glutamine to produce glucosamine-6-phosphate (GlcN-6P) and glutamate [62]. The HBP is regarded as a nutrient sensor since the end product is UDP-GlcNAc, which is composed of substrates derived from the metabolism of amino acids (glutamine), nucleotides (uridine), carbohydrates (glucose), and fatty acids (acetyl-CoA) [62]. The UDP-GlcNAc substrate is used in a wide variety of cellular processes, such as N-glycosylation, N-glycan...
The most common physiological size of the HA polymer in tissues is about 0.5–2 MDa [66], corresponding to high molecular weight HA (HMW-HA). HMW-HA has viscoelastic and anti-inflammatory properties and is a ligand of CD44. Smaller HA polymers of less than 0.5 MDa are known as low molecular weight HA (LMW-HA), and are usually generated during HA turnover but can also accumulate at sites of inflammation with hyaluronidase, oxidative stress, and/or hypoxia [67]. Generally, LMW-HA is regarded as a proinflammatory factor. Numerous studies have demonstrated the pathological function of LMW-HA in human respiratory diseases, including ARDS [67].

CONSEQUENCES OF GLUTAMINE DEFICIENCY AND COVID-19

COVID-19 high-risk groups, such as the elderly, diabetics, obese people, and those with cardiovascular disease, share a background of low glutamine and enhanced HBP activation [68–71]. As mentioned previously, GFAT is a rate-limiting enzyme for HBP (Fig. 3), and a direct transcriptional target of ATF4 (the activating transcription factor 4) [72], which is activated by glutamine deprivation [73]. In addition, the high risk groups tend to show glucose intolerance [74–76], which will cause high glucose flux to the uronic acid pathway as well as HBP (Fig. 3), producing the substrates UDP-GlcUA and UDP-GlcNac, respectively, for HA synthesis. Therefore, the combination of low glutamine and high glucose levels could predispose the high-risk groups to produce pathological amounts of HA.

As the role of glutamine in the immune system is broad, here we focus on its functions in neutrophils for NETs formation (NETosis), the development of myeloid-derived suppressor cells (MDCs), and the differentiation into Foxp3+ Treg cells, which are all involved in the pathogenesis of severe COVID-19.

NETosis

Neutrophilia is common in COVID-19, and the neutrophil/lymphocyte ratio (NLR) is higher in critical patients as compared to moderately ill or healthy persons [36]. In fact, neutrophilia is
intimately associated with NETosis [41]. The major chemoattractant of neutrophils, IL-8, is clearly involved not only in the recruitment of neutrophils but also in the induction of NETosis [77]. One of the stimuli for IL-8 secretion from lung cells is possibly UDP-glucose, a product of the glucuronic pathway (Fig. 3) and a type of danger signal [78] released from the infected cells. Adjacent lung cells are then stimulated through P2RY14 to secrete IL-8, which acts as a chemo-attractant for neutrophils [79]. It is also possible that UDP-glucose directly stimulates the P2RY14 expressed on neutrophils to attract them to the site of infection [79, 80]. Recruited neutrophils sometimes control infection by the production of NETs. Ouwendijk et al. suggested that regulated NETs formation may defend hosts against SARS-CoV-2 infection in asymptomatic or mild cases, but additional factors may lead to excessive NETs production and lung obstruction [25]. Comorbidity-associated glutamine deficiency may be one of the factors contributing to pathologic NETs production, as glutamine impaired the chemotactic migration of neutrophils to infection sites in an animal model [81], and glutamine deprivation induced the expression of IL-8 [82, 83]. Therefore, it is possible that glutamine limits the production of MDSCs indirectly, through inhibiting CRP production.

**Tregs**

Glutamine also contributes to CD4⁺ T cell differentiation. Upon glutamine restriction, CD4⁺ T cells differentiated into FoxP3⁺ Treg cells despite the presence of Th1-directing cytokines [51, 91]. A decrease in the intracellular amount of glutamine-derived α-KG shifted the balance of Th1 and Treg cells toward that of a Treg phenotype [51]. The altered profile of Tregs in severe COVID-19 [43, 44] may result from low glutamine levels and the resultant α-KG deficiency. The consequences of this immunosuppression are thus widespread, and some of the likely targets may be the tissue-resident immune cells, such as alveolar macrophages, MAIT (Mucosal associated invariant T) cells and γδ T cells [92–95]. COVID-19 exhibits a wide range of the combination of hyperinflammation and immunosuppression. As these immunological perturbations can be explained as consequences of glutamine deficiency, it is advantageous to maintain appropriate glutamine levels for COVID-19 prevention and treatment. Interestingly, malnutrition is linked to higher serum HA levels [96]. Furthermore, the long-term effects of malnutrition predispose patients to severe COVID-19 in an age-dependent manner [97], and are associated with hyperinflammation and immunosuppression [98]. How malnutrition affects glutamine levels remains to be determined.

**GLUTAMINE DEFICIENCY AT THE CROSSROADS OF COVID-19 AND ITS COMORBIDITIES**

Based on the above considerations, we now provide an overview of the pathophysiology of COVID-19 in terms of comorbidity-associated glutamine deficiency (Fig. 4).

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**Fig. 3 HBP and hyaluronan.** Schematic representation of metabolic pathways that lead to the production of substrates for the HAS2 enzyme, UDP-GlcUA and UDP-GlcNAc. The monomer unit of HA is shown. LMW-HA activates PAI-1 and promotes a hyaluronan storm. HMW-HA contributes to immunosuppression. UDP-Glc is released from the infected cells and serves as a danger signal to neighboring cells, resulting in NETs formation. Glc-6P glucose-6-phosphate, UDP-Glc uridine diphosphate glucose, UDP-GlcUA uridine diphosphate glucuronic acid, F-6P fructose-6-phosphate, GlcN-6P glucosamine 6-phosphate, UDP-GlcNAc uridine 5'-diphospho-N-acetylglucosamine, GFAT glutamine-fructose-6-phosphate transaminase, HAS2 hyaluronan synthase 2, HA hyaluronan.
Before the infection, comorbidity-associated glutamine deficiency (1) and comorbidity-associated NAD\(^+\) deficiency (2) lead to low \(\alpha\)-KG (4) and impaired SIRT1 activity (3), respectively. These metabolic changes initiate the hyperproduction of HA and PAI-1, and immunodeficiency. After SARS-CoV-2 infection, STAT3 is activated through the EGFR pathway (5) and the extracellular UDP-Glucose-stimulated P2RY14 pathway (6). Activated STAT3 can induce the transcription of HAS2 (7). The HAS2 enzyme is stabilized by O-GlcNAcylation, and HA is produced (8). In addition, a critical HAS2 negative regulator, SIRT1 (3), is neutralized by SARS-CoV-2 infection and low NAD\(^+\) levels. This results in increased HAS2 activity and higher HA levels, and contributes to a hyaluronan storm. LMW-HA derived from excess HA production stimulates the production of PAI-1 (9), and PAI-1 indirectly activates STAT3 (10) leading to coagulopathy. Danger signals, such as UDP-glucose, activate the innate immune responses and the formation of NETs (NETosis), thus exacerbating the coagulopathy. Glutamine deficiency during the infection leads to immunosuppression through the increase in the populations of systemic Ti-Tregs (tumor-infiltrating-like Tregs) (11) and MDSCs (12). Ti-Tregs are increased by the over-production of HMW-HA. Details of these events are described in the main text.

SARS-CoV-2 ORF6 binds the nuclear pore complex, NUP98/Rae1, and inhibits STAT1 translocation to the nucleus [100]. SARS-CoV-2 NSP1 protein blocks STAT1 phosphorylation and nuclear translocation but also efficiently blocks IFN-\(\iota\) induction [101]. STAT3 is compensatorily activated through the EGFR pathway [2] (5, Fig. 4). In addition, P2RY14 can activate STAT3 by the extracellular UDP-Glucose released from damaged cells [102] (6, Fig. 4).

Activated STAT3 induces the transcription of HAS2 (7, Fig. 4) [2, 102], and the membrane-bound HAS2 enzyme is stabilized by O-GlcNAcylation as it produces HA (8, Fig. 4). In addition, SIRT1, a critical negative regulator of the HAS2 gene, is disabled (3, Fig. 4) due to low levels of its substrate NAD\(^+\) under conditions of low glutamine and aging. Furthermore, SARS-CoV-2 significantly decreased the SIRT1 expression in the PBMCs and lung tissue of infected patients [39, 103]. Therefore, SIRT1’s anti-HAS2 activity is neutralized in two distinct manners, leading to increased HAS2 activity and higher HA levels.

The LMW-HA derived from excessive HA production stimulates the production of PAI-1 (9, Fig. 4), which indirectly activates STAT3 (10, Fig. 4) [2]. Consequently, a positive feedback loop between activated STAT3 and PAI-1 is established. A hyaluronan storm is evoked by the combination of decreased negative regulation by SIRT1 and activation of HAS2 by STAT3 and O-GlcNAcylation.

Another complication in severe COVID-19 is coagulopathy, in which PAI-1, as well as NETs formation (NETosis), are involved. Neutrophils are recruited to the site of infection through the innate immune response to danger signals like UDP-glucose, and they use NETosis as a tactic to combat infection. Aggregated NETs-induced vessel occlusion was observed in the lungs, glomeruli, and hepatic periportal fields in the autopsied specimens, implicating NETs aggregation in the multi-organ damage by COVID-19 [104].

SARS-CoV-2 infection exacerbates the glutamine deficiency that leads to immunosuppression through increases in the systemic FoxP3\(^+\) Treg (11, Fig. 4) and MDSC populations (12, Fig. 4). Consistent with these findings, considerable associations with co-infections (other infections upon the diagnosis of COVID-19) and/or superinfection (other infections following COVID-19) have been reported in severe COVID-19 [105, 106]. Galvan-Pena et al. found...
that FoxP3+ Tregs from COVID-19 patients had a similar gene expression pattern to tumor-infiltrating Tregs ([11, Fig. 4]), which are known to suppress local antitumor responses ([43]). Interestingly, in a murine model, tumor-infiltrating FoxP3+ Tregs acquired elevated levels of CD44, an HA receptor expressed on activated and memory Tregs ([107]). CD44 is stimulated by HMW-HA to promote Treg persistence and function ([108]). Therefore, in the presence of HA overproduction, HMW-HA stimulates FoxP3+ Tregs. Conversely, LMW-HA has proinflammatory effects, including the induction of PAI-1. In this regard, M-DCs are possibly involved in the production of LMW-HA. One report stated that tumor-infiltrating M-DCs express hyaluronidase 2, which degrades HMW-HA in the ECM to generate proinflammatory LMW-HA ([109]). The distinct immunological natures of COVID-19-associated M-DCs and tumor-infiltrating M-DCs continue to be examined.

The metabolic environment of low glutamine is present in both comorbidities and upon SARS-CoV-2 infection itself. The enhanced metabolic dysfunction occurs in a background of immunosuppression that exacerbates the pathologies of NETosis, coagulopathy, and the hyaluronan storm.

**SIMILARITIES BETWEEN SEVERE COVID-19 AND ADVANCED CANCER**

Severe COVID-19 and advanced cancer share common aspects of their pathologies. Recently, Nan et al. performed a protein-protein network analysis between COVID-19 and lung cancer databases and identified 10 common hub genes associated with both diseases. The genes encoding proteins that potentially share a common hub of biological activity were ALB (albumin), IL-8, FGFR2, IL-6, INS (insulin), MMP2, MMP9, PTGS2 (Prostaglandin-Endoperoxide Synthase 2), VEGFA and STAT3 ([110]). Significantly, half of these genes are downstream targets (IL-8, MMP2, MMP9, PTGS2, and VEGFA), and three are upstream regulators (FGF2, INS, and IL-6) of STAT3. These results are consistent with our proposal that STAT3 plays a central role in the severe pathologies of COVID-19 and that commonalities exist in the pathogenesis of advanced cancer and COVID-19 ([2]). One of the hallmarks in cancer is the Warburg effect, or aerobic glycolysis. It is well established in a variety of cancers ([111] and recently identified in SARS-CoV-2-infected cells ([112]). The widely-applied cancer detection method, the PET (positron emission tomography) scan, was developed based on the Warburg effect, and incidental detections of PET/CT positive SARS-CoV-2-infected lesions in cancer patients have been reported ([113]), indicating the increased glycolysis in infected cells. This Warburg effect in COVID-19 may be the result of activated STAT3, as STAT3 is involved in the Warburg effect ([114]) and activated in infected alveolar epithelial cells ([3]). The cited similarities of COVID-19 with cancer-related biological signatures such as the Warburg effect and the involvement of PAI-1, HA, Tregs, and EGFR, are shown in Table 2. Glutamine levels linked to COVID-19 and cancer are also listed, although the range of effects are limited. However, in colorectal cancer, low levels of serum glutamine and other amino acids abnormalities were associated with advanced cancer stages and poor prognosis ([115]).

From these similarities, we can envisage that severe COVID-19 is a cancer-like metabolic disorder, but one that develops immediately after SARS-CoV-2 infection in high-risk individuals who suffer from at least one of multiple metabolic disorders with low glutamine levels. We propose repurposing the following drugs, which are mostly used in cancer therapy, because of the similarities in the pathophysiology of COVID-19 and advanced cancer. As described later, serum/plasma HA is upregulated in all high-risk groups analyzed, including cancer. Here, we primarily focus on the drugs that regulate HA production. As such, the proposed drugs are categorized into two targets: I. Drugs targeting hyaluronan, II: Drugs targeting STAT3.

**I. DRUGS TARGETING HYALURONAN**

**Anti-diabetic measures**

To prevent and treat severe COVID-19, the first priority is to control glucose levels. Chen et al. reported that severe COVID-19 was associated with higher blood glucose (WMD 2.21, 95% CI:1.30–3.13, P < 0.001) ([116]), and elevated glucose levels favor SARS-CoV-2 infection in vitro ([117]). Logetti et al. found evidence linking elevated glucose to each major step of the lifecycle of the virus, progression of the disease, and presentation of symptoms, after systematically retracted the steps of the SARS-CoV-2 infection ([118]). However, an extreme reduction of glucose levels that leads to compensatorily activated HBP ([119]) should be avoided, and consultations with diabetes-specialized doctors are required.

**Glutamine**

Glutamine has anti-diabetic activities that help to reduce the glucose input into the uronic acid pathway and HBP. Studies have revealed that glutamine supplementation can lead to a decrease in the levels of fasting blood glucose and postprandial glucose, and an increase in insulin production ([120]). Glutamine

![Table 2. Similarities between COVID-19 and advanced cancer.](image-url)
supplementation also resulted in higher levels of glucagon-like peptide-1 (GLP-1), a gut hormone known to increase insulin levels [120].

Prophylactic glutamine supplementation is recommended to those in high-risk groups; however, glutamine supplementation after the infection should be carefully considered. Glutamine supplementation may favor SARS-CoV-2 proliferation [121], although metabolomic analyses revealed that glutamine levels are relatively low [8–12]. In addition, small clinical trials showed that glutamine reduced the severity after infection in standard risk COVID-19 patients [122, 123]; however, these preliminary findings need to be expanded to confidently assess glutamine supplementation in treating COVID-19. Compared to the beneficial effects of glutamine, its adverse side effects are minimal. Risk assessments of glutamine supplements indicated that they are safe for healthy individuals in amounts up to 14 g per day [124]. There are rare contraindications to glutamine supplementation and caution should be exercised with patients with high plasma glutamine levels or acute hepatic insufficiency, and/or renal failure [125, 126]. However, in 2013, a randomized clinical trial study, REDOXS, showed that glutamine use in critically ill patients was associated with increased mortality, with no beneficial effects [127]. Although the authors used higher doses of glutamine (giving around 1 gram/kg/day) than recommended and included patients that fulfilled the contraindication criteria for its supplementation [126, 128], these results shifted the guidelines to downgrade the use of glutamine in critically ill patients. However, glutamine supplementation has been widely used in critical care situations [126, 128]. Clearly, the effects of long term use of high-dose glutamine supplementation need to be carefully determined.

### Dexamethasone

Dexamethasone showed some success in treating COVID-19 [129]. This empirical effect can be attributed to its glutamine synthetase promoting activity [130], and/or inhibition of HAS2 [131]. However, its significant immunosuppressive activity could compound the already existing immunosuppressed state in severe COVID-19, thus posing a higher risk of secondary infections and/or reactivation of quiescent infections such as tuberculosis [132].

**4-MU (4-Methylumbelliferone)**

Besides dexamethasone, 4-MU also has anti-HAS2 activity [133, 134] and therefore inhibits the production of HA. Last year, Shi et al. proposed the application of 4-MU to treat the hyaluronic storm in COVID-19 [17]. Similar proposals were made by other groups after identifying abundant HA in the infected alveoli of severe COVID-19 cases [20, 21]. 4-MU has been used for more than 20 years in humans to treat biliary spasms in France, Germany, Japan, and other countries [135]. Recently, the involvement of HA in cancer progression has become increasingly appreciated (Table 2) and 4-MU has become a promising anti-cancer agent [135]. 4-MU is a well-tolerated oral drug, and in one clinical trial, prolonged (3 months) oral doses as high as 2400 mg/day were safely administered [135]. Recently, a clinical trial using high doses (up to 3600 mg/day) of 4-MU to block HA production has begun [136]. Positive results of this trial will justify the use of 4-MU in COVID-19.

**NAD+ boosting drugs (Niacin, NR, NMN)**

Increasing NAD+ levels with NAD+ boosting agents in high-risk people could be associated with a range of beneficial effects, and the application of NAD+ boosting drugs in COVID-19 has been proposed by several groups [137, 138]. Using a mouse-adapted SARS-CoV-2 model, Jiang et al. reported that a global gene expression analysis of the infected mouse lungs revealed the dysregulation of genes associated with NAD+ metabolism, correlating with the results from COVID-19 patients [139]. They found that the pneumonia phenotypes, including excessive inflammatory cell infiltration and embolization in SARS-CoV-2-infected murine lungs, were significantly rescued with an intraperitoneal injection of NAD+ [139]. In addition, recently developed first-in-class drug for diabetes, imeglimin, has been reported to enhance glucose-stimulated ATP generation and induce the synthesis of NAD+ [140]. One concern is that during the infection, NAD+ boosters cannot completely restore SIRT1’s anti-HAS2 activity, as the expression of SIRT1 is critically impaired in severe COVID-19 [39, 103]. Therefore, NAD+ boosters would be effective for the prevention of COVID-19 or immediately after the infection with SARS-CoV-2.

**Vitamin D**

1,25 Dihydroxyvitamin D (vitamin D) reportedly inhibits HAS2 expression [141]. However, it also suppresses glutamine metabolism [142], indicating a possible reduction of α-KG that may result in high FoxP3+ Treg differentiation.

## II. DRUGS TARGETING STAT3

### STAT1 activators

The SARS-CoV-2 virus has mechanisms to inhibit the activity of STAT1, which initiates a cascade of deleterious events, including the activation of STAT3 [2]. Therefore, STAT1 activators will have the effect of inhibiting STAT3. Like interferons, retinoids increase STAT1 expression, up-regulate its phosphorylation, and enhance its translocation to the nucleus [143]. Retinoids inhibit infections by measles, norovirus, and HCV through IFN-I signaling in several ways [144]. A recent report showed that the retinoid inducible gene-I (RIG-I) had dramatic antiviral activity in an in vitro model of SARS-CoV-2 infection [145]. It is important to carefully modulate IFN inducing signaling in COVID-19 because it may worsen the disease in the late stages of infection [2].

### STAT3 inhibitors

Besides the use of the STAT3 targeting drugs, Danvatirsen and Napabucasin [2], the regulation of the upstream signaling molecules is also important. Wang et al. reported that, in A549 cells, decreased NAD+ inactivated SIRT1, resulting in increased STAT3 acetylation and phosphorylation, and STAT3 activation. Repletion of nicotinamide or nicotinic acid inactivated STAT3 [146]. However, as mentioned above, we cannot expect the full restoration of SIRT1 activity by NAD+ boosters, as SIRT1 expression is inhibited by SARS-CoV-2 infection. We should also keep in mind that glutamine has been reported as a STAT3 activator in some cancer cell lines [84, 147], whereas others found that glutamine has STAT3 inhibiting activity [83, 148].

### EGFR inhibitors

EGFR signaling is upregulated in SARS-CoV-2-infected cells in vitro [149, 150], and we believe that this signaling is responsible for maintaining the STAT3 activity in severe COVID-19 [2]. Repurposing drugs targeting EGFR, such as Erlotinib, Gefitinib, Cetuximab, and others, are already used in some cancer therapies. The major concern is that these treatments often cause severe interstitial pneumonia that resembles pneumonia in COVID-19, and will thus make a differential diagnosis more difficult [151].

### Immune checkpoint inhibitors (ICIs)

A hallmark of COVID-19 is lymphopenia, and efforts have been made to restore T-cell competency by ICIs. In fact, immune checkpoint proteins may be connected to other types of immunosuppression seen in COVID-19. Glutamine deficiency increases the expression of PD-L1 [152], which is known to be activated by STAT3 [153], and biopsy results indicated increased PD-L1 expression in the infected lung tissue of COVID-19 patients [3]. Several groups are exploring anti-PD-L1 and anti-CTLA-4 inhibitors.
antibodies, alone or in combination with anti-IL-6R, and clinical trials are underway [154].

In this review, we have focused on the major risk factors of COVID-19 that are: aging, hypertension, cardiovascular disease, diabetes, and obesity [1]. These major risk factors generally exhibited a normal level of serum HA [163], however, CF sputum HA levels, on the other hand, are consistently elevated in plasma/sputum of risk groups such as chronic lung disease (COPD [156], interstitial pneumonia [157], asthma [158]), chronic kidney disease [159], stroke [160, 161], and chronic liver disease [162]. CF exhibited a normal level of serum HA [163], however, CF sputum had 20-fold excess of HA than healthy controls [21]. Similarly, asthma [164], and COPD [165] had elevated levels of sputum HA. Therefore, irrespective of glutamine levels, any disease leading to increased HA production may have a predisposition to severe COVID-19. Thus, we may have identified a common mechanism in high-risk groups that confers more susceptibility to severe COVID-19. We suggest a simple nutritional supplementation that could neutralize this susceptibility and restrict the disease to common cold-like symptoms. Glutamine deficiency and HA overproduction appear to be the primary metabolic commonalities that not only are shared amongst the COVID-19 comorbidities, but also contribute to the immunological dysfunction that is exacerbated by SARS-CoV-2 infection. While it is presently unclear whether glutamine supplementation post-infection leads to an overall positive outcome, addressing glutamine deficiency prophylactically for those in high-risk groups is a safe and simple strategy for their protection in the era of COVID-19.

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We would like to thank Brenda Guthrie Yoshinaga (Skybay Scientific Editing) for editing of the manuscript. We thank Masaru Taniguchi (Riken Institute), Ryuichi Sakanishi for providing updated information on COVID-19.

ACKNOWLEDGEMENTS

Matsuyama T, Matsuoka et al.
AUTHOR CONTRIBUTIONS
All authors contributed equally in edition and proofreading of the manuscript. TM, SKY and KS wrote the manuscript and TM and SKY prepared the figures. TWM provided critical analysis and overall guidance of the science.

COMPETING INTERESTS
The authors declare no competing interests.

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