Immunogenetic Association Underlying Severe COVID19

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Abstract: SARS-CoV2 has caused the current pandemic of new coronavirus disease 2019 (COVID-19) worldwide. Clinical outcomes of COVID-19 illness ranges broadly from asymptotic and mild to a life-threatening situation. This casts uncertainties for defining host determinants underlying the disease severity. Recent genetic analyses based on extensive clinical sample cohorts using genome-wide association studies (GWAS) and high throughput sequencing curation revealed genetic errors and gene loci associated with about 20% of life-threatening COVID-19 cases. Significantly, most of these critical genetic loci are enriched in two immune signaling pathways, i.e., interferon-mediated antiviral signaling and chemokine-mediated/inflammatory signaling. In line with these genetic profiling studies, the broad spectrum of COVID-19 illness could be explained by immuno-pathological regulation of these critical immunogenetic pathways through various epigenetic mechanisms, which further interconnect to other vital components such as those in the renin–angiotensin–aldosterone system (RAAS) because of its direct interaction with the virus causing COVID-19. Together, key genes unraveled by genetic profiling may provide targets for precisely early risk diagnosis and prophylactic design to relieve severe COVID-19. The confounding epigenetic mechanisms may be key to understand the clinical broadness of COVID-19 illness.

36 **1.   The broad spectrum and critical illness in COVID-19 progression**

37   The coronavirus disease 2019 (COVID-19), which has been declared being a
38   worldwide pandemic by the WHO since the March of 2020, is caused by the novel
39   coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1-4]. The
40   virus evolves highly contagious in human beings with a basic reproduction number
41   (R0) ranging at 1.4-5.7. The clinical outcome of COVID-19 varies broadly among
42   infected people ranging from asymptotic infection and common cold-like sickness to a
43   severe pneumonia leading to acute respiratory distress syndrome (ARS) and multi-
44   organ complications that potentially have fatal prognosis [5-8]. Complications of
45   severe COVID-19 include vasculitis, coagulopathy, thrombosis, septic shock, and even
46   multi-organ failure [5-8]. The epidemiology of COVID-19 shows a diverse pattern
47   across people who are different in age, sex, ethnicity, and particularly pre-existing
48   medical conditions [6-11]. For example, the US statistics showed that older patients
49   (aged ≥65 years) accounted for 31% of all cases, 45% of hospitalizations, 53%
50   admissions of intensive care unit (ICU), and 80% of deaths, with the highest incidence
51   of severe outcomes in patients aged ≥85 years [1,4,8]. Similarly, increased risk of
52   critical and life-threatening illnesses were reported to associate with males and
53   particularly pre-existing comorbidities, including cardiovascular, renal, liver,
54   diabetes, and other autoimmune diseases as well as obesity condition [4-11]. In
55   contrast, evidence indicates that children (median age 4-7 years) have a lower
56   susceptibility and risk for critical illness. However, under the circumstance of
57   comorbidity and genetic risks, the disparity of the risk for severe COVID-19 becomes
58   vague concerning the factors of age, sex, and ethnicity [4-11]. Per a critical viral
59   disease like COVID-19, illness comes from both the virus infection and interacting
60   with immune responses, especially consequential imbalance of harmful
61   immunopathies over proper immune responses. Upon exposure to the same virus,
62   whereas individuals show asymptotic or mild illness plausibly mounting effective
63   immune reactions, severe COVID-19 patients, however, may reflect dysfunctional
64   immune reactions that further leads to pathological exacerbation accompanying
65   uncontrolled virus spreading and immune overwhelming [9-17]. As the virological
66   branch focuses on diminishing viral spreading and virulence to cause disease,
67   deciphering the genetic and especially epigenetic associations underlie severe
68   COVID-19 will grasp the immunogenetic theme for severity prognosis in the host,
69   thus provide manageable targets for early risk diagnosis and development of
70   prophylactic and therapeutic remedies to face current pandemic [18-20].

71

72 **2.   Genetic association: Interferon and chemokine response representing the centric**
73   **immune determinants underlying severe COVID-19**

74   About two months post the WHO declared the COVID-19 pandemic, a global
75   initiative of COVID-19 Host Genetics was commenced to elucidate the role of host
76   genetic factors in SARS-CoV2 susceptibility and COVID-19 severity [21]. The first
77   report about genome-wide association study (GWAS) of severe COVID-19 with ARS
78   detected two genetic susceptibility loci at Chr3p21.31 and Chr9q34.2 using a meta-
79   analysis of the two case/control panels including 835/1225 and 775/950 samples from
80   Italy and Spain, respectively (Table 1) [22]. Significantly, the association within the
81   locus Chr3p21.31 spans the genes SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, XCR1,
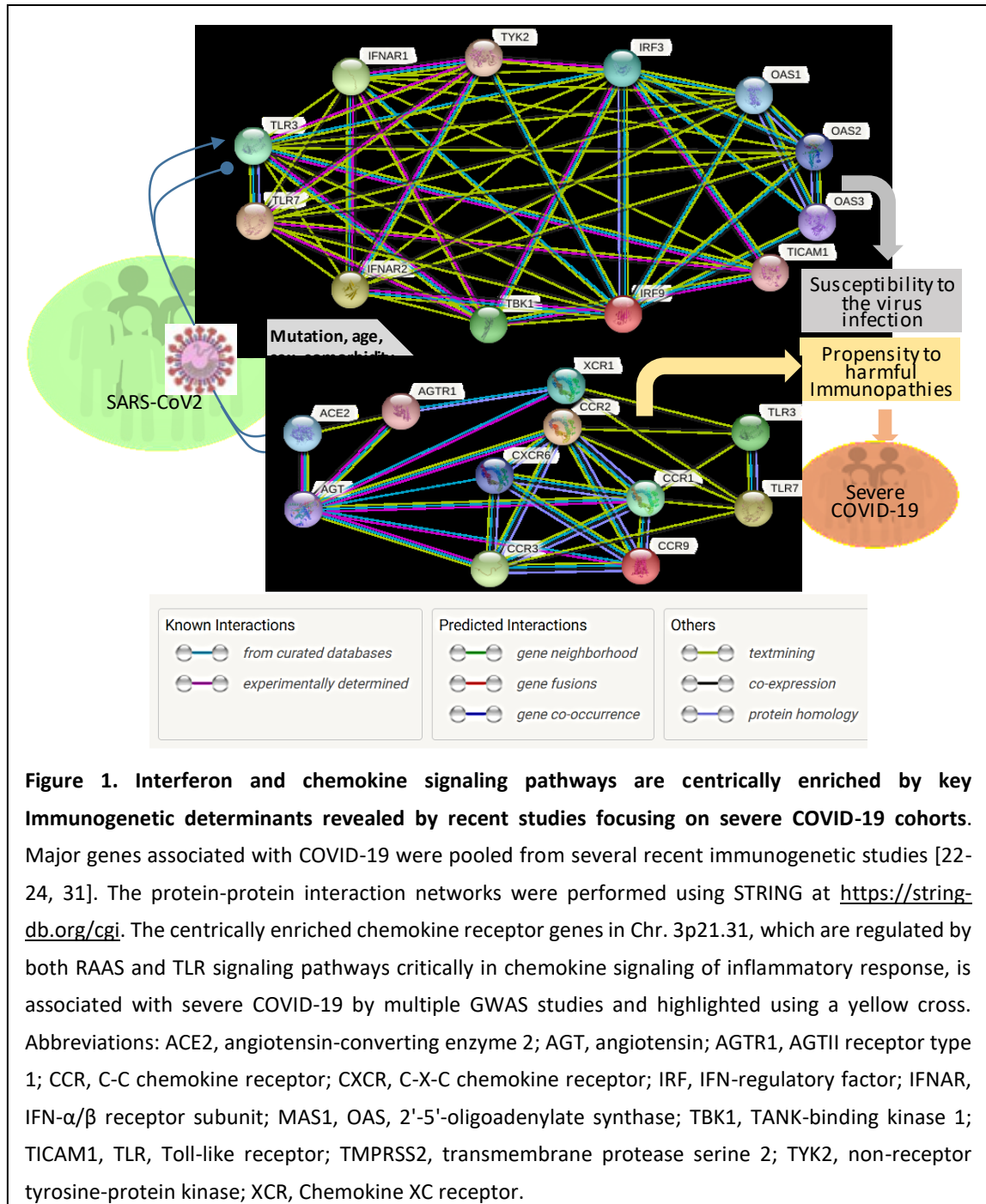
Table 1. Genetic inborn or epigenetic obtaining errors associated with severe COVID-19*

Chr. Location (Key genes covered, or epigenetic effect)	Association (Appr./OR: Freq.)	Major immune pathway involved	References & Notes
3p21.31 (SLC6A20, LZTFL1, FYCO1, CXCR6, XCR1, and CCR9; Neanderthal-originated allelic region)	GWAS 95% CI/ (1.95-2.79: 1610 vs. 2205)[22] (2.14: 2244 vs. ~5X 2244)[23]	ACE2 mediated amino acid transport (SLC6A20); Chemokine and Inflammation signaling, chemotaxis, immunopathies for lung injury (others)	Associated at [22-24]
6p22.1-33 (HLA-G, CCHCR1, NOTCH4)	GWAS 95% CI/ (1.30-1.85: 2244 vs. ~5X 2244)	Antigen processing and presentation (HLA); P-body component for RNA metabolism, associated with psoriasis (CCHCR1); lymphocyte development (NOTCH4)	Associated by [23]
9q34.2 (ABO blood type locus)	GWAS 95% CI/ (1.37-1.45: 1610 patient vs. 2205 control)	Blood type-dependent pathological reaction, such as coagulation and thrombolysis	Associated by [22]
12q24.13 (OAS1, OAS2, OAS3)	GWAS 95% CI/ (1.29: 2244 vs. ~5X 2244)[23]	IFN-mediated antiviral signaling	Associated by [23]
19p13.3 (DPP9, TYK2)	GWAS 95% CI/ (1.36-1.59: 2244 vs. ~5X 2244)[23]	Innate antiviral defense (TYK2), and antigen presentation, CXCL10 signaling, and associated to obesity, diabetes, and cancer (DPP9)	Associated by [23]
21q22.1 (IFNAR2)	GWAS 95% CI/ (1.28: 2244 vs. ~5X 2244)[23]	IFN-mediated immune signaling	Associated by [23]
Several Chr. (TLR3, UNC93B1, TICAM1, TRAF3, TBK1, IRF3/7/9, IFNAR1/2, STAT1/2)	NGS and variant calling, wet-bench validation (3.5% of 659 severe COVID-19 vs few in 534 control)	IFN mediated immune signaling	Detected by [31]
Epigenetic obtaining (Autoantibody against IFNs, 94% in male)	Wet-bench detection (13.7% of 987 severe COVID-19 vs 0.33% in 1227 control)	IFN mediated immune signaling	Detected by [39]
Epigenetic obtaining (Higher incidence of severe COVID-19 in aged, male, and comorbid patients)	Inclusive studies and evidence (Higher incidence of severe COVID-19 in aged, male, and comorbid patients)	Dysregulated IFN and chemokine responses, chronic/systemic inflammation, impaired other immune responses	Exemplified by [39,18-20, 44,45]

*Defined as accompanying respiratory failure in hospitalized patients. Abbreviation: Appr., Approaches to associate the gene loci with severe COVID-19 in the references; CI, confidence intervals; Chr., human Chromosome from genome build hg38; GWAS, Genome wide association study; IGV, Integrative genomics viewer; NGS, Next-generation sequencing; OR: Freq., Odds ratio: frequency in severe COVID-19 patient vs in the control groups; The gene symbols are standard ones from NCBI, see Figure 1 legend for definitions.

82 CCR1, and CCR3 (Gene symbols are standard ones from NCBI, see Figure 1 legend
83 for definitions of abbreviations), which include several chemokine receptors (CCRs,
84 CXCR6, and XCR1) mediating chemokine signaling pathways for leukocyte
85 chemotaxis, inflammatory regulation and relevant immunopathies causing lung
86 injury. Notably, Chr3p21.31 locus has been reproducibly associated with severe
87 COVID-19 by at least three GWAS studies, indicating it constitutes a common genetic
88 mechanism underlying severe COVID-19 [22-24]. Interestingly, an independent study
89 also identified the ~50 kb region of locus Chr3p21.31 representing an allelic risk that
90 was inherited from Neanderthals and is carried by ~50% of people in South Asia and
91 ~16% of people in Europe today, who was predicted to be prone to the progression of
92 severe COVID-19 [24]. In addition, the association of Chr3p21.31 locus was also
93 reflected by the critical illness in the younger patients (<65 years) with less
94 comorbidity, indicating a *de facto* genetic correlation [22-24]. Several clinical
95 observations correlated blood types with the severity of COVID-19, i.e., O blood type
96 seems more protective compared to a higher risk of non-O, especially A blood type
97 [25-27]. One GWAS assay using two case-control European panels associated severe-

98   COVID-19 with locus Chr9q34.2, which concurs the ABO blood group locus [22].
99   However, this association was not significantly demonstrated in two other GWAS
100   assays published [23,24], indicating that the association of blood type locus with
101   severe COVID-19 is not as universal as the chemokine receptor locus at Chr3p21.31
102   (Table 1). Therefore, more studies are needed to extensively verify the association of

Figure 1. Interferon and chemokine signaling pathways are centrically enriched by key Immunogenetic determinants revealed by recent studies focusing on severe COVID-19 cohorts. Major genes associated with COVID-19 were pooled from several recent immunogenetic studies [22-24, 31]. The protein-protein interaction networks were performed using STRING at https://string-db.org/cgi. The centrically enriched chemokine receptor genes in Chr. 3p21.31, which are regulated by both RAAS and TLR signaling pathways critically in chemokine signaling of inflammatory response, is associated with severe COVID-19 by multiple GWAS studies and highlighted using a yellow cross. Abbreviations: ACE2, angiotensin-converting enzyme 2; AGT, angiotensin; AGTR1, AGTII receptor type 1; CCR, C-C chemokine receptor; CXCR, C-X-C chemokine receptor; IRF, IFN-regulatory factor; IFNAR, IFN-α/β receptor subunit; MAS1, OAS, 2'-5'-oligoadenylate synthase; TBK1, TANK-binding kinase 1; TICAM1, TLR, Toll-like receptor; TMPRSS2, transmembrane protease serine 2; TYK2, non-receptor tyrosine-protein kinase; XCR, Chemokine XC receptor.

103   blood types with the progression of COVID-19 severity. In addition, no mechanistic
104   research about the association of blood types with COVID-19 severity has been
105   reported. In general, antigens determining blood types can serve as direct receptors or
106   co-factors for some pathogenic infections; indirectly, many blood group antigens
107   facilitate cell adhesion, substance intake and signaling transduction [22, 25-27]. Given
108   the reported inconsistency on association of blood types with COVID-19 severity, we

109   interpret an indirect role (such as regulation through the RAAS system, see next
110   section) of blood types on COVID-19 susceptibility and disease progression [22,25-27].

111   Pairo-Castineira et al. released their GWAS analysis using a bigger case/control cohort
112   (2244/10220) from UK hospitals, which represent >95% of all ICU beds in the UK
113   (Table 1) [23]. In addition to the detection of a strong association signal at the
114   Chr3p21.31 locus, the study identified and replicated four novel genome-wide
115   significant associations. These include: (1) at Chr6p22.1-33 region spanning major
116   histocompatibility complex, class I-G, HLA-G, and Coiled-Coil Alpha-Helical Rod
117   Protein 1, CCHCR1 genes; (2) at Chr19p13.3 locus within the gene encoding
118   dipeptidyl peptidase 9 (DPP9); (3) at Chr12q24.13 locus spanning a gene cluster
119   encoding antiviral restriction enzyme activators (OAS1, OAS2, OAS3); and (4) at
120   Chr21q22.1 spanning the interferon receptor gene IFNAR2) [23]. Elegantly, the study
121   also supplemented GWAS illumination with evidence using Mendelian
122   randomization (MR) and transcriptome-wide association (TWAS) assays to define a
123   causal link from the low expression of IFNAR2, and high expression of TYK2, to life-
124   threatening COVID-19. TWAS in lung tissue determined the association of severe
125   COVID-19 with increased expression of the monocyte/macrophage chemotactic
126   receptor CCR2 [23]. Collectively, this study robustly determined genetic signals
127   relating to key host antiviral defense mechanisms, especially that mediated by
128   interferon (IFN)-signaling and chemokine receptors in orchestrating chemotactic and
129   inflammatory responses as clinically demonstrated commonly in severe Covid-19
130   cases (Figure 1) [12-14, 28-30].

131   Using an approach combining both next-generation sequencing (NGS) and
132   experimental validation, Zhang et al. elucidated an enrichment of genetic risk variants
133   at thirteen human loci governing the Toll-like receptor (TLR)-3- and IFN-regulatory
134   factor (IRF)-7-dependent type I IFN immunity in 659 patients with life-threatening
135   COVID-19 [31]. In contrast, few of these genetic risk variants were detected in the 534
136   control subjects with asymptomatic or benign infection. These 13 genetic risk loci
137   displayed functional deficiency of these immune genes. They accounted for 3.5% of
138   severe COVID-19 patients who aged 17 through 77 years and progressed to a life-
139   threatening pneumonia without prior severe infection, indicating a determining role
140   of dysfunctional IFN-mediated antiviral immunity underlying the progression of
141   severe COVID-19 (Table 1 and Figure 1) [31].

142

143   **3.   Epigenetic association: Undermined interferon and RAAS responses leading to**
144   **antiviral dysfunction, hyperinflammation, and autoimmunity**

145   As discussed above, the inborn genetic errors in IFN signaling were associated with
146   3.5% life-threatening COVID-19 [31]. This, as the evidence representing natural loss-
147   of-function genetic variants, verifies a determinant role of IFN signaling in the disease
148   susceptibility and severity. On the other hand, these variants only represent a small
149   portion of extremal examples that carry genetic deficiency incapable of mounting
150   effective antiviral immunity. Logically, a large portion of severe COVID-19 cases may
151   have resulted from deficiency or dysfunction of the biological mechanisms beyond
152   the genetic DNA codes, i.e., at the epigenetic level that developmentally obtained

153 from interacting gene expression networks upon various environmental situations
154 experienced by different individuals [18-20].

155 One prominent feature of immunity is to distinguish self versus non-self and resist
156 the invasion of non-self [32-34]. So, primary humoral antibodies are selectively against
157 pathogenic antigens not reacting to self-antigens [32-34]; however, autoreactive
158 antibodies (auto-Ab) that mistakenly target and react with self-antigens have been
159 reported in patients with chronic infections and especially as a biomarker for various
160 autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus
161 (SLE), Sjogren's syndrome, and multiple sclerosis [28,35]. Not only the pre-existing
162 autoimmune condition associate with a higher risk of severe COVID-19 incidences as
163 repeatedly reported [28,35], several studies also suggested that SARS-CoV2 infection
164 and COVID-19 progression could potentially trigger an imbalance prone to the
165 autoimmune and autoinflammatory response. The prevalence of auto-Abs has been
166 reported in 20-50% of different COVID-19 patient cohorts [28,35]. Symptoms of severe
167 COVID-19 patients resemble someway with the autoimmune diseases, including
168 immune thrombocytopenic purpura (ITP), Guillian-Barrè syndrome (GBS), and
169 Kawasaki like disease (KD) in terms of thrombosis, coagulopathy, chilblain, and
170 vasculitis [28,35-38]. Significantly, auto-Abs identified in severe COVID-19 were
171 evidently reactive to neutralize almost all type I IFN subtypes, thus preventing the
172 major antiviral IFN action immunologically beyond the genetic scenario [39]. Bastard
173 et al. identified the auto-Abs reactive to type I IFNs as an immuno-deficient cause for
174 about 15% of 987 severe COVID-19 patients who had life-threatening pneumonia.
175 These auto-Abs were primarily capable of neutralizing type I IFNs, mostly IFN-α and
176 IFN-ω subtypes, which represent major circulatory IFN subtypes inducing systemic
177 antiviral response and otherwise cause IFN-mediated immunopathies in a persistent
178 infection or autoimmune condition [40-43]. By contrast, these IFN-targeting auto-Abs
179 were not present in 663 patients with asymptomatic or mild COVID-19 and were only
180 found in a few (4/1227) of healthy individuals as the control [39]. Reckoning the
181 higher risk of severe COVID-19 in male sex, reactive auto-Abs were identified
182 primarily in males (94%), indicating that IFN-targeting autoimmunity may contribute
183 to higher incidence of severe COVID-19 in males [39]. The auto-Abs' neutralizing
184 activity diminished effective IFN peptides in the serum and functionally blocked IFN-
185 mediated antiviral action. In addition, the vast presence of IFN-reactive auto-Abs
186 indicates the persistence of type I IFNs, which generally correlates to an
187 immunopathological response rather than a protective role during the late phase of
188 the viral infection, such as in most cases of severe COVID-19 [40-43]. Notably,
189 although the emerging of auto-Abs involves somatic hyper-mutation of the antibody
190 genes in B cells, the sequential process for self-antigen selection and passing the
191 checkpoint for antibody production should be mostly regulated at the epigenetic even
192 post-translation levels, which is facilitated by an inflammatory or autoimmune
193 condition commonly observed in severe COVID-19 progression [28,35,36].

194 The SARS-CoV2 virus evolves to adapt its deadliness and contagiousness for efficient
195 spreading in humans [6,7]. The viral infection causes substantial differences in
196 susceptibility and disease severity in people of different ages, genders, and
197 preexisting comorbidities [8-11]. For the severe COVID-19 cases, except the ~19% with
198 life-threatening pneumonia that is caused by IFN-deficiency functionally through

199 genetic and autoimmune errors as described above [31,39], the severity progression in
200 the other majority of severe COVID-19 patients may be underlain by epigenetic
201 regulation of host factors connected to the IFN and chemokine signaling pathways as
202 genetically elucidated [22-24]. Epigenetic regulation, which molecularly acts on gene
203 expression through DNA methylation, histone modification, and regulatory RNA
204 operation, provides a dynamic scenario and toolkit to understand the outcome
205 broadness of COVID-19 [18,19, 44-46]. Few studies have directly examined epigenetic
206 regulation in SARS-CoV2 infection and the progression of severe COVID-19 in the
207 host [20,45-47]. Collective evidence indicates that epigenetic mechanisms play an
208 important role in the severity progression of COVID-19 [45-47] and regulate the
209 overall process from the virus initial interaction with its primary cell receptor,
210 angiotensin-converting enzyme 2 (ACE2), to the complication into severe illness
211 [20,44-47]. Indeed, dysregulation of IFN, chemokine, and other immune pathways
212 have been correlated with aging, gender difference, and exceedingly various
213 comorbid conditions, which have been recently observed for association with a higher
214 risk of severe COVID-19 [8-11]. For examples, compared with juveniles, the secretion
215 of both type I and type III IFNs by dendritic cells (DCs) in the blood or lung is
216 severely impaired in aged individuals; by contrast, blood DCs from aged individuals
217 produce higher basal levels of proinflammatory cytokines/chemokines including
218 interleukin-6 (IL-6), C-X-C motif chemokine-8 (CXCL-8), CXCL-10, and tumor
219 necrosis factor (TNF-α) [48,49]. This aging-associated aberrancy in DC response,
220 together with the other observation of neutrophilia [50], invokes lung inflammation,
221 impair antiviral resistance and exaggerates major clinical signs as observed in severe
222 COVID-19 [1-7]. For most preexisting comorbidities such as hypertension,
223 cardiovascular diseases, or diabetes mellitus that increase the risk of severe COVID-19
224 [51], various studies have shown the progressive association of IFN insensitivity and
225 chemokine/cytokine-mediated chronic inflammation and have been reviewed
226 elsewhere [41-44]. In addition to the autoimmune reaction incited by SARS-CoV2
227 infection, immunopathies from IFN-persistence, inflammation, and specifically auto-
228 Abs represent typical pathological mechanisms underlying most preexisting
229 autoimmune diseases such as SLE, diabetes, and sclerosis [41-44]. Auto-Abs, which
230 bookmark different autoimmune diseases, may target self-antigens, including critical
231 cytokines like IFNs [39,52-54]. The prevalence of auto-Abs against innate immune
232 IFNs in life-threatening COVID-19 patients indicates an autoimmune ambient
233 accompanied by an overwhelmed IFN response dysregulated by pathogenic DNA
234 from massive cell death caused by the robust virus infection, which is mediated
235 through a cyclic GMP–AMP synthase (cGAS) and signaling effector stimulator of
236 interferon gene (STING) pathway (Figure 2) [56-58]. For the gender difference, Webb
237 et al. recently reported that plasmacytoid dendritic cells (pDC) from healthy females,
238 especially after puberty, produced more type I IFNs via TLR7-mediated signaling
239 than males [59, 60]. This finding indicates that the inferiority of males in the early
240 antiviral IFN induction, an adequate period demonstrated by most IFN-based clinical
241 trials on combating the viral infections [61]. The study also identified that this sex-
242 associated difference in IFN production is related to ChrX number and serum
243 testosterone concentration [59]. Because no loci in ChrX has been genetically
244 associated with severe COVID-19 [21-24], we interpret that SARS-CoV2 binding and
245 inducing ACE2 degradation may indirectly cause gender difference involving both
246 renal endocrine and immune responses through the renin-angiotensin-aldosterone

247   system (RAAS) axis [62-64]. Many studies have indicated the critical role of the virus-
248   ACE2 interaction in disease susceptibility and disruption of RAAS in disease severity
249   progression [65-70]. The key points emphasize that: (1) evolutionary affinity of SARS-
250   CoV2 to ACE2 determines the virus-cell permissiveness and host species tropisms
251   [20,65]; (2) the binding of the viral spike protein (S) to ACE2 inhibits and disrupt
252   angiotensin (Ang) conversion and relevant Ang humoral homeostasis; and (3) the
253   RAAS is then diverted to physio-pathological induction of vasoconstriction,
254   hypertension, fibrosis, oxidative stress, and proinflammation [62-71]. Cross-pathway
255   component analysis indicates that the key chemokine-receptor loci on Chr3 are
256   intricately connected to both TLR3/7-mediated immune signaling and RAAS signaling
257   (Figure 1). This indicates that whereas dysregulated IFN-signaling may determine the
258   disease susceptibility [12-15], hyperinflammation signified by an overreaction of
259   chemokine signaling is intersected by both immune and pathophysiological
260   regulation through RAAS [55-58,68,70] (Figure 1 and Figure 2).

261   Correspondingly, hypercytokinemia has been overserved in severe COVID-19.
262   Inflammatory mediators, including calprotectin (S100A8/9), CRP, IL-1, IL-10, and
263   TNF-α are increased 2–100 fold, whereas IL-6 can be elevated more than 1000 fold
264   above normal in reported cases [13, 71-75]. Several cohort studies reported that
265   markedly elevated serum IL-6 levels in the 100–10,000 pg/mL range in severe COVID-
266   19 patients [13,73-75]. Of 15 clinical parameters diagnosed at hospital admission,
267   elevated CRP (at a cutoff of 87.5 mg/L) and IL-6 levels (at a cutoff of 86 pg/mL) were
268   significantly correlated to death prediction [74]. Clinically reflected in life-threatening
269   respiratory failure in COVID-19, elevated serum IL-6 is also associated with
270   lymphopenia, functional T-cell deficiency, and vasculitis [71]. Likewise, in severe
271   COVID-19, various biomarkers of immune dysregulation exacerbate to a common
272   terminal hyperinflammation indicated by robust incidence of IL-6 and lymphopenia
273   accompanying respiratory failure, which may directly or indirectly intersect to the
274   dysfunctional IFN- and chemokine-signaling pathways that are significantly enriched
275   by the genetic associations [13,21-24,71-75]. In addition, these findings suggest severe
276   COVID-19 may be viewed as an inflammatory vasculitis, which is induced post the
277   viral infection of pneumocytes, endothelial and epithelial cells, and the viral
278   suppression of the RAAS system [71-75]. These may rear an epigenetic ambient,
279   leading to inflammatory and immunopathic consequence associated with severe
280   COVID-19 progression locally in the lung or systemically in multiple organs. As a
281   piece of supporting evidence, numerous drug-repurposing studies of cytokine
282   blockade (such as using anakinra and tocilizumab) and JAK inhibition (such as using
283   baricitinib) have shown promise [71-75]. A relevant proposal is that targeting
284   management of epigenetic regulation may provide valuable approaches to relieve
285   inflammatory and immunopathic overdrive in severe COVID-19 [76]. In summary,
286   GWAS and NGS profiling unravel the significant association of severe COVID-19
287   with multiple genetic errors at the gene loci enriching in IFN and chemokine signaling
288   pathways [22-24,31]; however, the immuno-pathological determinants for the other
289   major part of severe COVID-19 cases may be complicated by the interaction of the
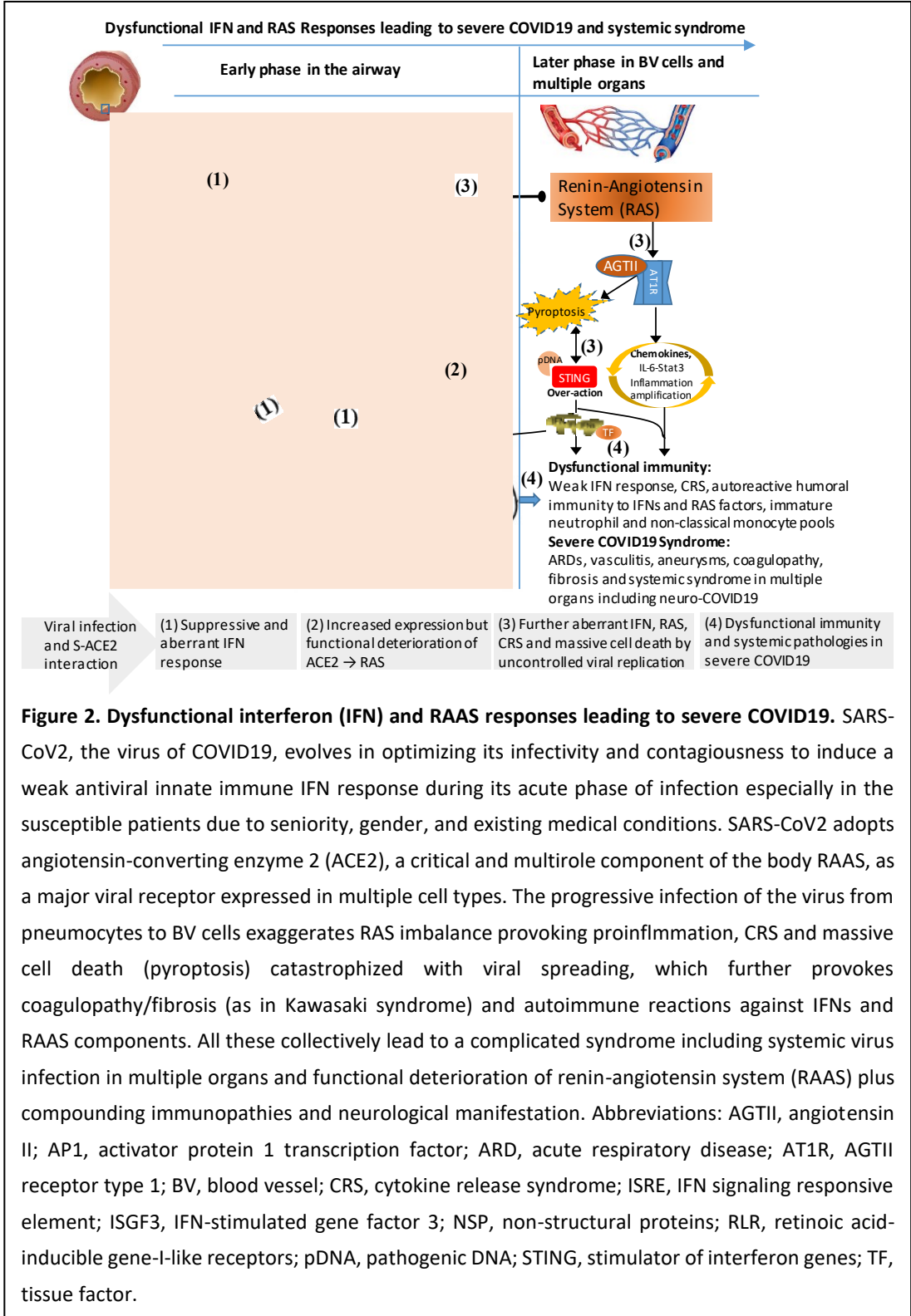
Figure 2. Dysfunctional interferon (IFN) and RAAS responses leading to severe COVID19. SARS-CoV2, the virus of COVID19, evolves in optimizing its infectivity and contagiousness to induce a weak antiviral innate immune IFN response during its acute phase of infection especially in the susceptible patients due to seniority, gender, and existing medical conditions. SARS-CoV2 adopts angiotensin-converting enzyme 2 (ACE2), a critical and multirole component of the body RAAS, as a major viral receptor expressed in multiple cell types. The progressive infection of the virus from pneumocytes to BV cells exaggerates RAS imbalance provoking proinflmmation, CRS and massive cell death (pyroptosis) catastrophized with viral spreading, which further provokes coagulopathy/fibrosis (as in Kawasaki syndrome) and autoimmune reactions against IFNs and RAAS components. All these collectively lead to a complicated syndrome including systemic virus infection in multiple organs and functional deterioration of renin-angiotensin system (RAAS) plus compounding immunopathies and neurological manifestation. Abbreviations: AGTII, angiotensin II; AP1, activator protein 1 transcription factor; ARD, acute respiratory disease; AT1R, AGTII receptor type 1; BV, blood vessel; CRS, cytokine release syndrome; ISRE, IFN signaling responsive element; ISGF3, IFN-stimulated gene factor 3; NSP, non-structural proteins; RLR, retinoic acid-inducible gene-I-like receptors; pDNA, pathogenic DNA; STING, stimulator of interferon genes; TF, tissue factor.

viral and especially host factors at the epigenetic levels [18-20,44-48,57]. The IFN- and chemokine-centric determinants verified through the systemic genetic approaches confer critical nodes to decipher host immune mechanisms underlying the severity progression in COVID-19, thus facilitating host-originated designs for early risk diagnosis and repurposing prophylactic/drugs for mitigating severe COVID-19 [22-24,31,39,67].

296

4. Conclusion remarks: Precise early-risk diagnosis and drug repurposing for severe COVID19 based on immunogenetic association

Clinical outcomes of SARS-CoV2 infection is extensively broad in complication further with symptoms mimicking various inflammatory and autoimmune syndromes in severe COVID-19. Remarkably, most of these symptomatic signs reflect immuno-pathological regulation through the epigenetic mechanisms, which facilitate us to explain the broadness and the dynamics of the clinical outcomes but shadow the focus of key immune determinants triggering the severity of COVID-19 [18-20,44-48,57]. GWAS and NGS profiling, which pursue genetic commons shared by the big cohorts of clinical samples, thus enable to probe determining factors owe to genetic variance behind the environmental variables (mostly through epigenetic regulation) that complicates the illness outcome at various extents [21-24; 44-48,57]. Thus, these genetic risk factors comprise a panel of biomarkers for precise early diagnosis and precaution of severity in relevant people before the infection and disease progression. The elucidation of these genetic risk loci that enrich in IFN- and chemokine-signaling also direct the critical targets for prophylactic designs through either new drug invention or repurposing the existing drugs [77-81]. Notably, type I IFN-signaling represents a critical antiviral innate immunity, which is favorable primarily at the early phase of viral infection prior to progression into a severe situation [61,77]. Accordingly, most prophylactic IFN applications, but not recent therapeutic IFN-based trials of severe COVID-19, are likely more promising [61,77]. For the treatment of hospitalized severe COVID-19, interventions targeting the RAAS imbalance and chemokine/inflammation exaggeration seem more effective (Figure 2). For instance, a recent clinical study reported that intravenous delivery of a recombinant human soluble ACE2 (hrsACE2) for seven days relieved the illness of a severe COVID-19 patient, showing the suppression of inflammatory biomarkers, reduction of viral load, and increase of Ang II and virus-neutralizing antibody production [82]. Although genetic loci in the RAAS pathway have not been associated with severe COVID-19 [21-24,31], this study suggests that the components of RAAS could be physio-pathological determinants underlying severe COVID-19 because ACE2 is directly adopted by SARS-CoV2 for infection and RAAS exerts functionally crosstalk to immune response and regulation such as intersecting to chemokine/inflammatory regulation[65-69,82].

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