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Mild COVID-19 in APS-1

Mild COVID-19 despite autoantibodies to type I IFNs in Autoimmune-Polyendocrine-Syndrome Type 1 (APS-1)

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Disclosure of conflict of interests
VMC together with Euroimmun GmbH holds a patent regarding SARS-CoV-2 diagnostics via antibody testing. All other authors have no conflict of interest to declare. (Patentanmeldung Nr. EP 20158626.0 – 1118/3715847 „A method and reagents for the diagnosis of SARS-CoV-2“)
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**Key words:** Autoimmune Polyendocrine Syndrome Type 1 (APS-1) – anti-cytokine-autoantibodies – type I interferon – Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) – COVID-19
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Abstract
Autoantibodies to interferon (IFN)-α and IFN-ω (type-I-IFNs) were recently reported as causative for severe COVID-19 in the general population. Autoantibodies against IFN-α and IFN-ω are present in almost all patients with Autoimmune-Polyendocrine-Syndrome Type 1 (APS-1) caused by biallelic deleterious or heterozygous dominant mutations in AIREF. We therefore hypothesized that autoantibodies against type-I-IFNs also predispose patients with APS-1 to severe COVID-19. We prospectively studied six patients with APS-1 between April 1st, 2020 and April 1st, 2021. Biobanked pre-COVID-19 sera of APS-1 subjects were tested for neutralizing autoantibodies to IFN-α and IFN-ω. The patients’ sera ability to block recombinant human IFN-α and IFN-ω was assessed by assays quantifying phosphorylation of signal transducer and activator of transcription 1 (STAT1) as well as infection-based IFN-neutralization assays. We describe four patients with APS-1 and pre-existing high titers of neutralizing autoantibodies to IFN-α and IFN-ω who contracted SARS-CoV-2, yet developed only mild symptoms of COVID-19. None of the patients developed dyspnoea, oxygen requirement or high temperature. All infected patients with APS-1 shared female sex and age younger than 26 years. Clinical penetrance of neutralizing autoantibodies against type I IFNs for severe COVID-19 is not complete.
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Introduction

Mutations in AIRE (gene for the Autoimmune Regulator) cause Autoimmune-Polyendocrine-Syndrome-Type-1 (APS-1) (1-3). AIRE is expressed in thymic epithelium and secondary lymphoid organs (4). AIRE regulates promiscuous gene expression of tissue-specific self-antigens in the thymus, a prerequisite for central negative selection of autoreactive T cells. Further, AIRE contributes to the generation of naturally occurring, CD4^+CD25^+CD127^{low/-}FOXP3^+, regulatory T cells (5). Patients with APS-1 develop autoimmunity in endocrine and non-endocrine organs, chronic mucocutaneous candidiasis (CMC) and enamel hypoplasia (6, 7). Patients with APS-1 build autoantibodies against TH-17 cytokines, IFN-α and IFN-ω (type-I-IFNs) (8). The role of autoantibodies against IL-17 for CMC in patients with APS-1 is well-defined (9). In contrast, a role of autoantibodies against type-I-IFNs for infectious diseases has only recently been suspected as patients with APS-1 developed severe coronavirus disease 2019 (COVID-19) caused by infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (10-12). However, to date there is no prospective follow-up of patients with APS-1 who contracted SARS-CoV-2.

By blocking the cytokine's biological function, patients with neutralizing anti-cytokine autoantibodies may present with a clinical phenotype resembling corresponding genetic disorders (13). Autoantibodies against type-I-IFNs were reported in patients with severe COVID-19 (11), among whom a strong bias towards males (95%) and patients elder than 65 y/a (>50%) was also noted (11). Autoantibodies against type-I-IFNs in severe COVID-19 were confirmed in additional cohorts (14-17). However, to date only cohorts collected for severe COVID-19 had been analysed (11, 15-18). We are not aware of a prospective follow-up of patients with pre-existing autoantibodies against type-I-IFNs. Even if pre-existing autoantibodies against type-I-IFNs are a strong risk factor for severe COVID-19 in pre-selected cohorts, the clinical penetrance of pre-existing neutralizing autoantibodies against type-I-IFNs for severe COVID-19 is unknown on the individual, as well as on the population level.

As >95% of patients with APS-1 develop high titers of neutralizing autoantibodies against type-I-IFN (8), APS-1 is a model disease to prospectively study the role of pre-existing autoantibodies to type I IFNs for severe COVID-19. To date three patients with APS-1 and severe COVID-19 (10, 12, 19), as well as severe COVID-19 in 15 of 22 patients in a series of APS-1-patients have been described (18). We therefore hypothesized that autoantibodies against type-I-IFNs predispose patients with APS-1 to severe COVID-19. Here, we report on six patients with APS-1 and high titers of pre-existing neutralizing autoantibodies against IFN-
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α and IFN-ω, of whom four contracted SARS-CoV-2, yet developed mild COVID-19. Our study comprises only patients in regular follow-up for APS-1 who were not recruited due to COVID-19.

Results and Discussion

Patients with APS-1 develop autoimmunity

Already prior to the COVID-19 pandemic all patients were followed up at Charité-Universitätsmedizin Berlin for > 70 patient years (Table 1). Patient 1 is a 13 years old Caucasian girl who developed hypoparathyroidism at 1 ¼/12 and adrenal insufficiency at 4 y/a. Compound heterozygous mutations in AIRE were diagnosed. She further developed CMC, retinal degeneration with optical atrophy, hypergonadotrophic hypogonadism. She is treated with hydrocortisone, fludrocortisone, recombinant parathyroid hormone (rPTH), calcium, magnesium and sex hormone substitution. She irregularly takes liposomal amphotericin B.

Patient 2 is a 13 years old girl of Arabic origin who presented with hypoparathyroidism at 2 y/a. She experienced an enteroviral meningoencephalitis at 3 y/a, followed by autoimmune encephalitis at 7 y/a (20). Upon encephalitis, she was treated with plasmapheresis and receiving mycophenolate-mofetil for months. Compound heterozygous mutations in AIRE were diagnosed at 11 y/a. She also developed atrophic gastritis, growth hormone deficiency and hypergonadotrophic hypogonadism. She is treated with rPTH, calcium, vitamin D and recombinant human growth hormone. Patient 3 is a 15 years old Caucasian boy of who presented with hypoparathyroidism at 8 y/a, when adrenal insufficiency was also noticed and a homozygous mutation in AIRE was identified. At 10 y/a he developed alopecia totalis. He is treated with calcium, calcitriol, hydrocortisone and fludrocortisone. Patient 4 is a 25 years old woman of Arabic origin who had been treated for systemic onset juvenile idiopathic arthritis before being diagnosed with hypoparathyroidism at 11 y/a and adrenal insufficiency at 13 y/a. The diagnosis of APS-1 became evident at 22 y/a. APS-1 is most likely caused by the same homozygous mutation in AIRE as in her younger sister (Patient 5). Patient 4 is treated with calcitriol, calcium, hydrocortisone, fludrocortisone and estradiol for ovarian insufficiency.

Patient 5, the younger sister of patient 4, is a 14 years old girl. At 2 ½ y/a she presented with unilateral parotitis and adrenal insufficiency at 8 y/a. A homozygous mutation in AIRE was found at 11 y/a. She is treated with hydrocortisone and fludrocortisone. Patient 6 is a 22 years old woman of Turkish origin who developed hypoparathyroidism at 4 y/a. Compound heterozygous mutations in AIRE were diagnosed at 4 y/a. She receives calcitriol. All patients show enamel hypoplasia.
Infections with SARS-CoV-2 caused mild COVID-19 in four patients with APS-1

Patient 2 presented with vomiting, headache and rhinitis. SARS-CoV-2 smear was positive. Three days later smell and taste sense were absent. Fatigue, temperatures up to 38.5 °C, slight pain in both knees, as well as headaches for 10 days were reported. Smell and taste returned 10 days after onset of symptoms. Patient 4 presented with up to 39°C, “flu like symptoms” and cough. SARS-CoV-2 smear was positive. Symptoms resolved after seven days. Patient 5, living in the same household as patient 4, reported mild rhinitis, cough for 5 days and normal body temperature. In patient 6 SARS-CoV-2 was suspected because of a positive test in the household. The patient reported cough, rhinitis, headaches, myalgia, a sore throat, normal body temperature and loss of taste for 4 days. After 7 days all symptoms resolved apart from fatigue for one more week. As patients developed neither high fever, nor dyspnoea, all were seen by their local physician and adhered to quarantine measures. None of the patients was admitted to the hospital. When quarantine measures were lifted, serology for SARS-CoV-2 was performed. All patients who reported SARS-CoV-2 infection-compatible symptoms proved seropositive for antibodies specific to SARS-CoV-2 (Table 2). In summary, four patients with APS-1 contracted SARS-CoV-2 but all presented with mild COVID-19.

Patients with APS-1 have high titers of preexisting neutralizing autoantibodies against type I IFNs

We assessed pre-existing sera of all APS-1 patients for autoantibodies against IFN-α, IFN-ω, IFN-β, IL-6, IFN-γ and GM-CSF. All were positive for autoantibodies against IFN-α and IFN-ω, none for autoantibodies against IFN-β, IL-6, IFN-γ or GM-CSF (Figure 1A). Dilution experiments showed high titers of autoantibodies against IFN-α and IFN-ω, as a serum dilution of up to 1:100 000 was necessary to reach background levels of healthy, autoantibody-negative controls (Figure 1B-C). Titers of autoantibodies against type-I-IFNs rose slightly in APS-1 patients upon infection with SARS-CoV-2 (sup Figure 1). Neutralizing activity of autoantibodies against IFN-α was assessed by comparing STAT1-phosphorylation in monocytes upon ex vivo-stimulation with recombinant IFN-α2 in whole blood of a healthy control and in patients. While 1 ng/ml IFN-α2 was sufficient to induce maximum STAT1-phosphorylation in monocytes in whole blood from a healthy donor, the phospho-STAT1 signal in samples from APS-1 patients was suppressed even after stimulation with 10 ng/ml IFN-α2. In contrast, IFN-γ induced STAT1-phosphorylation was similar between patients and control sample (Figure 1D).
Type I IFN-mediated inhibition of SARS-CoV-2 replication is abolished by autoantibodies in patients’ plasma in vitro

Neutralizing activity of autoantibodies against IFN-α and IFN-ω was further assessed by quantifying their ability to nullify the antiviral effect of exogenous IFN in a SARS-CoV-2 infection model of respiratory epithelial Calu-3 cells. As expected, treatment of cells with recombinant IFN-α2a and IFN-ω in the absence of serum or in the presence of a healthy individual’s serum reduced their susceptibility to SARS-CoV-2 infection, as assessed by quantification of viral RNA in culture supernatant (Figure 2 A-B). In contrast, SARS-CoV-2 efficiently infected Calu-3 cells that were inoculated with the patients’ sera, even in the presence of fixed doses of IFN-α2a (Figure 2A) and IFN-ω (Figure 2B), respectively. In general, IFN-neutralization was serum concentration-dependent. Specifically, for most sera, virus replication in the presence of a fixed dose of type-I-IFN was strongest when Calu-3 cells were incubated with 1% and weakest when incubated with 0.001% of patients’ sera (sup Figure 2A-B). Interestingly, we failed to out-titrate serum of patient 1 in the presence of IFN-α2a, indicating high anti-IFN-α2a neutralization capacity, which is in line with the highest titer of autoantibodies in this serum (Figure 1). The neutralizing activity of autoantibodies against IFN was further confirmed by assessing the infectivity of released virions (Figure 2D-F, sup Figure 3). In the absence of IFNs and serum, inoculation of cells with SARS-CoV-2 gave rise to abundant de novo virus production. Addition of exogenous IFNs efficiently prevented virus production both, in the absence of serum and in the presence of serum of an auto-antibody negative individual. However, incubation of cells with the individual patients’ sera allowed efficient production of infectious virions even in the presence of IFN-α2a (Figure 2D) and IFN-ω (Figure 2E), confirming efficient neutralization of antiviral IFNs, mirroring our results obtained by RT-PCR (Figure 2A-B). IFN-neutralization was generally serum concentration-dependent, again with exception of serum of patient 1 in the presence of IFN-α2a (sup Figure 2C-D). Importantly, in the absence of IFNs, healthy individuals’ and patients’ sera did not modulate infection efficiency as compared to the condition without serum addition (Figure 2C and 2F), arguing for a specific proviral effect exerted by the patients’ sera that manifests itself specifically in the presence of IFNs. In summary, all patients with APS-1 in our cohort exhibit autoantibodies at titers that are sufficient for functional neutralization of type I IFNs in an IFN-sensitive SARS-CoV-2 infection assay.

Mild COVID-19 despite high titers of neutralizing autoantibodies to type I IFNs in four patients with APS-1
Here, we describe four patients with APS-1 and high titers of pre-existing, neutralizing autoantibodies against type-I-IFNs, who experienced only mild COVID-19. Our observation may seem difficult to be reconciled with reports of three patients with APS-1 who developed severe COVID-19 (10, 12, 19). Further, autoantibodies against type I IFNs were described as a risk factor for severe COVID-19 in at least 10% of patients with severe COVID-19 (11). Lately, a study described severe COVID-19 in 15 of 22 patients in a cross-sectional case series of patients with APS-1, however also 7 patients of the same 22 developed mild to moderate COVID-19, of whom three were not even hospitalized (18). SARS-CoV-2 is sensitive to the antiviral properties of type-I-IFNs, as shown extensively in vitro, ex vivo and in vivo (21). Therefore, it appears intuitive that interference with these cytokines results in a worsened outcome of SARS-CoV-2 infection. Strikingly, all individuals with high titers of pre-existing and neutralizing autoantibodies against type-I-IFNs, yet mild COVID-19 in our study were young females (13, 14, 22 and 25 y/a), whereas a pronounced excess of males older than 65 y/a was noted among most patients with autoantibodies against type-I-IFNs and severe COVID-19 (11). We are not able to verify to what extent autoantibodies against IFN-α and IFN-ω block the respective IFNs in our patients in vivo. So, our surprising observation of mild COVID-19 despite high titers of neutralizing autoantibodies against both, IFN-α and IFN-ω, in young females may be explained by the assumption that these autoantibodies do not fully neutralize either type-I-IFN in vivo. Consequently, if autoantibodies against IFN-α and IFN-ω do not completely block, but only dampen the biological activity of IFN-α and IFN-ω in vivo, elder males may exhibit additional risk factors for severe COVID-19 that are yet absent or less frequent/less present in most young patients and/or females.

Rescue treatment in patients with APS-1 only in severe COVID-19

In conclusion, even if pre-existing autoantibodies against type-I-IFNs increase the risk for severe COVID-19, penetrance for severe COVID-19 is not complete. Importantly, and in contrast to previous studies (10, 12, 18, 19), our report is the first based on a prospective follow-up of patients with pre-existing autoantibodies against type-I-IFNs. Large prospective studies may help to estimate the true risk of patients with pre-existing autoantibodies against type-I-IFNs, such as in patients with APS-1 for severe COVID-19. As clinical penetrance for severe COVID-19 in the presence of pre-existing autoantibodies against type-I-IFNs is neither clear on the population, nor on the individual level, we do not advise to admit all patients with APS-1 who contracted SARS-CoV-2 to the hospital for upfront therapies (e.g. monoclonal antibodies, IFN-β, plasmapheresis). Nevertheless, we strongly advise to inform all patients with
autoantibodies against type-I-IFNs about their increased risk for severe COVID-19. As severe
COVID-19 has been described also in young and in female patients with APS-1, all patients
with APS-1 who contracted SARS-CoV-2 must be followed-up closely.

Study approval
All procedures performed in studies involving human participants were in accordance with the
ethical standards of the institutional and/or national research committee (Charité -
Universitätsmedizin Berlin, Germany, EA2/132/11) and with the 1964 Helsinki declaration and
its later amendments or comparable ethical standards. Written informed consent was obtained
from all individual participants included in the study.

Authorship Contributions
CM, CG, HVB planed the study. TM, OS assessed autoantibodies and STAT1-phosphorylation.
BA assessed IFN-neutralization in Calu-3 cells. TK, EL, DS recruited patients. CD provided
SARS-CoV-2 isolate. VMC generated serology data. MAM, UK, NU critically discussed the
manuscript. HVB wrote the initial version, CM, CG, HVB the final version of the manuscript.
All authors read and approved the final version of the manuscript.

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References


### Basic Characteristics, Clinical Phenotype, and Immunological Phenotype of Patients with APS-1

**Table 1:** Basic characteristics, clinical and immunological phenotype of patients with APS-1. “AI” = AutoImmunity.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Family</th>
<th>Age</th>
<th>Sex</th>
<th>Mutations in AIRE</th>
<th>AI in endocrine organs</th>
<th>AI in non-endocrine organs</th>
<th>Enamel Hypoplasia</th>
<th>anti-IFNα auto-antibody titer (pre/post infection)</th>
<th>anti-IFNω auto-antibody titer (pre/post infection)</th>
<th>Inhibition of STAT1-phosphorylation upon IFNα2</th>
<th>Neutralization of the ability of IFNα2 to block replication of SARS-CoV-2</th>
<th>Neutralization of the ability of IFNω to block replication of SARS-CoV-2</th>
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<tr>
<td>1</td>
<td>1</td>
<td>13</td>
<td>f</td>
<td>c.967_979del13/c.784delC</td>
<td>parathyroid adrenal cortex gonads</td>
<td>retina</td>
<td>+</td>
<td>1:100.000</td>
<td>1:1000</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>13</td>
<td>f</td>
<td>c.62C&gt;T/c.1096-1G&gt;A</td>
<td>parathyroid gonads pituitary gland</td>
<td>gastritis anti-GABA-receptor encephalitis</td>
<td>+</td>
<td>1:1000 / 1:1000</td>
<td>1:1000 / 1:1000</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>15</td>
<td>m</td>
<td>c.769 C&gt;T homozygous</td>
<td>parathyroid adrenal cortex</td>
<td>alopecia totalis</td>
<td>+</td>
<td>1:1000</td>
<td>1:10.000</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>25</td>
<td>f</td>
<td>c.1096-1G&gt;A homozygous</td>
<td>parathyroid adrenal cortex gonads</td>
<td>systemic onset juvenile idiopathic arthritis</td>
<td>+</td>
<td>1:10.000 / 1:10.000</td>
<td>1:10.000 / 1:10.000</td>
<td>not done</td>
<td>+</td>
<td>+</td>
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<tr>
<td>5</td>
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<td>12</td>
<td>f</td>
<td>c.1096-1G&gt;A homozygous</td>
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<td>parotitis</td>
<td>+</td>
<td>1:1000 / 1:10.000</td>
<td>1:1000 / 1:10.000</td>
<td>+</td>
<td>+</td>
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<td>5</td>
<td>22</td>
<td>f</td>
<td>c.247A&gt;G/c.607C&gt;T</td>
<td>parathyroid</td>
<td>calcification of basal ganglia</td>
<td>+</td>
<td>1:10.000</td>
<td>1:10.000</td>
<td>not done</td>
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Table 2: Serology for SARS-CoV-2 in patients with APS-1.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time Point Relative to SARS-CoV-2 Infection</th>
<th>S1-IgG ELISA</th>
<th>S1-IgA ELISA</th>
<th>SARS-CoV-2 IgG SeraSpot</th>
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<tr>
<td></td>
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<td>S1-IgG Ratio</td>
<td>S1-IgA Ratio</td>
<td>N</td>
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<tr>
<td>1</td>
<td>No infection reported</td>
<td>0,1 neg</td>
<td>0,6 neg</td>
<td>0</td>
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<td>2</td>
<td>pre</td>
<td>0,13 neg</td>
<td>0,31 neg</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>post</td>
<td>3,89 pos</td>
<td>5,6 pos</td>
<td>0,6</td>
</tr>
<tr>
<td>3</td>
<td>No infection reported</td>
<td>0,07 neg</td>
<td>0,55 neg</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>pre</td>
<td>0,07 neg</td>
<td>0,54 neg</td>
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<td>post</td>
<td>4,2 pos</td>
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<td>8,24 pos</td>
<td>&gt;12 pos</td>
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</tr>
<tr>
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<td>pre</td>
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<td>0</td>
</tr>
<tr>
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<td>post</td>
<td>3,08 pos</td>
<td>1,7 pos</td>
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**Figure 1.** Neutralizing auto-Ab against IFN-α2 and IFN-ω in patients with APS-1: (A) ECLIA based assay for detection of IgG auto-Abs against IFN-α2, IFN-ω, IFN-β, IFN-γ, IL-6 and GM-CSF in sera (1:100 dilution) from patients with APS-1 (P1-P6), healthy controls (n=17, NEG), and patients with known auto-Ab against IFN-γ, IL-6 and GM-CSF (n=1, POS). Detection of auto-Ab against (B) IFN-α2 and (C) IFN-ω in serial serum dilutions of patients P1-P6. Dotted lines indicate the maximum LSC signal in the anti-IFN-α2 and anti-IFN-ω assay in the cohort of healthy controls. (D) FACS histograms depicting STAT1 phosphorylation (pSTAT1) in whole blood monocytes from a healthy control and four APS-1 patients stimulated with IFN-α2 (1 and 10 ng/ml) or IFN-γ (10 ng/ml).
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Figure 2. Auto-Abs in patients with APS-1 neutralize the ability of type I IFNs to inhibit SARS-CoV-2 infection: Calu-3 cells were mock-treated (no serum) or pretreated with indicated concentrations of human serum in the presence or absence of 200 IU/ml IFN-α2a (A, D) or 5 ng/ml IFN omega (B, E) for 16 hours before infection. IFN and serum were removed, and cells were then infected with SARS-CoV-2 at MOI 0.01 for one hour, washed and fresh medium was applied to the cells. 24 hours post-infection, supernatant was harvested for viral RNA extraction and plaque assays. A-C Viral RNA was extracted from supernatant and SARS-CoV-2 genome equivalents/ul were quantified by Q-RT-PCR using primers targeting the E gene region. D-F Supernatants were titrated on Vero E6 cells and incubated for plaque formation for 3 days. Plaques were counted and PFU/ml were determined. Data were generated in two independent assays. Values obtained in the absence of serum and IFN were set to 100%.