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Autoantibodies Neutralizing Type III Interferons Are Uncommon in Patients with Severe Coronavirus Disease 2019 Pneumonia

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Autoantibodies (AABs) neutralizing type I interferons (IFN) underlie about 15% of cases of critical coronavirus disease 2019 (COVID-19) pneumonia. The impact of autoimmunity toward type III IFNs remains unexplored. We included samples from 1,002 patients with COVID-19 (50% with severe disease) and 1,489 SARS-CoV-2-naive individuals. We studied the prevalence and neutralizing capacity of AABs toward IFNλ and IFNα. Luciferase-based immunoprecipitation method was applied using pooled IFNα (subtypes 1, 2, 8, and 21) or pooled IFNλ1–IFNλ3 as antigens, followed by reporter cell-based neutralization assay. In the SARS-CoV-2-naive cohort, IFNλ AABs were more common (8.5%) than those targeting IFNα2 (2.9%) and were related with older age. In the COVID-19 cohort the presence of autoreactivity to IFNλ did not associate with severe disease [odds ratio (OR) 0.84; 95% confidence interval (CI) 0.40–1.73], unlike to IFNα (OR 4.88; 95% CI 2.40–11.06; $P < 0.001$). Most IFNλ AAB-positive COVID-19 samples (67%) did not neutralize any of the 3 IFNλ subtypes. Pan-IFNλ neutralization occurred in 5 patients (0.50%), who all suffered from severe COVID-19 pneumonia, and 4 of them neutralized IFNα2 in addition to IFNλ. Overall, AABs to type III IFNs are rarely neutralizing, and do not seem to predispose to severe COVID-19 pneumonia on their own.

Keywords: type III interferons, autoantibodies, COVID-19, type I interferons

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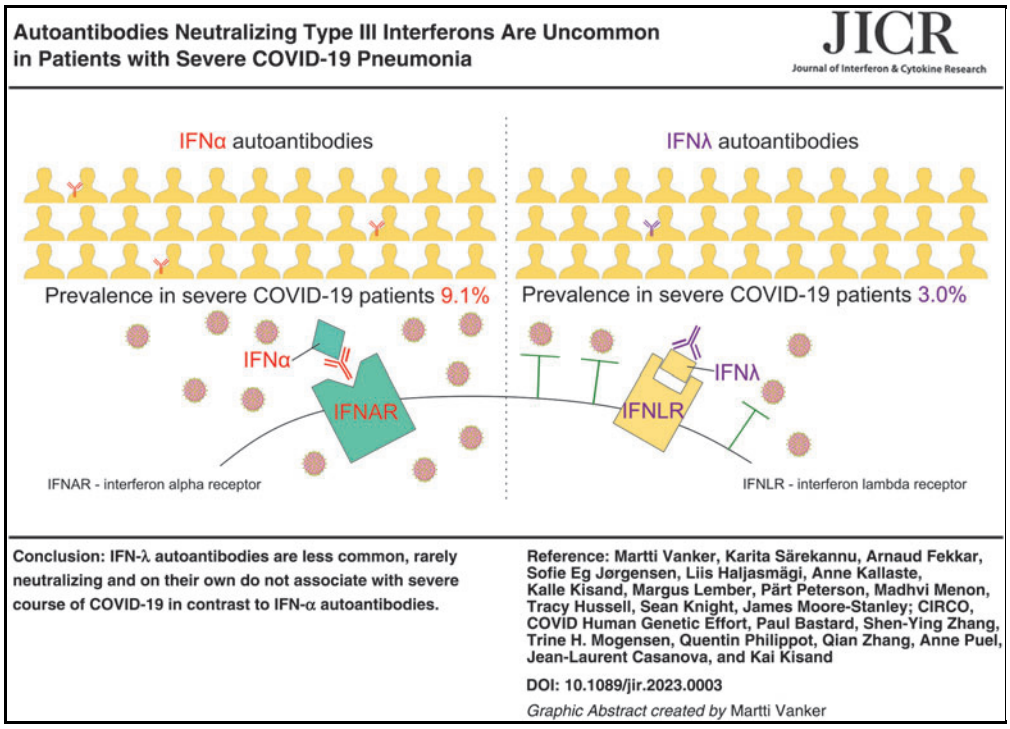

Introduction

The clinical course of coronavirus disease 2019 (COVID-19) varies from asymptomatic infection to life-threatening disease requiring mechanical ventilation or other means of organ support. The risk of hospitalization or death increases with age, doubling every 5 years from childhood onward (Levin et al., 2020). A crucial factor determining disease severity may be the host immune response, particularly the early production of type I and type III interferons (IFN) in the respiratory tract (Andreakos et al., 2019; Bastard et al., 2022b; Galani et al., 2021; Hadjadj et al., 2020; Prokunina-Olsson et al., 2020; Smith et al., 2022; Sposito et al., 2021). The effects of IFN-I/III are mediated by induction of IFN-stimulated genes (ISGs), which encode proteins capable of inhibiting viral replication through various mechanisms (Schoggins, 2019).

The essential role of type I IFNs in protective immunity against SARS-CoV-2 has been amply documented. Inborn errors of TLR3- or TLR7-dependent type I IFN immunity underlie 1%–5% of cases of critical COVID-19 pneumonia (Asano et al., 2021; Casanova and Abel, 2022; Zhang et al., 2022). Moreover, neutralizing autoantibodies (nAABs) against IFN-Is are present in 15% of COVID-19 patients in critical condition, whereas these autoantibodies (AABs) are not or rarely found in asymptomatic patients (Bastard et al., 2021a; Bastard et al., 2020; Casanova and Abel, 2022; Troya et al., 2021; Zhang et al., 2022). Importantly, the risk of critical COVID-19 pneumonia increases with the number and concentration of type I IFNs neutralized (Manry et al., 2022).

These findings have been independently replicated in many different centers around the globe (Abers et al., 2021; Arrestier et al., 2022; Bastard et al., 2022a; Bastard et al., 2021b; Chauvineau-Grenier et al., 2022; Eto et al., 2022; Goncalves et al., 2021; Mathian et al., 2022; Smith et al., 2022; Solanich et al., 2021; Troya et al., 2021; van der Wijst et al., 2021; Wang et al., 2021; Zhang et al., 2020). NAABs pre-exist infection with SARS-CoV-2 (Bastard et al., 2021b). Moreover, the proportion of individuals carrying IFN-I AABs increases with age, with a prevalence between 0.3% and 1% younger than the age of 65 years (for neutralization of high and low concentrations of IFNs), and a rise to 4%–7% in the aged population.

The contribution of type III IFNs to protective immunity to SARS-CoV-2 is less studied. As IFN-I, IFN-III is also transiently expressed upon recognition of pathogen-associated molecular patterns, mostly from viruses. In humans, the family of IFN-III comprises 4 members: IFNλ1/IL-29, IFNλ2/IL-28A, IFNλ3/IL-28B, and IFNλ4, that is either a pseudogene due to a certain variant (rs368234815), or poorly secreted (Hong et al., 2016; Kotenko et al., 2003; Prokunina-Olsson et al., 2013; Vlachiotis and Andreakos, 2019).

IFNλ2 and IFNλ3 are virtually identical, with 96% amino acid identity, and IFNλ1 is sharing ∼80% of amino acids with them (Sheppard et al., 2003). IFN-IIIs are involved not only in the front line of antiviral defense since their heterodimeric receptors (IFNλR1/IL-10RB) are mainly expressed on epithelial cells of respiratory mucosa and other anatomical barriers, but also on a set of immune cells (Goel et al., 2021; Kotenko et al., 2003; Lazear et al., 2019; Ye et al., 2019). In contrast, IFN-I receptors are expressed ubiquitously—it is therefore speculated that the systemic response elicited by IFN-Is is reserved to situations where the effect of IFN-IIIs does not suffice (Andreakos et al., 2019).

Indeed, IFN-IIIs efficiently restricted the proliferation of SARS-CoV-2 *in vitro* (Felgenhauer et al., 2020; Stanifer et al., 2020; Vanderheiden et al., 2020) and higher serum

IFN-III levels were associated with faster viral clearance in COVID-19 patients (Galani et al., 2021). COVID-19 treatment trials with IFN-IIIs have either shown faster viral clearance (Feld et al., 2021; Santer et al., 2022) or protection from hospitalization and emergency department visits (Reis et al., 2023), but no benefit from a single dose of subcutaneous Peginterferon Lambda-1a over placebo (Jagannathan et al., 2021).

In contrast to IFN-I AABs, it is poorly studied whether AABs against IFN-III (IFNλ AABs) underlie life-threatening COVID-19, apart from a recent report in a very limited number of patients (Credle et al., 2022). It also remains unknown whether age and gender are factors contributing to the formation of IFNλ AABs in the general population, as it was proven for IFN-I AABs. Some findings also suggest that IFNλ may be essential in defense against fungal infections such as invasive pulmonary aspergillosis, which according to a study by Fekkar et al. (2021) affects about 5% of intensive care unit admitted COVID-19 patients (Espinosa et al., 2017; Ye et al., 2019).

It has not, however, been studied whether NAABs targeting IFNλ predispose to severe COVID-19 *per se*, and/or predispose COVID-19 patients to aspergillosis superinfection. We aimed to analyze auto-Abs to type III IFNs in the general population and in patients with COVID-19, with or without aspergillosis.

Materials and Methods

Study population

This study included 1,002 COVID-19 patients from Estonia, Denmark, France, and the United Kingdom (Table 1). The patients were allocated to 2 severity groups according to the WHO guidelines (World Health Organization, 2022). Mild disease corresponded to WHO grades 1–2 [WHO1: symptomatic patients without evidence of pneumonia; WHO2: evidence of pneumonia, but no signs of severe pneumonia (SpO_2 ≥90% in room air)], and severe COVID-19 corresponded to WHO grades 3–4 (WHO3: pneumonia plus one of the following—respiratory rate ≥30 breaths/min or SpO_2 <90% and WHO4: patients with acute respiratory distress syndrome, sepsis, or septic shock). A total of 50% of the study group developed severe COVID-19. Median age among COVID-19 patients was 51 years [interquartile range (IQR) 22 years], 47% of patients were male.

We also included serum samples from 1,489 Estonian SARS-CoV-2 naive subjects either collected prior COVID-19 pandemic or tested negative for antibodies specific for SARS-CoV-2 (Table 2). Median age among SARS-CoV-2-naive individuals was 66 years (IQR 36 years), 43% of subjects were male. Plasma or serum samples were collected from all study participants to analyze IFNα and IFNλ AAB levels and AAB bioactivity.

Written informed consent was obtained from all study participants. Study protocols were approved by the Ethics Review Committee of Human Research of the University of Tartu (Protocols 272/T-12, 275/M-17, 368M-4, and 318/T-1) from the French Ethics Committee ''Comité de Protection des Personnes,'' the French National Agency for Medicine and Health Product Safety, and the ''Institut National de la Santé et de la Recherche Médicale,'' in France (Protocol C10-13, ID-RCB No. 2010-A00634-35), and the Rockefeller University Institutional Review Board in New York (Protocol JCA-0700), Danish National Committee on Health research ethics: (#1-10-72-80-20), Ethical approval obtained from the National Research Ethics Service (REC reference 15/NW/0409 for ManARTS and 18/WA/0368 for NCARC). The research was completed in accordance with the Declaration of Helsinki as revised in 2013.

Luciferase-based immunoprecipitation system

The sequences encoding IFNα subtypes (IFNα1, IFNα2, IFNα8, IFNα21) or IFNλ subtypes IFNλ1–IFNλ3 (IL-29, IL-28A, IL-28B) were cloned into pPK-CMV-F4 plasmid (PromoCell GmbH) where NanoLuc luciferase sequence (Promega) was inserted instead of firefly luciferase. HEK293 cells were used to produce the fusion proteins. The cells were cultured in Dulbecco's modified Eagle's medium (DMEM; Lonza, Switzerland) supplemented with 10% fetal bovine serum (FBS), 100 U/mL penicillin and 100 μg/mL streptomycin at 37°C in a 5% CO_2 atmosphere. Cells were transfected with the constructs, 72 h later, cell media containing the secreted fusion proteins was collected. Patient sera were diluted 1:10 using buffer A (50 mM Tris pH 7.5, 100 mM NaCl, 5 mM $MgCl_2$, 1% Triton X-100). A volume of 25 μL serum dilution and 25 μL of protein G agarose bead suspension (Exalpha Biologicals) was coincubated in a 96-well microfilter plate (Merck Millipore) on a shaker at room temperature for 1 h.

Afterward, a mix of each fusion protein corresponding to 1×10^6 luminescent unit for each, was pipetted into each well. The plate was incubated on a shaker for 1 h. A vacuum system (Millipore) was used to wash the plate first with buffer A and thereafter with 1 × phosphate-buffered saline (PBS). Into each well, 20 μL of 1:1,000 PBS-diluted luciferase substrate (Promega) was added, and VICTOR X Multilabel Plate Reader (PerkinElmer Life Sciences) was used to quantify luminescence. The same 3 AAB-negative control serum samples were run in duplicates with each 96-well plate. For each sample, a fold change of luminescence relative to the mean of 3 negative control samples was calculated by dividing the mean luminescence value of the test sample with the mean of the negative control samples.

Neutralization assays

The blocking activity of IFNα2 AABs in patient serum samples from France was determined with a reporter luciferase activity as described in Bastard et al. (2021a). In brief, HEK293T cells were transfected with a plasmid containing the firefly luciferase gene under the control of the human *ISRE* promoter in the pGL4.45 backbone, and a plasmid constitutively expressing *Renilla* luciferase for normalization (pRL-SV40). Cells were transfected in the presence of the X-tremeGene9 transfection reagent (Sigma-Aldrich) for 24 h. Cells in DMEM (Thermo Fisher Scientific) supplemented with 2% fetal calf serum and 10% healthy control or patient serum/plasma (after inactivation at 56°C, for 20 min) were either left unstimulated or were stimulated with IFNα2 (Miltenyi Biotech, Germany) at 100 pg/mL, for 16 h at 37°C. Each sample was tested once for each cytokine and dose.

Finally, cells were lysed for 20 min at room temperature and luciferase levels were measured with the Dual-

Table 1. The Main Characteristics of Coronavirus Disease 2019 Subsamples by the Country of Origin

Country	No. of patients	Male, %	Median age	WHO3+ WHO4, %	COVID-19 vaccination, %	IFNα AAB SPos (n)	IFNλ AAB SPos (n)	AAB DP (n)	IFNα neut tested	IFNλ neut tested	Serum collection period	References
France	392	42	51	74	100	8.7% (34)	2.0% (8)	1.8% (7)	392	14	February 2021–May 2021	[a]
Estonia	290	44	55	22	0	3.8% (11)	4.5% (13)	1.7% (5)	4	8	April 2020–May 2020	—
Denmark	213	55	47.5	21	0	1.9% (4)	3.8% (8)	1.0% (2)	0	7	June 2020–March 2021	—
UK	107	55	56	100	32	5.6% (6)	4.7% (5)	2.8% (3)	107	8	March 2020–April 2022	—
Total	1,002	47	51	50	43	5.5% (55)	3.4% (34)	1.7% (17)	504	37	—	—

[a]IFNα AAB results for French subsample were published in Bastard et al. (2022a).

AAB DP, interferon α and interferon λ autoantibody double positive; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; IFNα AAB SPos, interferon α autoantibody single positive; IFNα neut tested, the number of serum samples subjected for interferon alpha neutralization assay; IFNλ AAB SPos, interferon λ autoantibody single positive; IFNλ neut tested, the number of serum samples subjected to interferon λ neutralization assay; WHO3, hypoxemic pneumonia (respiratory rate ≥30 breaths/min or SpO_2 <90%); WHO4, patients with ARDS, sepsis or septic shock.

Table 2. The Main Characteristics of the SARS-CoV2-Naive Study Group

Subsample name	No. of patients	Male, %	Median age	IFNα AAB SPos (n)	IFNλ AAB SPos (n)	IFNα neut tested	IFNλ neut tested	Serum collection period	References[a]
1. COVID-19 epidemiological study[b]	724	44	44	1.7% (12)	4.0% (29)	1	14	May 2020–July 2020	Jõgi et al. (2021)
2. Estonian Gene Bank donors	309	53	70	1.6% (5)	16.2% (50)	0	23	September 2011–January 2012	Bastard et al. (2021a), Tserel et al. (2015)
3. Internal medicine clinic	216	26	76	5.1% (11)	9.7% (21)	8	15	November 2017–June 2018	Bastard et al. (2021a), Salumets et al. (2022)
4. Dermatology clinic	195	40	75	7.2% (14)	11.8% (23)	7	14	January 2018–September 2019	Bastard et al. (2021a), Salumets et al. (2022)
5. Non-COVID-19 respiratory infection[b]	45	49	54	2.2% (1)	8.9% (4)	1	2	June 2020–August 2020	Kallaste et al. (2022)
Total	1,489	43	66	2.9% (43)	8.5% (127)	17	68	—	—

[a]IFNα AAB data for subsamples 2–4 were published in Bastard et al. (2021a). The remaining serum collections were newly tested for this study and previous studies referenced included other parameters from the same individuals.

[b]For subsamples 1 and 5, only serum samples that were negative for antibodies specific for SARS-CoV-2 were selected.

Luciferase® Reporter 1000 assay system (Promega), according to the manufacturer's protocol. Luminescence intensity was measured with a VICTOR X Multilabel Plate Reader (PerkinElmer Life Sciences). Firefly luciferase activity values were normalized against *Renilla* luciferase activity values. These values were then normalized against the median induction level for non-neutralizing samples and expressed as a percentage. Samples were considered neutralizing if luciferase induction, normalized against *Renilla* luciferase activity, was below 15% of the median values for controls tested the same day.

For the serum samples over the cutoff for IFNα luciferase-based immunoprecipitation system (LIPS) assay from the SARS-CoV-2-naive cohort and from Estonian, Danish, and British patient cohorts, IFNα neutralizing capacity was measured by using a reporter cell line HEK-Blue IFNα/IFNβ (InvivoGen) as previously described (Meyer et al., 2016). The cells were grown in DMEM (Lonza) with heat inactivated FBS (10%), 30 g/mL Blasticidin (InvivoGen), and 100 g/mL Zeocin (InvivoGen). IFNα2 (Miltenyi Biotech) was used at the concentration of 25 U/mL. Threefold serially diluted serum samples were coincubated with IFNs for 2 h at 37°C, 5% CO_2. Reporter cells (10^5) were added to 96-well tissue-culture plate wells and incubated 20–24 h at 37°C, 5% CO_2. QUANTI-Blue (InvivoGen) colorimetric enzyme assay was used to determine AP activity in overnight supernatants.

Optical density (OD) was measured at 620 nm with Multiscan MCC/340 enzyme-linked immunosorbent assay (ELISA) reader (Labsystems). Neutralization activity was expressed as IC_{50}, which was calculated from the dose-response curves and represents the serum dilution at which the IFN bioactivity was reduced to half of its maximum (Supplementary Fig. S1). If the lowest serum dilution (1:20) did not reduce the maximum signal induced by IFNα2 by half, the serum was considered non-neutralizing. In addition, the full British patient cohort was tested with 100 pg/mL IFNα2 coincubated 16 h with 10% of patient serum. Neutralization was calculated as a percentage from the mean signal gained with non-neutralizing control samples. Samples were considered neutralizing if OD values were reduced below 15% of the mean values for non-neutralizing control sera tested the same day.

The neutralization activity of IFNλ AAB-positive sera was assessed with the help of HEK-Blue™ IFNλ cells (InvivoGen)—a reporter cell-line expressing alkaline phosphatase under the control of ISG54 promoter. The cells were cultured in DMEM (Lonza) supplemented with 10% heat inactivated FBS and the following antibiotics: 100 U/mL penicillin, 100 μg/mL streptomycin, 10 μg/mL blasticidin (InvivoGen), 1 μg/mL puromycin (InvivoGen), Zeocin™ 100 μg/mL (InvivoGen) a 37°C 5% CO_2. Serum serial dilutions (3×) starting from 1:20 were made on 96-well cell culture plates using supplemented DMEM. Next, IFNλ1 (IL-29; BioLegend, CA) at a final concentration of 12.5 pg/mL or either IFNλ2 (IL-28A) or IFNλ3 (IL-28B) fusion proteins produced for use in LIPS assay was pipetted to the serum dilutions. The IFNλ2 and IFNλ3 fusion proteins were used in a final dilution that induced approximately similar alkaline phosphatase expression as the optimized IFNλ1 concentration.

For the positive control wells, no serum was added, and for the negative control wells neither IFNλ nor serum was added. The plate was preincubated (37°C 5% CO_2) for 2 h. After the preincubation step 5×10^4 of HEK-Blue IFNλ cells were added to each well and the plate was incubated (37°C 5% CO_2) overnight. Alkaline phosphatase secreted into cell media was quantified colorimetrically after adding QUANTI-Blue™ (InvivoGen) solution. OD was measured after 30 min of incubation at 620 nm with Multiskan MCC/340 (Labsystems) ELISA plate reader. OD results were normalized to cell viability assessed by use of CellTiter-Glo® luminescent cell viability assay (Promega). In brief, CellTiter-Glo was added to wells, well contents were transferred to opaque-welled plates. After a 10-min incubation step, luminescence was measured with VICTOR X Multilabel Plate Reader.

A half maximal inhibitory concentration (IC_{50}) for each neutralizing serum was calculated from dose-response curves using GraphPad Prism 9 (GraphPad Software, Inc.) based on the normalized OD values of the serial dilution. Neutralization activity was expressed as IC_{50}, which was calculated from the dose-response curves and represents the serum dilution at which the IFN bioactivity was reduced to half of its maximum (Supplementary Fig. S1). If the lowest serum dilution (1:20) did not reduce the maximum signal induced by IFNα2 by half, the serum was considered non-neutralizing.

Statistical analysis

Cutoffs for determining AAB positivity were chosen based on the distribution of AAB titer values across the whole sample ($n = 2{,}491$). The Gaussian mixture models algorithm (R code in Supplemetary Materials) was used to determine 3 normal distribution clusters: low (healthy) level, intermediate level, and high level (Supplementary Fig. S2). AAB positivity cutoff was defined as the mean plus 1 standard deviation of intermediate cluster. The cutoff level was 4.94 for IFNα AAB and 4.88 for IFNλ AAB. The statistical significance of the difference between 2 groups was compared using Wilcoxon rank-sum test, and Kruskal–Wallis test was used in case of more than 2 groups. The level of significance was set at 0.05. Bonferroni correction was used for *post hoc* analyses.

Differences between the proportions of categorical variables of multiple groups were analyzed with chi-square test. Spearman correlation was used to study the association of 2 continuous variables. To evaluate the effect of IFN AABs (categorical variable) to COVID-19 severity, multivariable logistic regression was carried out in R using the package finalfit. Patient age and sex were used as confounding variables. Most of the plots were constructed with the package ggpubr. All statistical analyses were performed in R version 4.1.2 (Free Software Foundation, Boston, MA; www.r-project.org).

Results

IFN AAB prevalence and bioactivity in the SARS-CoV-2-naive cohort

To compare the prevalence of IFNα and IFNλ AABs in population, and its association with age and gender, we used LIPS assay for screening 1,489 serum samples collected from SARS-CoV-2-naive individuals. For IFNα AAB screening, we used the pool of 4 different IFNα subtypes

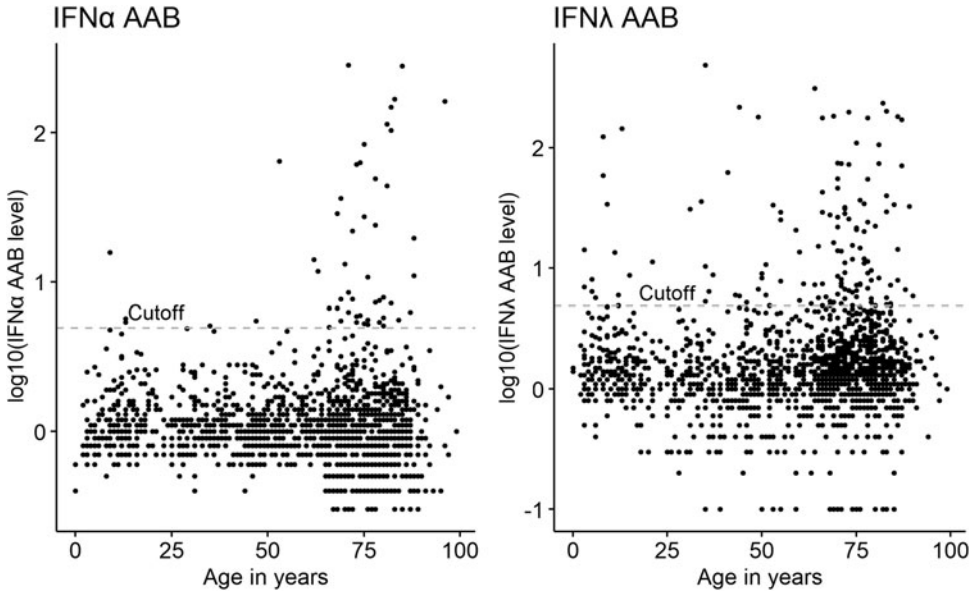

FIG. 1. Association of age and IFNα AAB (*left panel*) or IFNλ AAB (*right panel*) level in the SARS-CoV-2-naive group serum samples. AAB level was expressed on a common logarithmic (log10) scale. The cutoffs were 4.94 and 4.88 for IFNα AAB and IFNλ AAB, respectively. IFNα AAB, interferon α autoantibody; IFNλ AAB, interferon λ autoantibody.

(IFNα1, IFNα2, IFNα8, IFNα21) and for IFNλ AAB testing, 3 IFNλ subtypes IFNλ1–IFNλ3 (IL-29, IL-28A, IL-28B) were mixed. IFNλ4 was not included, because this is often a pseudogene due to a variant in the gene, and its secretion is inhibited in remaining individuals. Therefore, AABs are not expected to emerge. The prevalence of AABs among SARS-CoV-2-naive subjects (aged 2–99 years) was 2.9% [95% confidence interval (CI) 2.0%–3.9%] for IFNα AABs and 8.5% (95% CI 7.1%–10.1%) for IFNλ AABs. We identified only 9 individuals (0.6% CI 0.3%–1.1%) who tested double positive for both type I and type III IFN AABs.

The plots displaying AAB levels against age (Fig. 1) point to the accumulation of higher AAB values in older age groups. As expected, individuals with IFNα AAB were significantly older compared to AAB double-negative ones. Although the median age of IFNλ AAB-positive individuals was slightly higher in comparison to the double-negative group, these antibodies were detectable also in children in contrast to IFNα AABs (Fig. 2). While comparing the proportions of IFN AAB-positive and -negative individuals in different age groups, we found that the frequency of AAB double-negative cases was significantly higher in the younger (<65 y/o) age group, and IFN AAB-positive cases were more prevalent in the older (≥65 y/o) age group (Supplementary Table S1).

Sex was not associated with AAB prevalence (Supplementary Table S2). The biological impact of the slightly, although significantly, increased median levels of IFNα AABs in males, is probably low (Supplementary Fig. S3). While several AABs tend to be more prevalent in females, this is not the case for IFN AABs.

IFN AAB prevalence in COVID-19 patients

Next, we studied IFN AABs in COVID-19 patients. The overall prevalence of IFNα AABs in the COVID-19 cohort

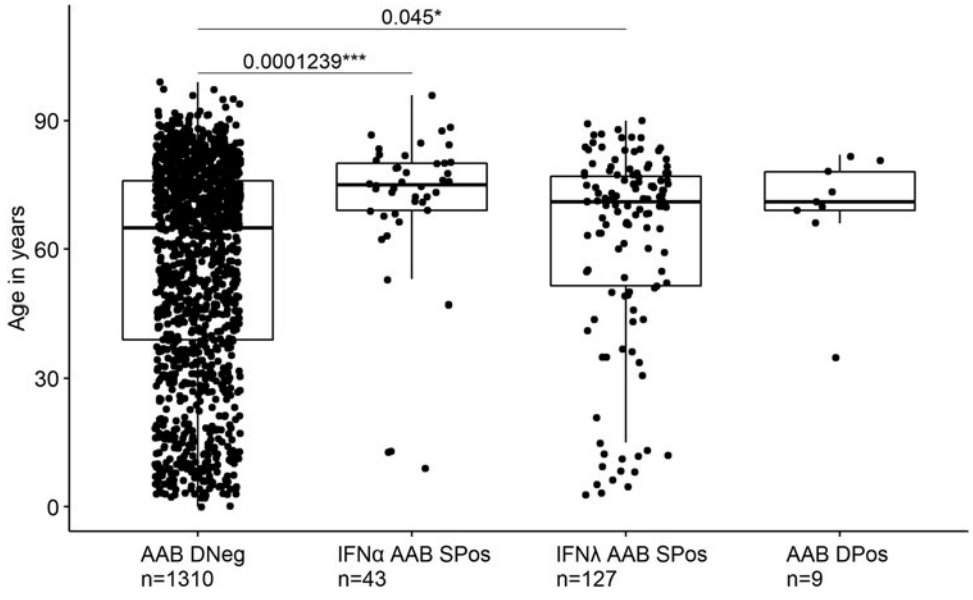

FIG. 2. Median age of SARS-CoV-2-naive individuals stratified by presence of anti-IFN AABs. The *upper* and *lower* edge of the *box* signify IQR and the whiskers correspond to 95% CI. Wilcoxon rank-sum test was applied to compare the groups pairwise, *P* value was adjusted with Bonferroni correction. AAB Dneg, IFNα, and IFNλ AAB negative; AAB DPos, IFNα and IFNλ AAB positive; CI, confidence interval; IFNα AAB SPos, interferon α autoantibody single positive; IFNλ AAB SPos, interferon λ autoantibody single positive; IQR, interquartile range.

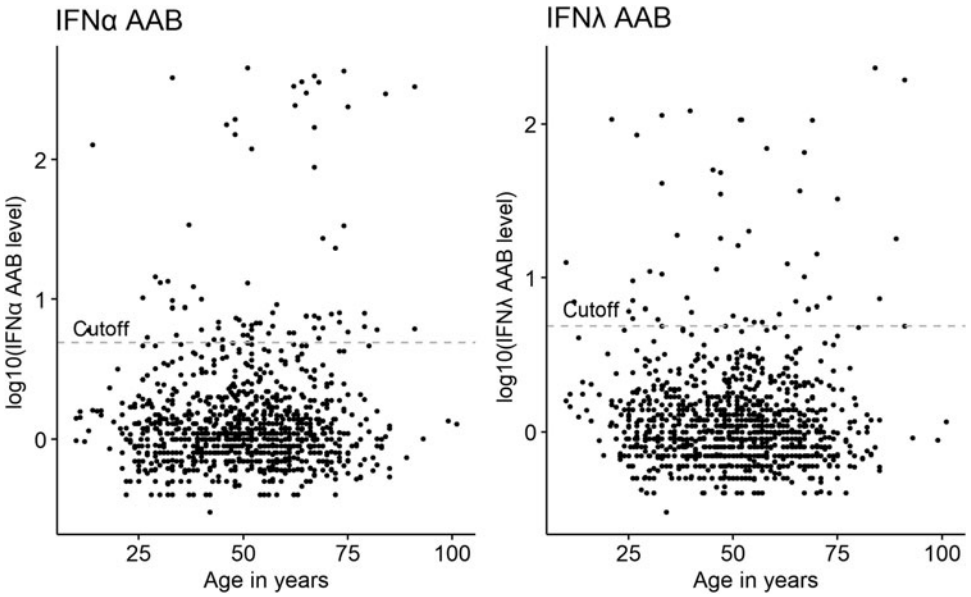

FIG. 3. Association of age and IFNα AAB (*left panel*) or IFNλ AAB (*right panel*) titer in COVID-19 patients. AAB titer was expressed on a common logarithmic (log10) scale. The cutoffs were 4.94 and 4.88 for IFNα AAB and IFNλ AAB, respectively. COVID-19, coronavirus disease 2019.

was 5.5% (95% CI 4.2%–7.1%), for IFNλ AABs, it was 3.4% (CI 2.4%–4.7%). Of patients, 1.7% (95% CI 1.0%–2.7%) were double positive. The proportion of double-positive serum samples among all IFN AAB-positive cases (either single- or double positive) was significantly higher in the COVID-19 group compared to SARS-CoV-2-naive individuals (16.0% vs. 5.0%, chi-square test of independence $P = 0.004$). IFNα AAB-positive COVID-19 patients were older than AAB-negative patients (Fig. 3 and Supplementary Fig. S4).

Bioactivity of IFN AABs assessed by neutralization assays

Apart from the level of binding AABs, their capacity to block IFN bioactivity is of importance. IFNα neutralization was tested in all COVID-19 patients from French and U.K. cohort. In SARS-CoV-2-naive individuals and in other COVID-19 cohorts, the assay was performed with samples above the cutoff level of binding AABs in serum samples available in sufficient quantities (numbers tested can be found in Tables 1 and 2). IFNα AAB level was significantly higher in neutralizing samples in comparison to non-neutralizing sera (Fig. 4).

Due to the relatively scant number of sera with available neutralizing data, we were not able to find a cutoff LIPS value using a receiver operating characteristic curve that would separate neutralizing sera from non-neutralizing sera. However, it can be estimated from the figure that for IFNα-neutralizing sera, the lowest IFNα AAB LIPS value was about 30, which indicates a luminescence signal 30 times higher than the mean value of the healthy controls ran with each LIPS assay.

Regarding the suggested importance of IFNλ for the protection of mucosal surfaces, the potential biological impact of IFNλ AABs is also of interest. Therefore, we performed neutralization assay with the reporter cells checking

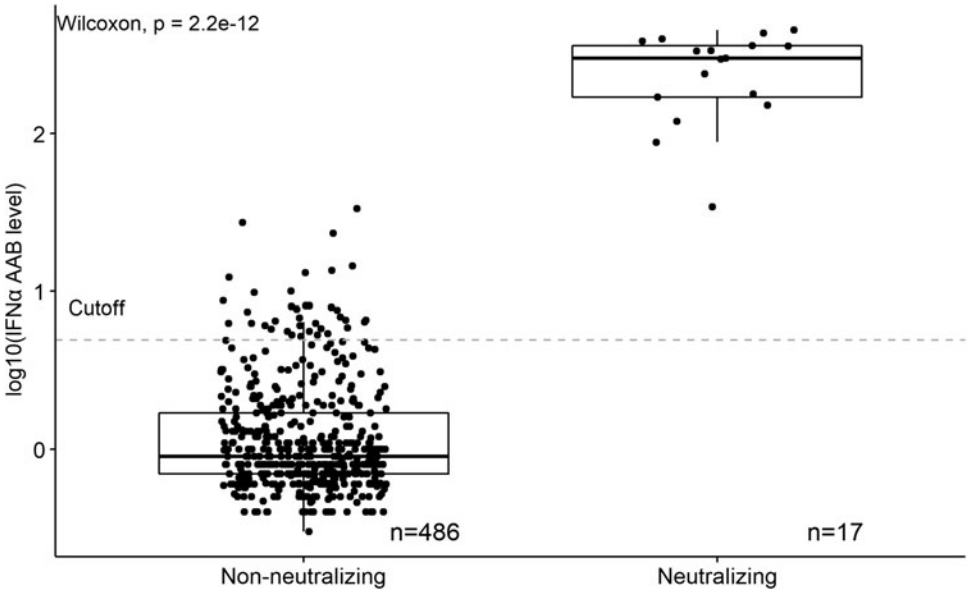

FIG. 4. IFNα AAB level difference between IFNα non-neutralizing and neutralizing COVID-19 patient sera. AAB level was expressed on a common logarithmic (log10) scale. The cutoff for IFNα AAB was 4.94. The *upper* and *lower* edge of the *box* signify IQR and the whiskers correspond to 95% CI. Wilcoxon rank-sum test was used to assess the statistical significance of the difference between the groups.

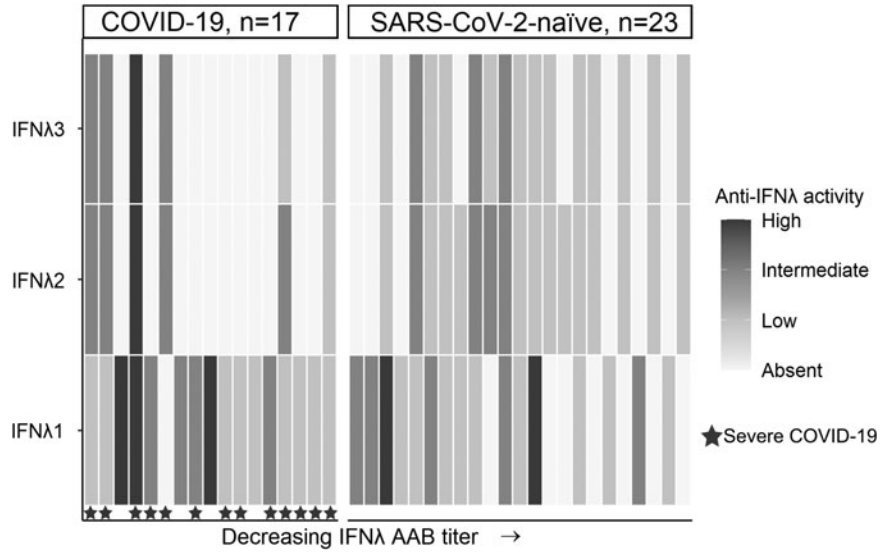

FIG. 5. IFNλ AAB neutralization activity against 3 IFNλ subtypes (IFNλ1–IFNλ3) among all sera with IFNλ AAB-binding value over 20. Analyzed sera are arranged based on IFNλ AAB level measured with LIPS (x-axis). For both COVID-19 and SARS-CoV-2-naive groups the sera (columns) on the left have the highest IFNλ AAB level. IFNλ neutralization activity was classified as follows: ''Absent''—IC_{50} ≤20; ''Low''—IC_{50} 20–500; ''Intermediate''—IC_{50} 500–10,000; ''High''—IC_{50} >10,000. Severe COVID-19 was defined according to WHO guidelines: pneumonia plus respiratory rate ≥30 breaths/min or SpO_2 <90% or patients with ARDS, sepsis or septic shock. ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; LIPS, luciferase-based immunoprecipitation system; WHO, World Health Organization.

the blocking activity of serum samples with or without IFNλ AABs using 3 different IFNλ subtypes separately. A total of 105 serum samples, including both COVID-19 patients (35%) and SARS-CoV-2-naive individuals (65%), were analyzed for IFNλ neutralization (Supplementary Table S3). All the serum samples with IFNλ AAB-binding value over 20 were selected ($n=71$) alongside with randomly selected sera with lower binding values or below the cutoff value. It was not necessary to test all seropositive sera on the lower end of the spectrum since previous experience demonstrated that significantly heightened AAB titers are a prerequisite for bioactivity.

The most common target of IFNλ NAABs was IFNλ1 (Fig. 5 and Supplementary Table S3), 16 COVID-19 patient samples inhibited the bioactivity of this IFN (prevalence in the whole group 1.6%) and 16 serum samples (1.1%) from the SARS-CoV-2-naive cohort. Only 5 serum samples from the COVID-19 cohort neutralized IFNλ2 and IFNλ3 in addition to IFNλ1, so that pan-IFNλ neutralization among the patients was as low as 0.5% (Supplementary Table S4). The respective percentage among SARS-CoV-2-naive samples was 0.6% (9 serum samples), while any of the 3 IFNλ subtypes was blocked by 23 serum samples (1.5%). The concentration of IFNλ1 neutralized by the serum samples ranged from 2 ng/mL to 10 μg/mL.

The association of IFNλ AAB level and IFNλ NAAB neutralization activity (as the sum of individually measured titers) was assessed both in the SARS-CoV-2-naive cohort and COVID-19 patients. We found that IFNλ AAB level of COVID-19 patients was in a strong correlation with IFNλ neutralization activity ($R=0.91$, $P<0.0001$, Fig. 6). In the SARS-CoV-2-naive cohort, a similar, although weaker, correlation was found ($R=0.72$, $P<0.0001$).

AABs and COVID-19 severity

Among COVID-19 patients with severe disease course, IFNα AABs were found in 9.1% (95% CI 6.7%–11.9%), which encompasses both IFNα-neutralizing and non-neutralizing sera. In comparison to IFNα AABs, IFNλ AABs were less prevalent (3.0%, 95% CI 1.7%–4.8%) among severe COVID-19 patients (Supplementary Figs. S5 and S6). The corresponding prevalence rates in patients with mild COVID-19 were 1.8% (95% CI 0.8%–3.4%) for IFNα AABs and 3.8% (95% CI 2.3%–5.9%) for IFNλ AABs. The results of multivariable logistic regression (additive model using age and sex as additional variables) performed in COVID-19 patients ($n=1,002$) point to IFNα AABs exclusively elevating the odds of developing severe disease—neither IFNλ AABs alone nor together with IFNα AABs had any significant effect on the disease course (Table 3).

Additional adjustment of the model with COVID-19 vaccination status did not change the results much (Supplementary Table S5). The median IFNα and IFNλ AAB levels were significantly different ($P=0.024$ for IFNα AABs and $P=0.0004$ for IFNλ AABs) between severe and mild COVID-19 groups, but as the means were very close, the biologic impact of the difference is probably negligible (Supplementary Fig. S6).

It is also important to study the association of IFNλ NAABs with the disease severity. Although there were too few neutralizing serum samples for proper statistical analysis, we could observe the following. All 5 patients who had pan-IFNλ NAABs suffered from severe COVID-19. Interestingly, 4 of them neutralized also IFNα (Supplementary Table S3). From 11 IFNλ1 selective-neutralizers 7 had severe disease and 1 of them had NAABs to IFNα too.

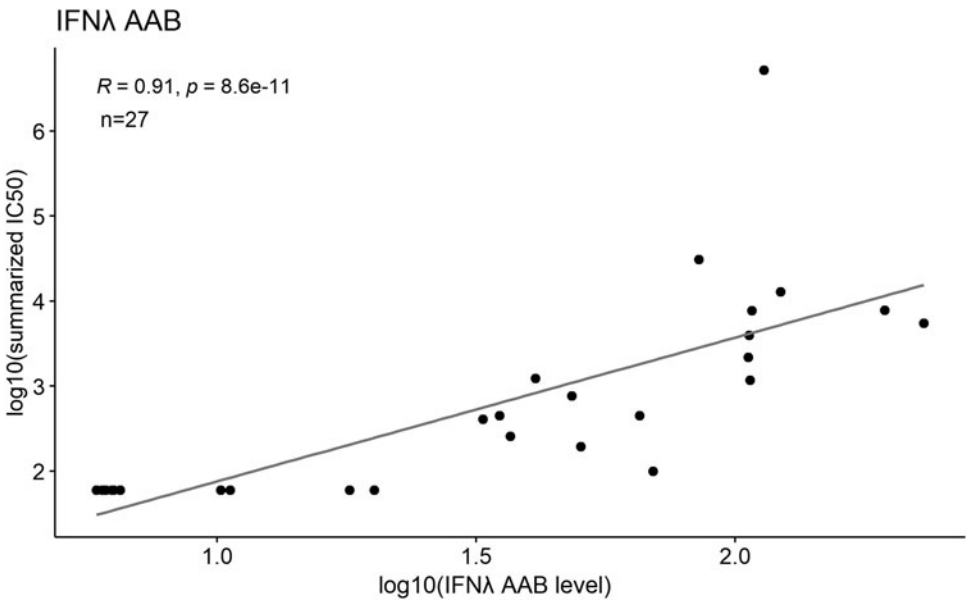

FIG. 6. Spearman correlation analysis of IFNλ AAB level and IFNλ AAB bioactivity expressed as IC_{50} (half maximal inhibitory concentration) in selected IFNλ AAB-positive COVID-19 patients ($n=27$). AAB bioactivity was obtained by summarizing the IC_{50} values against 3 IFNλ subtypes (IFNλ1, IFNλ2, and IFNλ3). Both AAB titer and bioactivity were plotted on a common logarithmic (log10) scale.

As IFN-IIIs have in addition to antiviral activity antifungal effects (Espinosa et al., 2017), we tested the association of IFNλ AABs with invasive pulmonary aspergillosis as a complication of COVID-19. Out of 13 patients with aspergillosis superinfection, only 1 patient exhibited neutralization of IFNλ (over the 3 subtypes).

In sum, NAABs toward IFN-IIIs are relatively infrequent in comparison to IFNα NAABs, and probably unable to modify COVID-19 course on their own. Their potentially aggravating role in combination with NAABs toward IFN-Is would require further studies.

Discussion

AABs to IFN-I and other cytokines are quantified using various methods, each of them having certain strengths and weaknesses (Puel et al., 2022). COVID-19-related studies embrace neutralization assay as a gold standard to which other methods are compared to (Eto et al., 2022; Manry et al., 2022). ELISA, although simple and accessible, can be prone to false positives and negatives (Eto et al., 2022). Gyros and bead-based assays perform better (Bastard et al., 2021a; Bastard et al., 2020; Chang et al., 2021). Screening methods that use full length proteins, as rapid extracellular antigen profiling (REAP), have permitted the discovery of IFNα AABs, but those that rely on the expression of shorter peptides as phage immunoprecipitation sequencing (PhIP-Seq) do not (Vazquez et al., 2022; Vazquez et al., 2020; Wang et al., 2021).

Many of the epitopes on IFNαs are conformational—when the proper 3D structure is disrupted, most of the binding activity of the AABs is lost (Kärner et al., 2013). LIPS, the method where the conformation of the antigens is well preserved, has shown very high sensitivity in previous studies (Meyer et al., 2016), and excellent match with the neutralization assay in the current study. According to LIPS-binding values, it is possible to predict the neutralization capacity of respective serum samples (Fig. 4). Neutralizing assays might seem an ideal option but sometimes also non-NAABs can give further valuable information: for example, they can contain a subpopulation of cytokine stabilizing/enhancing AABs as suggested by a recent study in systemic lupus erythematosus (SLE) patients and the broad screen of AABs in COVID-19 (Bradford et al., 2023; Wang et al., 2021).

The present study confirmed previous findings about IFNα AABs: their increased prevalence in older individuals and their association with severe COVID-19 (Bastard et al., 2021a; Bastard et al., 2020; Manry et al., 2022). The data about IFNω and IFNβ AABs in this study were not complete due to the limited volume of several patient samples, and therefore were omitted from the analysis.

The primary focus of the present study was IFNλ AABs. To date, IFNλ AABs have been detected in diseases that are characterized by high or moderate prevalence of AABs toward IFNα: autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), thymoma, and SLE (Bradford et al., 2023; Burbelo et al., 2010; Meager et al., 2006; Meyer et al., 2016). In APECED patients, IFNλ1 is the main target (AAB prevalence 30%) while IFNλ2 and IFNλ3 are bound only if AABs to IFNλ1 are also present (detectable in 15% of patients) (Meyer et al., 2016).

Table 3. Analysis of the Relationship Between Interferon Autoantibody Status and Disease Severity in Coronavirus Disease 2019 Patients ($N=1{,}002$) Using Multivariable Logistic Regression

AAB status	*Count (%)*	*Severe COVID-19, OR (95% CI)*	P
AAB DNeg	896 (89.4)	—	—
IFNα AAB SPos	55 (5.5)	4.88 (2.40–11.06)	<0.001
IFNλ AAB SPos	34 (3.4)	0.84 (0.40–1.73)	0.63
AAB DPos	17 (1.7)	1.78 (0.62–5.52)	0.30
Total count	1,002	—	—

Besides IFN AAB status, age and sex were used as explanatory variables.

AAB DNeg, IFNα and IFNλ AAB negative; CI, confidence interval; OR, odds ratio.

Approximately 2/3 of the type III AAB-positive APECED sera are neutralizing (Meager et al., 2006).

AABs to IFNλ are difficult to detect, possibly due to the epitopes that are extremely sensitive to conformational changes. Techniques that rely on the expression of shorter peptides (eg, PhIP-Seq), or antigen binding on the solid surfaces have failed to detect AABs to IFN-III (Chang et al., 2021; Vazquez et al., 2020) (our own unpublished observations). However, REAP method has recovered reactivity toward IFN-III in healthy controls as well as in COVID-19 patients (Wang et al., 2021). LIPS method has shown its advantages again in this study and in previous publications on APECED and thymoma (Burbelo et al., 2010; Meyer et al., 2016).

The discovery that IFN-I NAABs are an important risk factor for developing severe COVID-19 helped to verify the essential role of IFN-I in limiting the infection by SARS-CoV-2. An obvious next question is if we can learn about IFN-IIIs in a similar way. It is established that IFN-IIIs are specialized in epithelial surface protection and can restrict SARS-CoV-2 proliferation *in vitro*. Specific contribution from each subtype is less known. There are some hints that the relative resistance of children to COVID-19 may be the result of their higher local production of IFNλ1 in response to SARS-CoV-2 infection in comparison to adults (Gilbert et al., 2021), and that children and patients with mild disease have higher levels of serum IFNλ1 and IFNλ2/3 than patients with severe COVID-19 (Jeong et al., 2023).

We discovered that IFNλ AABs are relatively common in the SARS-CoV-2-naive cohort and among COVID-19 patients. Their frequency increases slightly with age but not as dramatically as is the case of IFNα AABs. Our SARS-CoV-2-naive sample contained 3 subgroups consisting of mainly older people (median age ≥70, Table 2) with increased prevalence of IFNλ AABs. This explains the seemingly higher prevalence of IFNλ AABs in SARS-COV-2-naive individuals in comparison to COVID-19 cohort. Importantly, the neutralizing capacity toward the 3 IFNλ subtypes remained below the detection limit in the majority of the IFNλ AAB-positive cases. Like in APECED patients, IFNλ1 was neutralized more often than the IFNλ2/3 subtypes in COVID-19 patients, while the SARS-CoV-2-naive group showed more equal distribution of AAB neutralization targets.

The frequency of IFNα and IFNλ AAB double-positive individuals is very low in SARS-CoV-2 naive cohort pointing to different causes for their induction. Significantly, higher proportion of double-positive serum samples in COVID-19 group is intriguing, suggesting that the tolerance toward IFNλ could be disrupted after SARS-CoV-2 infection in some cases.

COVID-19 patients are characterized by increased frequency of various AABs (Burbelo et al., 2022; Chang et al., 2021; Vazquez et al., 2022; Wang et al., 2021). Some of the specificities can be induced by SARS-CoV-2 infection, the others (among them IFNα AABs) were estimated to be pre-existing (Wang et al., 2021). The origin of IFNλ AABs remains unknown, but as the total frequency of IFNλ AABs was not increased in the COVID-19 cohort in comparison to the SARS-CoV-2-naive cohort, they are likely pre-existing in the majority of cases.

The role of type III IFNs in humans has not been genetically clarified, although the patients with IL-10RB deficiency have been mildly affected by SARS-CoV-2 (Abolhassani et al., 2022). This resistance, although, does not apply to all viral infections, as 2 siblings with defective IL-10RB have succumbed to fulminant viral hepatitis (Korol et al., 2023). Parallel hints can be derived from animal models. Stat2$^{-/-}$ (lacking both IFN-I and IFN-III responses) hamsters cannot control SARS-CoV-2 infection, whereas this infection is successfully controlled by Il-28r$^{-/-}$ (deficient for IFN-III response only) animals (Boudewijns et al., 2020).

We suggest that AABs to IFNλ are neutral to COVID-19 course due to their infrequent neutralization capacity and their interchangeability in case a single IFNλ subtype is blocked. However, taking into the account the analogy with IFN-I family, where the risk of severe COVID-19 increases with the number of family members affected, it is possible that additional pan-IFNλ neutralization can contribute to the equation even more. It may seem tempting to consider IFNλ AABs as potentially protective against severe COVID-19, but the odds ratio (OR) obtained from the multivariable logistic regression analysis (0.84; 95% CI 0.40–1.73) does not provide statistically significant support for this hypothesis.

This study has some limitations, which may have affected the results. First, the IFN AAB positivity cutoffs were relatively low—for this reason a large proportion of IFN AAB-positive sera are not capable of neutralizing IFNs. Second, IFNα AAB neutralization activity data were fully available for only 2 cohorts of COVID-19 patients and for IFNλ AABs, only sera containing high levels of IFNλ AABs were analyzed for bioactivity. Third, SARS-CoV-2-naive group represents only Estonian population containing a proportion of samples derived from patients from internal medicine and dermatology clinics, meaning that this cohort of patients should not be held for healthy controls. Finally, the low number of pan-IFNλ neutralizing sera prevents us drawing definite conclusions about the pathogenicity of these NAABs.

Conclusions

Although AABs toward IFN-III are readily detectable in serum samples derived from SARS-CoV-2-naive individuals as well as from COVID-19 patients, their neutralizing capacity is limited to very rare cases. Regarding all the current evidence, we suggest that IFNλ AABs on their own, even if neutralizing, are not capable of modifying COVID-19 course, but in combination with impaired type I IFN responses might further increase the susceptibility to severe COVID-19.

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Authors' Contributions

M.V., L.H., K.S, P.B., and A.F. generated the main data sets, analyzed, and interpreted them. M.V. performed statistical analysis and prepared the figures. S.E.J., A.K.,

K.Kalle., M.L., M.M., T.H., S.B.K., J.M.-S., CIRCO, COVID-HGE, and T.H.M. collected patient samples, curated, and analyzed clinical data. P.P., P.B., A.P., Q.P., and J.-L.C. supervised the research, K.Kai., A.P., Q.P., and J.-L.C. designed the study. K.Kai. coordinated the study, M.V., K.Kai., and J.-L.C. wrote the article. All authors discussed the results and commented and edited the article.

Author Disclosure Statement

J.-L.C. is an inventor on patent application PCT/US2021/042741, filed July 22, 2021, submitted by The Rockefeller University that covers diagnosis of susceptibility to, and treatment of viral disease and viral vaccines, including COVID-19 and vaccine-associated diseases.

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Supplementary Material

Supplementary Materials
Supplementary Figure S1
Supplementary Figure S2
Supplementary Figure S3
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Supplementary Figure S6
Supplementary Table S1
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