CORONAVIRUS

Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths

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Circulating autoantibodies (auto-Abs) neutralizing high concentrations (10 ng/ml; in plasma diluted 1:10) of IFN-α and/or IFN-ω are found in about 10% of patients with critical COVID-19 (coronavirus disease 2019) pneumonia but not in individuals with asymptomatic infections. We detect auto-Abs neutralizing 100-fold lower, more physiological, concentrations of IFN-α and/or IFN-ω (100 pg/ml; in 1:10 dilutions of plasma) in 13.6% of 3595 patients with critical COVID-19, including 21% of 374 patients >80 years, and 6.5% of 522 patients with severe COVID-19. These antibodies are also detected in 18% of the 1124 deceased patients (aged 20 days to 99 years; mean: 70 years). Moreover, another 1.3% of patients with critical COVID-19 and 0.9% of the deceased patients have auto-Abs neutralizing high concentrations of IFN-β. We also show, in a sample of 34,159 uninfected individuals from the general population, that auto-Abs neutralizing high concentrations of IFN-α and/or IFN-ω are present in 0.18% of individuals between 18 and 69 years, 1.1% between 70 and 79 years, and 3.4% >80 years. Moreover, the proportion of individuals carrying auto-Abs neutralizing lower concentrations is greater in a subsample of 10,778 uninfected individuals: 1% of individuals <70 years, 2.3% between 70 and 80 years, and 6.3% >80 years. By contrast, auto-Abs neutralizing IFN-β do not become more frequent with age. Auto-Abs neutralizing type I IFNs predate SARS-CoV-2 infection and sharply increase in prevalence after the age of 70 years. They account for about 20% of both critical COVID-19 cases in the over 80s and total fatal COVID-19 cases.

INTRODUCTION

Since the start of the coronavirus disease 2019 (COVID-19) pandemic in December 2019, more than 200 million people have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulting in at least 4 million deaths and probably closer to 7 to 9 million deaths worldwide. Interindividual clinical variability in the course of acute infection is vast, extending from silent or mild infection in about 90% of individuals to pneumonia and respiratory failure, both requiring hospitalization, in less than 10 and 2% of cases, respectively. Age is the major epidemiological risk factor for hospitalization or death from pneumonia, the risk doubling with every 5 years of age (*1*, *2*). The frequencies of critical disease and death from COVID-19 are higher in men than in women (*3*–*5*). With the COVID Human Genetic Effort (*6*), we previously reported that inborn errors of Toll-like receptor 3 (TLR3)– and interferon (IFN) regulatory factor 7 (IRF7)–dependent type I IFN induction and amplification can underlie life-threatening COVID-19 pneumonia in a small subset of patients (*7*, *8*). Autosomal dominant disorders were found in 19 patients, but our cohort also included four previously healthy unrelated adults aged 25 to 50 years with autosomal recessive, complete IRF7 ($N = 2$) or IFN-α/β receptor 1 (IFNAR1) ($N = 2$) deficiency. These findings indicated that type I IFN immunity is essential for protective immunity to respiratory infection with SARS-CoV-2 but unexpectedly redundant otherwise. We also reported that an autoimmune phenocopy of inborn errors of type I IFN–dependent immunity can underlie critical COVID-19 pneumonia (*9*). Autoantibodies (auto-Abs) neutralizing IFN-α2 and/or IFN-ω (10 ng/ml) were found in the blood of at least 10% of an international cohort of patients with life-threatening COVID-19 pneumonia but in none of the tested individuals with asymptomatic or paucisymptomatic infection (*9*). These auto-Abs were detected in serum or plasma diluted 1:10. The auto-Abs in the patients' undiluted

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blood can therefore probably neutralize as much as IFN-α2 and/or IFN-ω (100 ng/ml). The 17 subtypes of type I IFNs—including 13 IFN-α subtypes, IFN-ω, IFN-β, IFN-ε, and IFN-κ—bind to the same heterodimeric receptor (IFNAR1 and IFNAR2) (*10*). The 13 IFN-α subtypes and IFN-ω are closely related phylogenetically, whereas IFN-β, IFN-ε, and IFN-κ are more distant (*9*). The auto-Abs to IFN-α2 and/or IFN-ω were mostly found in men (95%) and in the elderly (half the patients with antibodies being over the age of 65 years) (*9*). These findings were later replicated in independent cohorts from Amsterdam, Lyon, Madrid, New Haven, and San Francisco (*11*–*16*).

These auto-Abs against type I IFNs were found in about 0.3% of a general population sample of 1227 individuals collected before the pandemic and aged 20 to 69 years, suggesting that they predated SARS-CoV-2 infection and caused critical COVID-19 rather than being triggered by it (*9*). Moreover, production of these antibodies can be genetically driven and can begin during early childhood, as attested by their presence in almost all patients with autoimmune polyendocrine syndrome type-1 (APS-1) due to germline mutations of *AIRE* (*17*–*19*). Patients with APS-1 are at very high risk of developing severe or critical COVID-19 pneumonia (*20*, *21*). These auto-Abs are also found in patients with combined immunodeficiency and hypomorphic mutations of *RAG1* or *RAG2* (*22*); in men with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome and mutations of *FOXP3* (*23*); and in women with incontinentia pigmenti and heterozygous null mutations of X-linked *NEMO* (*9*). They are also seen in patients treated with IFN-α or IFN-β (*24*, *25*) and in patients with systemic lupus erythematosus (*26*, *27*), thymoma (*28*), or with myasthenia gravis (*29*, *30*). Last, they underlie a third of adverse reactions to the 17D live-attenuated vaccine against yellow fever virus (YFV), further suggesting that they were present in these patients, as in patients with critical COVID-19, before viral infection (*31*). For all patients tested, the auto-Abs neutralized the protective effect of IFN-α2 (~400 pg/ml) against SARS-CoV-2 or YFV-17D in vitro, even when the plasma was diluted by >1:1000 (*9*). Because blood IFN-α concentrations during acute asymptomatic or paucisymptomatic SARS-CoV-2 infection typically range from 1 to 100 pg/ml (*32*, *33*) and IFN-α levels in the respiratory tract might be even lower yet protective, we hypothesized that auto-Abs neutralizing concentrations of type I IFNs below 10 ng/ml may underlie life-threatening COVID-19 pneumonia in more than 10% of cases. We also hypothesized that the prevalence of auto-Abs against type I IFNs in the general, uninfected population may increase with age and that these antibodies may be more common in men than in women.

RESULTS

High and intermediate levels of IgG auto-Abs against IFN-α2 and/or IFN-ω in ~20% of patients with critical COVID-19

We recruited a cohort of 3595 patients hospitalized with critical COVID-19 pneumonia [hereafter referred to as "critical patients" and defined as pneumonia in patients with critical disease, including (i) pulmonary, with high-flow oxygen (>6 liters/min) or mechanical ventilation (continuous positive airway pressure, bilevel positive airway pressure, and intubation), (ii) cardiovascular shock, or (iii) any other organ failure requiring admission to an intensive care unit], including 566 patients of our previously described cohort of 987 patients with critical COVID-19 pneumonia for whom residual samples were available (*9*), 623 individuals with severe COVID-19 pneumonia (with less than 6 liters/min of oxygen supplementation, hereafter referred to as "severe patients"), and 1639 individuals with asymptomatic or paucisymptomatic (mild) upper respiratory tract SARS-CoV-2 infection {the "controls," infected with SARS-CoV-2 [as demonstrated by a positive polymerase chain reaction (PCR) and/or serological test and/or displaying typical manifestations, such as anosmia/ageusia after exposure to a confirmed COVID-19 case] who remained asymptomatic or developed mild, self-healing, ambulatory disease with no evidence of pneumonia}, including 427 samples from the initial control cohort of 663 individuals (*9*). The patients originated from 38 different countries, across all continents. We did not include patients with moderate pneumonia who did not receive oxygen therapy (*7*, *9*). We searched for auto-Abs against IFN-α2 and IFN-ω by establishing novel, sensitive, and robust assays for the detection of circulating immunoglobulin G (IgG) auto-Abs. We used Gyros Technology (*34*), a high-throughput automated enzyme-linked immunosorbent assay (ELISA)–like assay capable of detecting a large range of auto-Ab levels (fig. S1A). We confirmed that the Gyros technique was as sensitive as the techniques previously used (ELISA and Luminex) and that all tested patients with high levels of anti–IFN-α2 and/or anti–IFN-ω auto-Abs on ELISA, as reported in our previous studies (defined as an optical density > 0.5), had high levels of auto-Abs when assessed with Gyros (defined as levels >100) (fig. S1B). We then screened newly recruited critical or severe patients and controls from our COVID-19 cohort (Fig. 1A). We found high levels of anti–IFN-α2 and/or anti–IFN-ω auto-Abs in 6.9% of critical patients, 3.4% of patients with severe COVID-19, and only 0.6% of the asymptomatic or paucisymptomatic controls (Fig. 1A). We also found that another 12.7% of patients with critical COVID-19 had intermediate levels of anti–IFN-α2 and/or anti–IFN-ω auto-Abs in Gyros assays (defined as levels >30 and <100, based on the distribution observed in healthy controls), whereas this was the case for 8.6% of patients with severe COVID-19 and 11% of the individuals in our control cohort. Collectively, these findings replicate and extend our previous results and those of other groups (*9*, *11*–*16*) while suggesting that intermediate levels of auto-Abs against type I IFNs might be neutralizing and underlie critical disease.

Auto-Abs neutralizing IFN-α2 and/or IFN-ω (10 ng/ml) in almost 10% of the critical patients

We investigated the ability of these auto-Abs to neutralize high concentrations of type I IFNs, as defined in our previous reports [IFN-α2 or IFN-ω (10 ng/ml) in medium containing 1:10 plasma or serum, the equivalent of IFN-α2 or IFN-ω (100 ng/ml) in undiluted plasma]. We tested not only the patients with high levels of auto-Abs, as in our previous study (*9*), but also all the available patients with critical COVID-19 (N = 3136), or severe COVID-19 (N = 623), and controls (N = 1076) from our expanded cohort. We designed a high-throughput luciferase assay in which we transfected human embryonic kidney (HEK) 293 T cells with (i) a plasmid containing five IFN-stimulated response element (ISRE) repeats and a firefly luciferase reporter and (ii) a plasmid encoding the *Renilla* luciferase. We stimulated these cells with an individual recombinant type I IFN (IFN-α2 or IFN-ω) in the presence of plasma diluted 1:10 (plasma 1:10) from patients or controls. We then measured firefly luciferase induction, normalized against *Renilla* luciferase activity (Fig. 1B). We confirmed the robustness of this assay by comparing the results with our previous phosphorylated signal transducer and activator of transcription 1 (pSTAT1) flow cytometry data (*9*). Consistent results were obtained for all 50 patients tested with both techniques

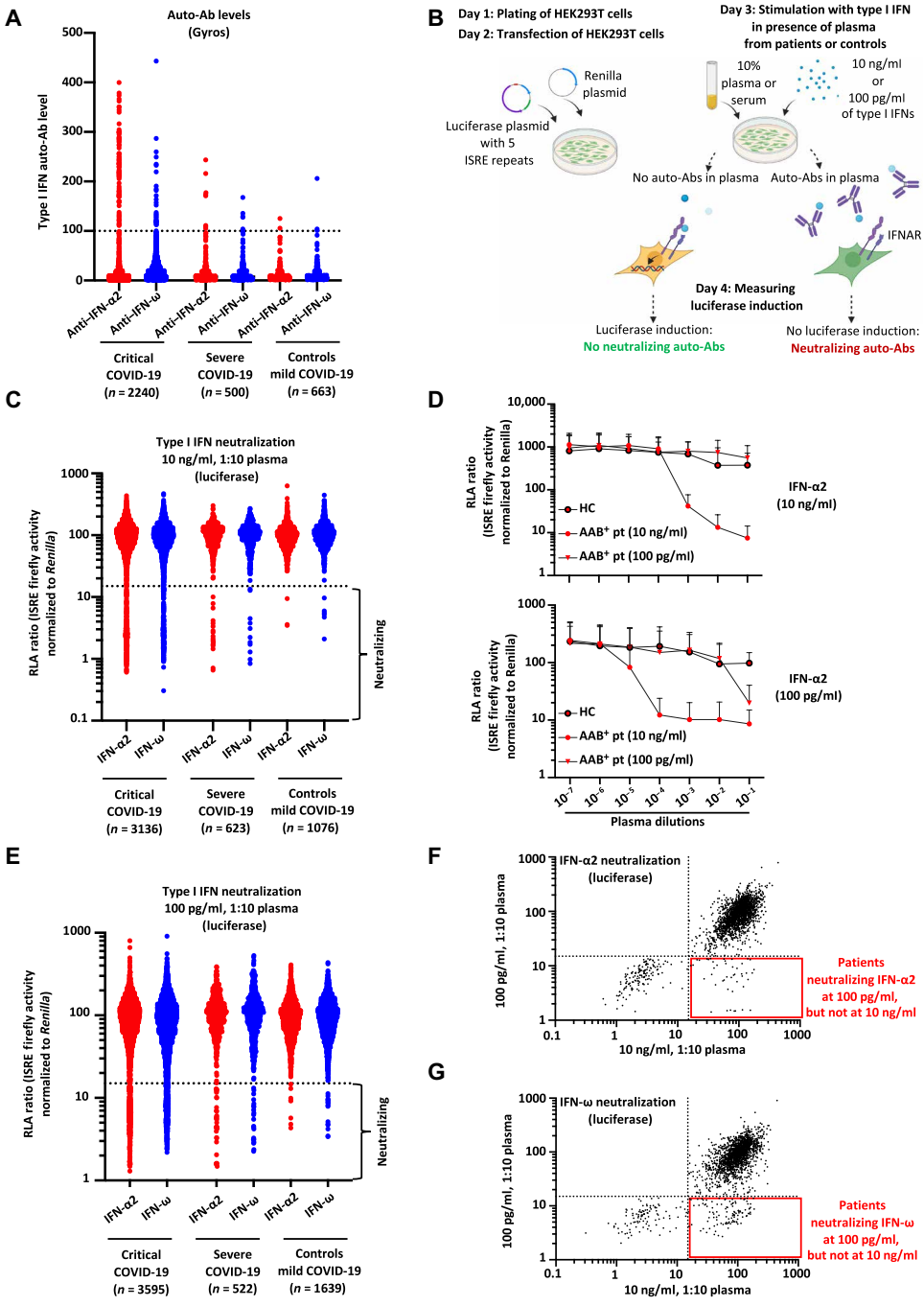

Fig. 1. Neutralizing auto-Abs against IFN-α2 and/or IFN-ω in patients with life-threatening COVID-19. (**A**) Gyros (high-throughput automated ELISA) results for auto-Abs against IFN-α2 and/or IFN-ω in patients with critical COVID-19 ($N = 2240$), severe COVID-19 ($N = 500$), or asymptomatic/mild SARS-CoV-2 infection ($N = 663$). (**B**) Schematic representation of the neutralization assay developed in HEK293T cells using a luciferase system. ISRE, interferon (IFN)–sensitive response elements. (**C**) Results for the neutralization of IFN-α2 or IFN-ω (10 ng/ml) in the presence of plasma 1:10 from patients with critical COVID-19 ($N = 3136$), severe COVID-19 ($N = 623$), or controls with mild/asymptomatic infection ($N = 1076$). Relative luciferase activity is shown (ISRE dual luciferase activity, with normalization against *Renilla* luciferase activity) after stimulation with IFN-α2 or IFN-ω (10 ng/ml) in the presence of plasma 1:10. RLA, relative luciferase activity. (**D**) RLA after stimulation with IFN-α2 at a concentration of 10 ng/ml or 100 pg/ml, with various dilutions of plasma from a positive control (from 1:10 to $1:10^7$) neutralizing 10 ng/ml of type I IFNs (AAB^+ pt, 10 ng/ml), a patient neutralizing type I IFNs (100 pg/ml) but not 10 ng/ml (AAB^+ pt, 100 pg/ml), and a healthy control (HC). AAB, auto-Ab. Pt, patient. (**E**) Neutralization IFN-α2 or IFN-ω (100 pg/ml) in the presence of plasma 1:10 from patients with critical COVID-19 ($N = 3595$), severe COVID-19 ($N = 522$), or controls with asymptomatic/mild infection ($N = 1639$). (**F**) Plot showing luciferase induction after stimulation with IFN-α2 (10 ng/ml or 100 pg/ml), in the presence of plasma from patients with critical COVID-19. Dotted lines indicate neutralizing levels, defined as induction levels below 15% of the mean value for controls tested the same day. Patients with auto-Abs neutralizing both IFN-α2 (10 ng/ml and 100 pg/ml) are shown in the bottom left corner, whereas the patients in the bottom right corner had auto-Abs capable of neutralizing only IFN-α2 (100 pg/ml). (**G**) Plot showing luciferase induction after stimulation with IFN-ω (10 ng/ml or 100 pg/ml) for patients with critical COVID-19.

(fig. S1, C and D). We then tested all patients and controls. Most plasma samples with high auto-Ab levels (>100) against IFN-α2 according to the Gyros assay were neutralizing (fig. S1E). We found that 9.8% (307 of 3136) of the critical patients tested and that 3.53% (22 of 623) of the severe patients had auto-Abs neutralizing IFN-α2 and/or IFN-ω versus only 0.37% (four of 1076) controls (Fig. 1C, Table 1, and table S1). In the patients with neutralizing auto-Abs, these auto-Abs were able to neutralize both IFN-α2 and IFN-ω in 175 of the 307 critical patients (57%), six of the severe patients (27%), and none of the controls; IFN-α2 alone in 106 critical patients (34.5%), 11 severe patients (50%), and only one of the controls (25%); and IFN-ω alone in 26 of critical patients (8.5%), five severe patients (22%), and three controls (75%) (table S1). None of the patients with these auto-Abs had inborn errors of TLR3- or TLR7-dependent type I IFN immunity (*7*, *35*).

Auto-Abs neutralizing IFN-α2 and/or IFN-ω (100 pg/ml) in at least 13.6% of critical patients and 6.8% of severe patients

Because the amounts of circulating type I IFNs in infected individuals are 100 to 1000 times lower than the amounts tested previously (*32*, *33*), we investigated the neutralization of more physiological concentrations of type I IFNs by performing assays with type I IFN (100 pg/ml). We observed a robust response in our luciferase system in the presence of 1:10 dilutions of control plasma (fig. S1F). The plasma or serum was diluted 1:10, so the concentration neutralized corresponds to IFN (1 ng/ml) in circulating whole blood. With diluted plasma samples from a positive control, we gained at least two orders of magnitude of sensitivity in terms of neutralizing activity, providing proof of concept that these auto-Abs can neutralize lower, more physiological, amounts of type I IFNs (Fig. 1D and fig. S1G), lower than the concentrations previously tested by a factor of 100 (*9*). We then retested all available samples from our extended cohort. Overall, 13.6% of all critical patients tested (N = 489 of 3595), 6.5% (N = 34 of 522) of the severe patients, and 1% of the controls (N = 17 of 1639) had circulating auto-Abs that neutralized IFN-α2 and/or IFN-ω (100 pg/ml) in plasma 1:10 (Fig. 1, E to G, Table 1, and table S1). In the patients with neutralizing auto-Abs, these auto-Abs were able to neutralize both IFN-α2 and IFN-ω in 256 of the 489 positive critical patients (52%), 18 of the 34 severe patients (53%), and 1 of the 17 controls (6%); IFN-α2 alone in 104 critical patients (21%), 14 severe patients (41%), and four of the controls (23.5%); and IFN-ω alone in 129 critical patients (26%), two severe

Table 1. Risk of critical COVID-19 pneumonia for individuals carrying auto-Abs to specific sets of type I IFNs, when compared with that of asymptomatic/mild infection, adjusted on age and sex. OR and *P* values were estimated by means of Firth's bias-corrected logistic regression. The numbers and proportions of individuals with critical COVID-19 pneumonia (patients) and asymptomatic or mild infection (controls) are shown in Figs. 1 to 3. Two combinations are not shown due to insufficient number of individuals: anti–IFN-β (10 ng/ml) and anti–IFN-α2 (100 pg/ml) auto-Abs only and anti–IFN-β (10 ng/ml) and anti–IFN-ω (100 pg/ml) auto-Abs only.

Anti–type I IFN auto-Ab positive (amount of type I IFN neutralized, in plasma diluted 1:10)	Proportion of critical patients with neutralizing auto-Abs	OR [95% CI]	*P* value
Anti–IFN-α2 and anti–IFN-ω auto-Abs (10 ng/ml)	5.6%	67 [4–1109]	7.8×10^{-13}
Anti–IFN-α2 and/or anti–IFN-ω auto-Abs (10 ng/ml)	9.8%	17 [7–45]	$<10^{-13}$
Anti–IFN-α2 auto-Abs (10 ng/ml)	9%	45 [9–225]	$<10^{-13}$
Anti–IFN-α2 auto-Abs only (10 ng/ml)	3.4%	21 [4–107]	1.8×10^{-09}
Anti–IFN-ω auto-Abs (10 ng/ml)	6.4%	13 [4–38]	1.4×10^{-12}
Anti–IFN-ω auto-Abs only (10 ng/ml)	0.8%	3 [0.9–10]	0.057
Anti–IFN-α2 and anti–IFN-ω auto-Abs (100 pg/ml)	7.1%	54 [11–275]	$<10^{-13}$
Anti–IFN-α2 and/or anti–IFN-ω auto-Abs (100 pg/ml)	13.6%	13 [8–21]	$<10^{-13}$
Anti–IFN-α2 auto-Abs (100 pg/ml)	10%	23 [10–55]	$<10^{-13}$
Anti–IFN-α2 auto-Abs only (100 pg/ml)	2.9%	10 [3–26]	2.8×10^{-09}
Anti–IFN-ω auto-Abs (100 pg/ml)	10.7%	13 [7–23]	$<10^{-13}$
Anti–IFN-ω auto-Abs only (100 pg/ml)	3.6%	6 [3–12]	3.9×10^{-10}
Anti–IFN-β auto-Abs (10 ng/ml)	1.3%	8 [2–36]	1.7×10^{-3}
Anti–IFN-β auto-Abs only (10 ng/ml)	0.96%	5 [1–25]	0.043
Anti–IFN-β auto-Abs (10 ng/ml) and anti–IFN-α2 and/or anti–IFN-ω auto-Abs (100 pg/ml)	0.34%	16 [0.5–497]	0.018
Anti–IFN-β (10 ng/ml) and anti–IFN-α2 and anti–IFN-ω auto-Abs (100 pg/ml)	0.28%	16 [0.5–502]	0.019

patients (6%), and 12 controls (70%) (table S1). Further dilution of a plasma sample from one patient neutralizing type I IFNs (100 pg/ml) led to a loss of neutralizing activity (Fig. 1D and fig. S1G). For four unrelated patients, all of whom suffered from critical COVID-19, including one who died, samples collected before COVID-19 were available and tested positive for neutralizing auto-Abs against type I IFNs. One neutralized IFN-α2 and IFN-ω at a concentration of 10 ng/ml, two neutralized both cytokines at 100 pg/ml, and one neutralized IFN-ω only at 100 pg/ml (fig. S1H). The four patients tested therefore had auto-Abs neutralizing IFN-α2 and/or IFN-ω (10 ng/ml or 100 pg/ml) before infection with SARS-CoV-2. These four patients and another two reported in our previous study (*9*) all, therefore, had auto-Abs neutralizing type I IFNs before infection with SARS-CoV-2. We then assessed the risk, adjusted for age and sex, of having critical or severe disease for individuals carrying auto-Abs against each individual IFN and the different possible combinations. We found that all auto-Abs, except those neutralizing only IFN-ω at a concentration of 10 ng/ml, were highly significant risk factors in comparisons of patients with critical or severe COVID-19 with controls (Table 1 and table S2). The strongest association was with auto-Abs against both IFN-α2 and IFN-ω neutralizing concentrations at 10 ng/ml [odds ratio (OR) = 67, $P = 8 \times 10^{-13}$] and 100 pg/ml (OR = 54, $P < 10^{-13}$), followed by those against IFN-α2 ± IFN-ω neutralizing concentrations at 10 ng/ml (OR = 45, $P < 10^{-13}$) and 100 pg/ml (OR = 23, $P < 10^{-13}$) (Table 1). Because the serum/plasma samples were diluted 1:10 in these assays, these findings suggest that more than 13.6% of patients with life-threatening COVID-19 have circulating auto-Abs neutralizing IFN-α2 and/or IFN-ω (1 ng/ml) in vivo, a greater proportion than the 10% of patients with auto-Abs neutralizing 100 ng/ml reported in previous studies (*9*, *11*–*16*).

Auto-Abs neutralize low concentrations of IFN-α2 protective against SARS-CoV-2

We previously reported that plasma diluted 1:100 from patients with auto-Abs against type I IFNs neutralized the ability of IFN-α2 (at a concentration of 20 pM, about 400 pg/ml) to block SARS-CoV-2 and YFV-17D replication in Huh-7.5 cells (*9*, *31*). This neutralization was seen in all patients tested, even for a 1000-fold dilution, and, in most patients, it was more potent than the neutralizing effect of a commercially available neutralizing monoclonal Ab (mAb) against IFN-α2. These auto-Abs against type I IFNs were, therefore, able to neutralize IFN-α2 at concentrations well beyond physiological levels. We therefore hypothesized that patients with lower titers of auto-Abs against type I IFNs, which can neutralize 100 pg/ml but not 10 ng/ml in plasma diluted 1:10, would also neutralize the protective effect of IFN-α2 against SARS-CoV-2. We therefore performed our SARS-CoV-2 assay with 5 pM (~100 pg/ml) or 20 pM (~400 pg/ml) IFN-α2 on five samples from patients with life-threatening COVID-19 and two samples from uninfected elderly individuals with auto-Abs neutralizing IFN-α2 (100 pg/ml but not 10 ng/ml). As controls, we tested a commercial mAb against IFN-α2, a sample from a patient with auto-Abs neutralizing IFN-α2 (10 ng/ml), samples from three patients with life-threatening COVID-19, and three healthy controls without detectable auto-Abs against type I IFNs. We found that the 1:100 dilutions of plasma from four of the five patients with critical COVID-19 and one of the two elderly individuals with auto-Abs neutralizing IFN-α2 (100 pg/ml) were able to neutralize the protective effect of IFN-α2 (~400 pg/ml) against SARS-CoV-2, whereas samples from all these individuals fully or partially neutralized IFN-α2 (~100 pg/ml) (Fig. 2A). No such neutralizing effect was observed for any of the auto-Ab–negative controls. Overall, our findings indicate that auto-Abs against type I IFNs capable of neutralizing IFN (100 pg/ml) in 1% plasma can block the protective effect of IFN-α2 (~100 or ~400 pg/ml) against SARS-CoV-2. These findings raise the possibility that even 100-fold lower levels of auto-Abs against type I IFNs, capable of neutralizing lower, physiological concentrations of IFN-α2 (10 pg/ml) may be present in an even larger proportion of patients. The testing of this hypothesis will require the development of new, more sensitive methods to screen for neutralization.

Neutralization of type I IFNs in the absence of detectable auto-Abs against IFN-α2 or IFN-ω

The neutralization assays performed on all patients and controls revealed that some patients with neutralizing activity against IFN-α2 and/or IFN-ω (10 ng/ml), as shown in luciferase assays, did not have high or even intermediate levels of IgG auto-Abs in Gyros assays (fig. S1E). We also observed that some patients with neutralizing auto-Abs had low or undetectable levels of auto-Abs in Luminex assays (fig. S1I). For these individuals, we assessed the prevalence of IgA and IgM auto-Abs against type I IFNs and found that none of the patients tested ($N = 12$) had detectable titers of IgA or IgM auto-Abs (fig. S1J). We then tested the alternative hypothesis that these auto-Abs were directed against the IFNAR1 or IFNAR2 chain of type I IFN receptors, assessing the ability of plasma samples from these patients to neutralize IFN-β. None of the samples from these patients neutralized IFN-β, suggesting that the auto-Abs in these patients were not directed against IFNAR1 or IFNAR2 (fig. S1K). An alternative plausible hypothesis is that the epitope recognized by the auto-Abs might be concealed by the binding of the cytokine to the plate (ELISA), biotinylation of the cytokine (Gyros), or covalent coupling of the cytokine to magnetic beads at lysine residues (Luminex) (*19*). This observation has important clinical implications, suggesting that a lack of detection of auto-Abs against type I IFNs does not rule out the possibility of such antibodies being present and having neutralization capacity.

Auto-Abs typically neutralize the 13 IFN-α subtypes and/or IFN-ω

In six patients with auto-Abs neutralizing IFN-α2 and/or IFN-ω (100 pg/ml but not 10 ng/ml), we tested the reactivity of the antibodies against the 17 type I IFNs (the 13 IFN-α forms, IFN-ω, IFN-β, IFN-ε, and IFN-κ). Similar to patients with auto-Abs neutralizing type I IFNs (10 ng/ml) (*9*), those capable of neutralizing only 100 pg/ml had detectable auto-Abs against most of the 13 IFN-α forms and/or IFN-ω, albeit at lower levels (Fig. 2B). Of the six patients with auto-Abs against IFN-α and/or IFN-ω tested, only one also had auto-Abs against IFN-β, and none had detectable auto-Abs against IFN-ε or IFN-κ. Overall, the patients with auto-Abs against IFN-α2 and/or IFN-ω capable of neutralizing IFN (100 pg/ml) displayed patterns of reactivity to the 17 type I IFNs similar to those reported in previously described patients with auto-Abs neutralizing 10 ng/ml (*9*). We then set up an assay for assessing neutralization of the 13 IFN-α forms using our luciferase-based assay. We tested two patients with auto-Abs neutralizing IFN-α2 and IFN-ω, two patients with auto-Abs neutralizing only IFN-α2, and two patients with auto-Abs neutralizing only IFN-ω. We found that the patient

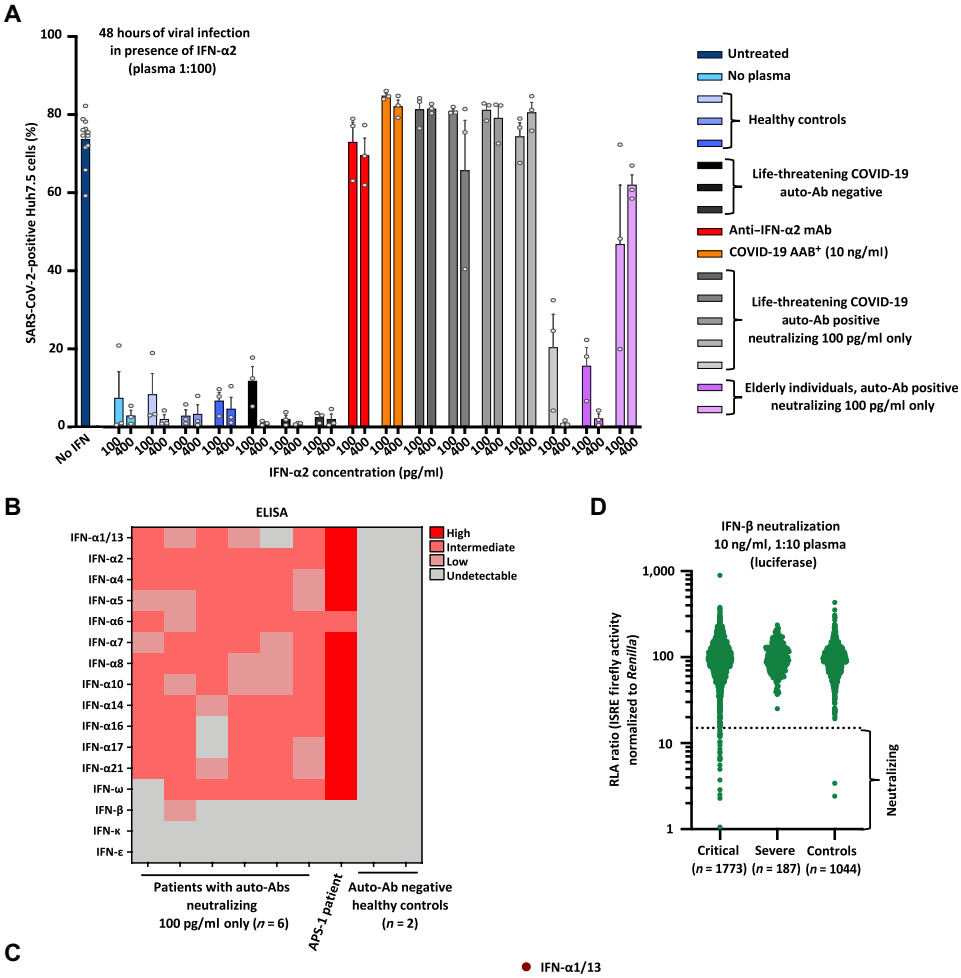

Fig. 2. Enhanced SARS-CoV-2 replication, despite the presence of IFN-α2, in the presence of plasma from patients with auto-Abs neutralizing IFN-α2 (100 pg/ml). (**A**) SARS-CoV-2 replication in Huh-7.5 cells untreated (in dark blue) or treated with IFN-α2 (~100 or ~400 pg/ml) in the presence of 1:100 plasma from healthy controls without auto-Abs ($N = 3$, in blue), from patients with life-threatening COVID-19 but without auto-Abs against IFN-α2 ($N = 3$, in black), a commercial anti–IFN-α2 antibody (mAb; in red); from a patient with life-threatening COVID-19 and auto-Abs neutralizing IFN-α2 (10 ng/ml) in plasma 1:100 (COVID-19 AAB$^+$; $N = 1$, in orange), from patients with life-threatening COVID-19 and auto-Abs neutralizing IFN-α2 (100 pg/ml) in plasma 1:100 ($N = 5$, in gray); and from elderly individuals with auto-Abs neutralizing IFN-α2 (100 pg/ml) in plasma 1:100 ($N = 2$, in purple). Each dot represents a technical replicate. All experiments were done in triplicate. (**B**) ELISA for auto-Abs against the 13 IFN-α forms, IFN-ω, IFN-β, IFN-ε, and IFN-κ in patients with life-threatening COVID-19 and auto-Abs neutralizing IFN-α2 (100 pg/ml) ($N = 6$), patient with APS-1 with life-threatening COVID-19 and auto-Abs neutralizing IFN-α2 and IFN-ω (10 ng/ml) ($N = 1$), and healthy controls ($N = 2$). (**C**) RLA after stimulation with the all individual IFN-α at a concentration of 1 ng/ml, with 1:10 plasma from a healthy control (negative control), a patient with APS-1 (positive control), and patients with life-threatening COVID-19 and neutralizing IFN-α2 and/or IFN-ω or a mAb anti–IFN-α2. (**D**) Neutralization of IFN-β (10 ng/ml) in the presence of plasma 1:10 from patients with critical COVID-19 ($N = 1773$), severe COVID-19 ($N = 187$), or asymptomatic/mild controls ($N = 1044$).

with APS-1 and the two patients with auto-Abs neutralizing IFN-α2 and IFN-ω (10 ng/ml) were able to neutralize all 13 IFN-α subtypes, as were the two patients with neutralizing auto-Abs against IFN-α2. Conversely, in the conditions tested, the two patients with auto-Abs neutralizing IFN-ω only, but not IFN-α2, were not able to neutralize any of the 13 IFN-α subtypes (Fig. 2C). In addition, to confirm that the IgG auto-Abs detected were the cause of the neutralization activity observed, we performed an IgG depletion experiment and found that the removal of the IgG fraction abolished the neutralizing activity, whereas the purified IgG fraction had full neutralizing activity (fig. S2A). Thus, patients with neutralizing auto-Abs against only IFN-ω do not seem to neutralize any of the 13 IFN-α subtypes, whereas patients with auto-Abs neutralizing IFN-α2 neutralize all these subtypes.

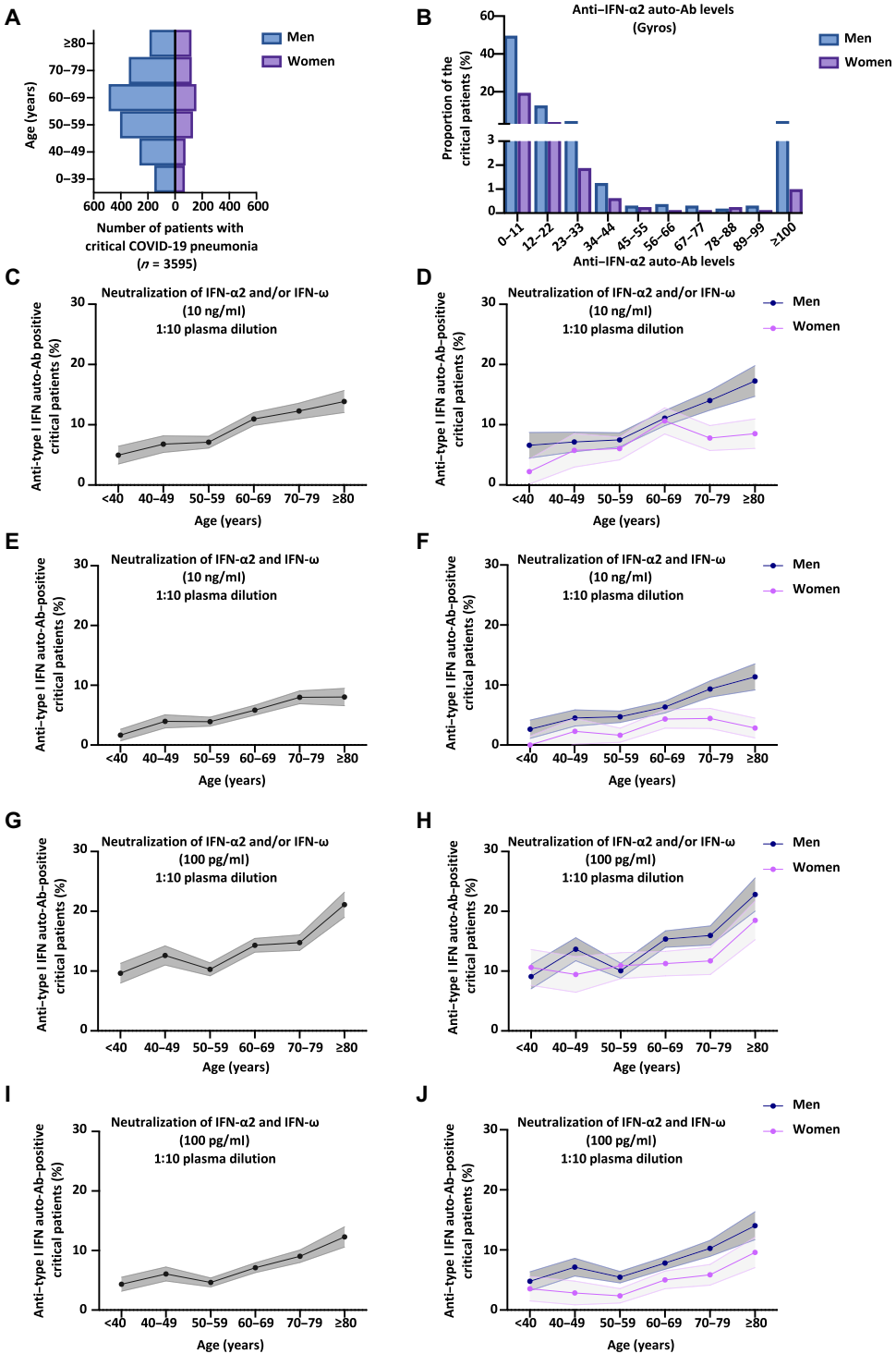

Fig. 3. Higher prevalence of neutralizing auto-Abs against type I IFNs in elderly patients with critical COVID-19. (**A**) Bar plot of the age and sex distribution of the patients with life-threatening COVID-19 included in our expanded cohort ($N = 3595$). (**B**) Graph showing the anti–IFN-α2 auto-Ab levels, assessed by Gyros, in patients with life-threatening COVID-19. Men and women are shown separately. The upper section of the *y* axis starts at 3%. (**C** to **J**) Proportion by decade of patients with critical COVID-19 and positive for neutralizing auto-Abs (in plasma 1:10) against (C) IFN-α2 and/or IFN-ω, at 10 ng/ml, for both sexes. (D) IFN-α2 and/or IFN-ω, at 10 ng/ml, for men or women. (E) IFN-α2 and IFN-ω, at 10 ng/ml, for both sexes. (F) IFN-α2 and IFN-ω, at 10 ng/ml, for men or women. (G) IFN-α2 and/or IFN-ω, at 100 pg/ml, for both sexes. (H) IFN-α2 and/or IFN-ω, at 100 pg/ml, for men or women. (I) IFN-α2 and IFN-ω, at 100 pg/ml, for both sexes. (J) IFN-α2 and IFN-ω, at 100 pg/ml, for men or women.

Auto-Abs neutralizing IFN-β in 1.3% of critical patients

We previously reported that auto-Abs neutralizing IFN-β were detected in only two of 101 critical patients with auto-Abs neutralizing IFN-α2 and/or IFN-ω (10 ng/ml) (*9*). Given the potential therapeutic use of IFN-β (*36*, *37*) and the absence of IFN-β neutralization data for patients with COVID-19, we tested a larger number of patients and controls, including patients without auto-Abs against IFN-α or IFN-ω, for auto-Abs against IFN-β, assessing the levels and neutralizing activity of auto-Abs against IFN-β (10 ng/ml). We screened 1773 patients with critical COVID-19 pneumonia and found that 1.3% ($N = 23$) had neutralizing auto-Abs against IFN-β; by contrast, such antibodies were present in none of the 187 severe patients tested and in only two of the 1044 controls tested (0.18%) (Fig. 2D, fig. S2B, and table S3). Only 6 of the 23 (21.7%) critical patients also had auto-Abs neutralizing IFN-α2 and/or IFN-ω at 100 pg/ml, and none of the controls had such antibodies. Five of these six patients had auto-Abs neutralizing all three cytokines. All the other critical patients and controls had only neutralizing auto-Abs against IFN-β. The presence of neutralizing auto-Abs against IFN-β was significantly associated with critical, but not severe, disease relative to the controls (Table 1 and tables S2 and S3). Gyros did not appear to be able to detect auto-Abs against IFN-β, perhaps because of the biotinylation of the cytokine hiding the epitope recognized by the auto-Abs. Because most (78.3%) of the patients with neutralizing auto-Abs against IFN-β did not have neutralizing auto-Abs against IFN-α2 or IFN-ω, this suggests that auto-Abs against IFN-β alone may also underlie life-threatening COVID-19 (Table 1).

Neutralizing auto-Abs against type I IFNs in at least 20% of critical patients over 80 years of age

We further assessed the percentage of patients with critical COVID-19 positive for neutralizing auto-Abs per decade of life and by sex (Fig. 3, A to J; fig. S3, A to W; and tables S1 to S4). In our previous report, we found that patients with critical COVID-19 with auto-Abs neutralizing IFN-α2 or IFN-ω at 10 ng/ml were older (more than half the patients with auto-Abs were over the age of 65 years) and more likely to be male (95% of the antibody carriers were men) (*9*). These results have been confirmed by other groups, albeit with a smaller proportion of men (*11*–*14*, *16*). In our expanded cohort of patients with critical COVID-19 pneumonia ($N = 3595$), the mean age was 61 years, and 73% of the patients were men (Fig. 3A and table S4). We confirmed that critical patients with auto-Abs neutralizing IFN-α and/or IFN-ω at 10 ng/ml were significantly older than those not carrying auto-Abs (mean age [SD], 65.8 years [14.1] versus 61.6 years [15.5], Firth's multivariable logistic regression, $P = 3 \times 10^{-6}$) and more likely to be male (78.5 versus 71%, Firth's multivariable logistic regression, $P = 0.003$). The proportion of patients with critical COVID-19 with auto-Abs neutralizing IFN-α2 and/or IFN-ω (10 ng/ml) increased continuously, with auto-Abs detected in 5% of patients under the age of 40 years, 6.8% of those between 40 and 49 years of age, 7.1% of those between 50 and 59 years of age, 10.7% of those between 60 and 69 years of age, 12.3% of those between 70 and 79 years of age, and almost 14% in those over 80 years of age (Fig. 3, C to F, and fig. S3, B to I). In severe patients, the proportion of auto-Abs was much more stable with age (Firth's multivariable logistic regression, $P = 0.16$; fig. S3, T to W) and sex (Firth's multivariable logistic regression, $P = 0.44$). Similar results were obtained for patients with critical COVID-19 with auto-Abs neutralizing IFN-α2 and/or IFN-ω (100 pg/ml) but with even higher proportions (Fig. 3, G to J, and fig. S3, L to S) (table S1). The proportion of patients with auto-Abs ranged from 9.6% of patients below the age of 40 years to more than 21% of those over 80 (Fig. 3, G to J, and fig. S3, L to S). In men, the proportion of patients with critical COVID-19 carrying auto-Abs neutralizing IFN-α2 and/or IFN-ω (100 pg/ml) increased up to 23% over 80 years of age. A very different pattern was seen for auto-Abs neutralizing IFN-β (10 ng/ml), with a more stable proportion of auto-Abs carriers according to age (Firth's multivariable logistic regression, $P = 0.68$; fig. S3, J and K) (table S3). Overall, the prevalence of auto-Abs neutralizing IFN-α2 and/or IFN-ω (10 ng/ml and/or 100 pg/ml) increased sharply with age in critical patients. A notable enrichment in patients with neutralizing auto-Abs against IFN-α2 and/or IFN-ω was observed in the elderly, with more than 20% of patients and 23% of men, over the age of 80 years with critical COVID-19 having neutralizing auto-Abs against these type I IFNs.

Neutralizing auto-Abs against type I IFNs in at least 18% of deceased patients

The prevalence of auto-Abs against type I IFNs in patients dying from COVID-19 pneumonia is unknown. For the 3595 patients with critical COVID-19, we analyzed data for the 1124 who died. These patients were aged 20 days to 99 years (mean age: 71 years), 73% were male, and all had confirmed SARS-CoV-2 infection and critical COVID-19 pneumonia before death (Fig. 4A). In these patients, we analyzed the presence of neutralizing auto-Abs against type I IFNs at concentrations of 10 ng/ml and 100 pg/ml for IFN-α2 and IFN-ω, respectively, and at 10 ng/ml for IFN-β (Fig. 4, B to J, and fig. S4, A to K). We found that 13.3% of the deceased patients carried auto-Abs neutralizing IFN-α2 and/or IFN-ω (10 ng/ml) (Fig. 4, B to F, and fig. S4, A to E). A total of 18.5% carried auto-Abs neutralizing 100 pg/ml of either or both cytokines (Fig. 4, G to J, and fig. S4, F to I). In addition, 0.9% had auto-Abs neutralizing IFN-β (fig. S4, J and K). An analysis of the prevalence of neutralizing auto-Abs against type I IFNs in these patients who died of COVID-19 by decade of age revealed a moderate increase with age for auto-Abs neutralizing 10 ng/ml (Firth's multivariable logistic regression, $P = 0.03$) or 100 pg/ml (Firth's multivariable logistic regression, $P = 0.01$) (tables S1 and S2). For a type I IFN concentration (100 pg/ml), the prevalence of auto-Abs neutralizing IFN-α2 and/or IFN-ω was 20% below the age of 40 years, 14% for individuals between 40 and 49 years old, 12.5% for those between 50 and 60 years old, 16.3% for those between 60 and 69 years old, 17.9% for those between 70 and 79 years old, and greater than 23% for those over the age of 80 years. Overall, at least 18% of patients dying from COVID-19 pneumonia have auto-Abs capable of neutralizing type I IFNs (100 pg/ml) in plasma 1:10.

Auto-Abs capable of neutralizing IFN-α2 and/or IFN-ω at 10 ng/ml in 0.53% and at 100 pg/ml in 2.3% of individuals from the general population

We previously tested a sample of 1227 individuals aged 20 to 65 years from the general population collected in 2015–2017. This sample had an equal sex distribution, and we identified four individuals with auto-Abs against type I IFNs among the 1227 tested (0.3%), suggesting that the auto-Abs predated COVID-19 (*9*). These findings were replicated at the University of California, San Francisco in a sample of 4041 individuals aged 4 to 90 years (0.32%) (*16*). In the current study, we tested a much larger cohort of 34,159 individuals

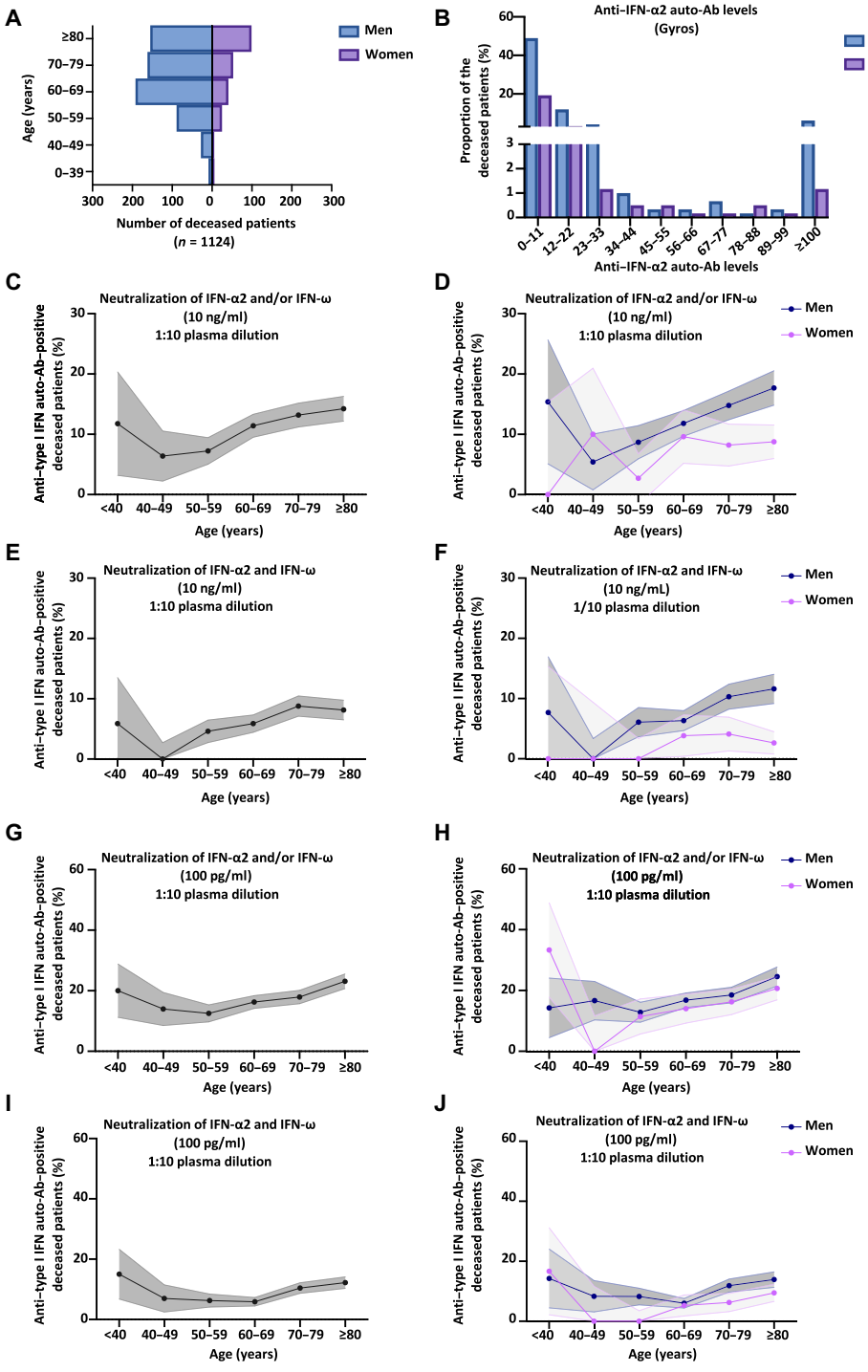

Fig. 4. Higher prevalence of neutralizing auto-Abs against type I IFNs in patients who died of COVID-19. (**A**) Bar plot of the age and sex distribution of the patients who died of COVID-19 included in our cohort ($N = 1124$). (**B**) Graph showing the anti–IFN-α2 auto-Ab levels, assessed by Gyros, in patients who died of COVID-19. Men or women are shown separately. The upper section of the *y* axis starts at 3%. (**C** to **J**) Proportion by decade of patients who died of COVID-19 and positive for neutralizing auto-Abs (in plasma 1:10) against (C) IFN-α2 and/or IFN-ω, at 10 ng/ml, for both sexes. (D) IFN-α2 and/or IFN-ω, at 10 ng/ml, for men or women. (E) IFN-α2 and IFN-ω, at 10 ng/ml, for both sexes. (F) IFN-α2 and IFN-ω, at 10 ng/ml, for men or women. (G) IFN-α2 and/or IFN-ω, at 100 pg/ml, for both sexes. (H) IFN-α2 and/or IFN-ω, at 100 pg/ml, for men or women. (I) IFN-α2 and IFN-ω, at 100 pg/ml, for both sexes. (J) IFN-α2 and IFN-ω, at 100 pg/ml, for men or women.

aged 20 to 100 years from the general population, with an equal distribution between the sexes (Fig. 5A). Samples were collected before 2018 for blood donors at the French Blood Bank (19,966 individuals) and the Three-City (3C) cohort (801) and in 2019 for participants in the French CONSTANCES cohort (8850) and Cerba HealthCare (4542). We performed serological tests for SARS-CoV-2

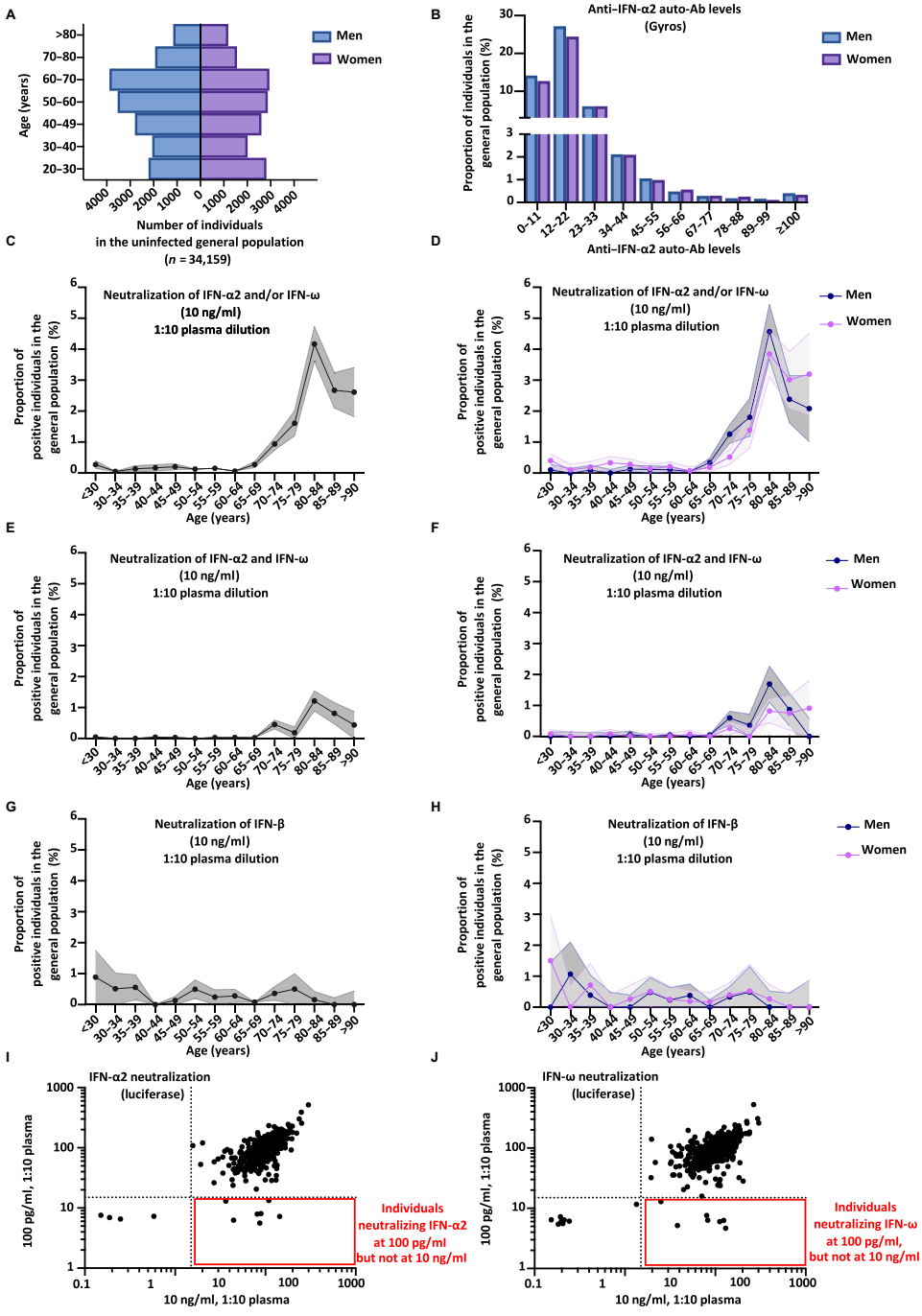

Fig. 5. Neutralizing auto-Abs against IFN-α2 and/or IFN-ω at 10 ng/ml are more prevalent in the elderly, in the general population. (**A**) Bar plot of the age and sex distribution of individuals from the general population ($N = 34,159$). (**B**) Graph showing the IFN-α2 auto-Ab levels, assessed by Gyros, in individuals from the general population. Men or women are shown separately. The upper section of the *y* axis starts at 3%. (**C** to **H**) Proportion by 5 years of individuals from the general population and positive for neutralizing auto-Abs (in plasma 1:10) against (C) IFN-α2 and/or IFN-ω, at 10 ng/ml, for both sexes. (D) IFN-α2 and/or IFN-ω, at 10 ng/ml, for men or women. (E) IFN-α2 and IFN-ω, at 10 ng/ml, for both sexes. (F) IFN-α2 and IFN-ω, at 10 ng/ml, for men or women. (G) IFN-β, at 10 ng/ml, for both sexes. (H) IFN-β, at 10 ng/ml, for men or women. (I) Plot showing luciferase induction after stimulation with IFN-α2 (10 ng/ml or 100 pg/ml) in the presence of plasma from individuals from the general population. Dotted lines indicate neutralizing levels, defined as induction levels below 15% of the mean value for controls tested the same day. Individuals with antibodies neutralizing both IFN-α2 (10 ng/ml and 100 pg/ml) are shown in the bottom left corner, whereas the individuals in the bottom right corner had antibodies capable of neutralizing only IFN-α2 (100 pg/ml). (J) Plot showing luciferase induction after stimulation with IFN-ω (10 ng/ml or 100 pg/ml) for individuals from the general population.

on the samples collected in 2019 and included only the individuals who had not been infected with SARS-CoV-2 in the sample. We used Gyros to screen this whole cohort for IgG auto-Abs against IFN-α2 and IFN-ω (Fig. 5B and fig. S5A). We did not measure auto-Abs against IFN-β by Gyros. We found that only 0.05 and 4.2% had anti–IFN-α2 and/or anti–IFN-ω auto-Abs above the thresholds of 100 and 30, respectively (Fig. 5B and fig. S5A). We then assessed the ability of these antibodies to neutralize IFN-α2 or IFN-ω (10 ng/ml) for all individuals with a high or intermediate level of IgG auto-Abs against IFN-α2 or IFN-ω. We found 181 individuals with neutralizing auto-Abs, for whom 1:10 dilutions of plasma neutralized IFN-α2 and/or IFN-ω (10 ng/ml), giving an overall prevalence of 0.53% (Fig. 5, C to F, and fig. S5, B to I) (table S5 and S6), consistent with our two previous reports (*9*, *16*). We may have slightly underestimated the number of positive individuals, because some may have had neutralizing auto-Abs at too low a titer for detection. Next, we assessed the prevalence of auto-Abs neutralizing IFN-β (10 ng/ml) in 9583 individuals and found an overall prevalence of 0.26% (Fig. 5, G and H and table S5 and S6). Last, for a subset of 10,778 samples, we further assessed the ability of serum/plasma samples (diluted 1:10) to neutralize IFN-α2 and/or IFN-ω (100 pg/ml) in the luciferase assay (Figs. 5, I and J, and 6, A to H). The prevalence of

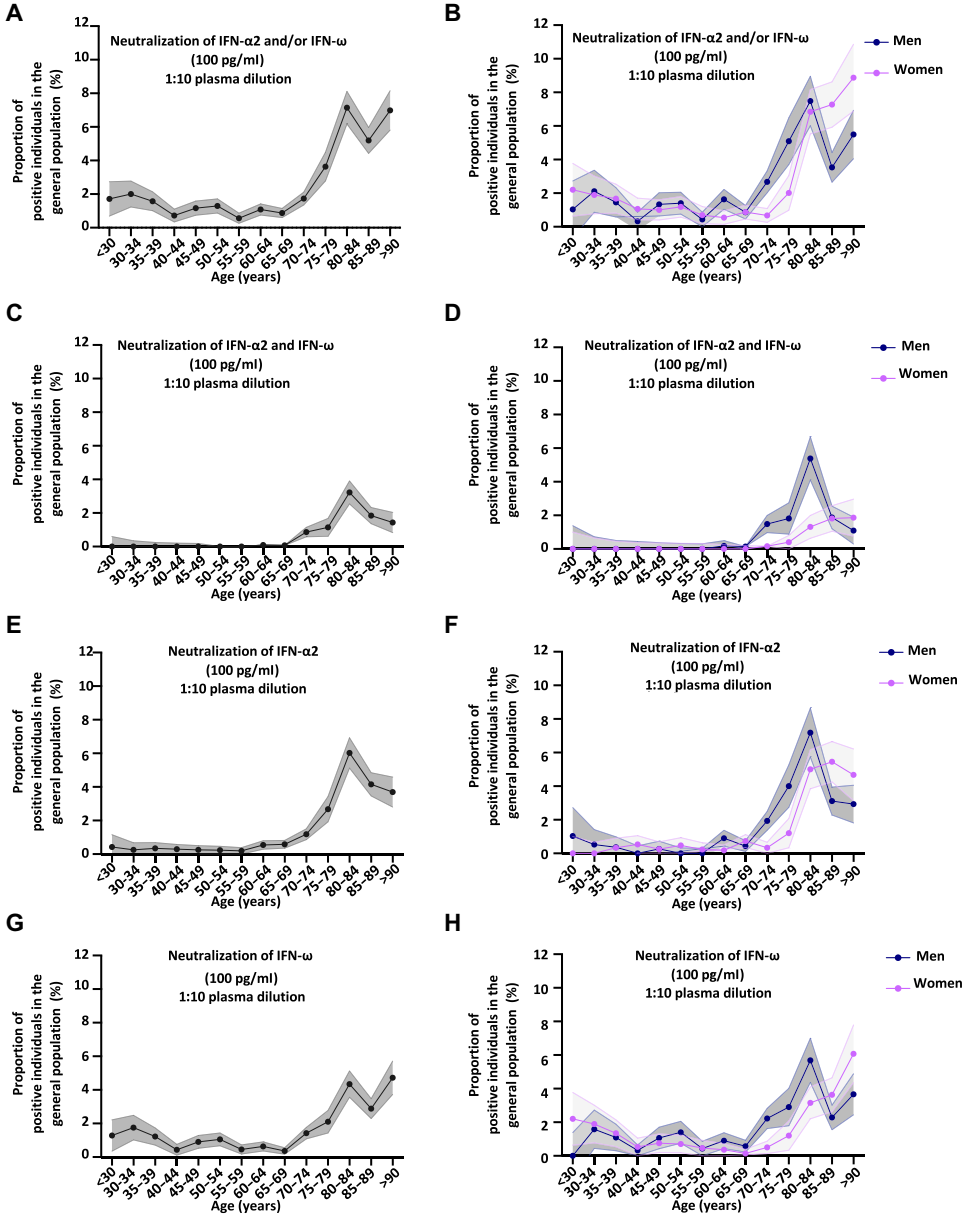

Fig. 6. Neutralizing auto-Abs against IFN-α2 and/or IFN-ω at 100 pg/ml are more prevalent in the elderly, in the general population. (**A** to **H**) Proportion, binned every 5 years, of individuals from the general population and positive for neutralizing auto-Abs (in plasma 1:10) against (A) IFN-α2 and/or IFN-ω, at 100 pg/ml, for both sexes. (B) IFN-α2 and/or IFN-ω, at 100 pg/ml, for men or women. (C) IFN-α2 and IFN-ω, at 100 pg/ml, for both sexes. (D) IFN-α2 and IFN-ω, at 100 pg/ml, for men or women. (E) IFN-α2, at 100 pg/ml, for both sexes. (F) IFN-α2, at 100 pg/ml, for men or women. (G) IFN-ω, at 100 pg/ml, for both sexes. (H) IFN-ω, at 100 pg/ml, for men or women.

auto-Abs neutralizing IFN-α2 and/or IFN-ω (100 pg/ml) was 2.3% (table S1).

Sharp increase in the prevalence of auto-Abs against IFN-α2 and/or IFN-ω after the age of 70 years in the general population

We then assessed the percentage of individuals from the general population positive for neutralizing auto-Abs per decade of life and by sex. We noted that the prevalence of auto-Abs neutralizing type I IFN (10 ng/ml) was more than 10 times higher in individuals over the age of 70 years than in those below this age (Firth's multivariable logistic regression, $P < 10^{-13}$) (Fig. 5, C to F; fig. S5, B to I; and tables S5 and S6). The prevalence of auto-Abs capable of neutralizing IFN-α2 and/or IFN-ω (10 ng/ml) was 0.17% in individuals below 70 years of age, 0.9% in individuals between 70 and 75 years of age, 1.6% between the ages of 75 and 80 years, and more than 4% between the ages of 80 and 85 years. After 85 years, the prevalence of these antibodies decreased to about 2.6%. These findings were replicated independently in two cohorts of 703 and 376 elderly individuals from Estonia and Japan, tested with luciferase-based immunoprecipitation (IP) assay (LIPS) and ELISA assays, respectively (fig. S5, J and K). A strong increase in the prevalence of auto-Abs neutralizing IFN-α2 and/or IFN-ω (100 pg/ml) was observed with age (Fig. 6, A to H, and fig. S6, A to D), with the prevalence almost doubling with every 5 years from 65 to 85 years of age. A total of 0.87% of individuals between the ages of 65 and 70 years, 1.73% of those between 70 and 75 years, and 7.1% of those between 75 and 80 years were positive for auto-Abs. There was an overall decrease in the prevalence of auto-Abs after 85 years of age, especially in men. By contrast, the prevalence of auto-Abs neutralizing IFN-β did not vary significantly with age (Fig. 5, G and H, and table S4). We then assessed the risk, adjusted for age and sex, of having critical or severe disease, for individuals carrying auto-Abs against each individual IFN and the different possible combinations, relative to the general population. We also found that all auto-Abs were highly significant risk factors in comparisons of patients with critical or severe COVID-19 with the general population (Table 1 and table S2). The strongest association was again that for auto-Abs neutralizing both IFN-α2 and IFN-ω at 10 ng/ml (OR = 30, $P < 1 \times 10^{-13}$), followed by those neutralizing IFN-α2 ± IFN-ω at 10 ng/ml (OR = 20, $P < 10^{-13}$) and IFN-ω ± IFN-α2 at 10 ng/ml (OR = 15, $P < 10^{-13}$) (Table 1). Auto-Abs neutralizing both IFN-α2 and IFN-ω at 100 pg/ml were also highly significant risk factors (OR [95% confidence interval (CI)] = 12 [9 to 16], $P < 10^{-13}$) (Table 1). Overall, these findings indicate that there is a sharp increase in the prevalence of auto-Abs neutralizing type I IFNs with age in elderly uninfected individuals, with at least 4% of those over the age of 70 years positive for auto-Abs against IFN-α2 and/or IFN-ω, and that these auto-Abs predate COVID-19.

DISCUSSION

We report that at least 20% of patients over 80 years of age with life-threatening COVID-19 pneumonia carry circulating auto-Abs neutralizing IFN-α2 and/or IFN-ω (100 pg/ml) and that such antibodies are present in more than 13.6% of patients of all ages with this condition. Some of these auto-Abs are not identified by immunoassays and are only detectable by a neutralization assay. In addition, at least 18% of deceased individuals in most age groups were found to have such auto-Abs. We also report that auto-Abs against IFN-β are found in about 1.3 and 0.9% of critical and deceased patients, most of whom do not have auto-Abs against IFN-α2 and/or IFN- ω. In all four patients tested for whom pre–COVID-19 samples were also available, the auto-Abs against IFN-α2 and/or IFN-ω were clearly present before SARS-CoV-2 infection, as in patients with APS-1 (*9*, *20*) and in two other previously described patients (*9*). Auto-Abs capable of neutralizing high concentrations of type I IFNs have been found in patients without inborn errors of TLR3- or TLR7-dependent type I IFN immunity (*7*, *35*), suggesting that both inborn errors and auto-Abs are independently causal of critical disease. It is also notable that inborn errors are more common in patients under the age of 60 years, whereas auto-Abs are more common in patients over the age of 70 years. We also report that the prevalence of auto-Abs neutralizing (10 ng/ml and 100 pg/ml) type I IFNs, except for IFN-β, increases significantly with age in the general population, with 0.17% (1.1%) of individuals positive for these antibodies before the age of 70 years and more than 1.4% (4.4%) positive after the age of 70 years, with a prevalence of 4.2% (7.1%) between the ages of 80 and 85 years.

These auto-Abs provide an explanation for the major increase in the risk of critical COVID-19 in the elderly. This increase with age is consistent with studies of various auto-Abs since the 1960s (*38*–*42*). These auto-Abs appear to have remained clinically silent in these individuals until SARS-CoV-2 infection. Our results also suggest that the neutralization of only one type I IFN (IFN-α2, IFN-ω, or IFN-β) can underlie life-threatening COVID-19 (Table 1 and tables S1 to S3). Auto-Abs neutralizing IFN-β (10 ng/ml) have a frequency only about one-tenth that of auto-Abs neutralizing the same concentrations of IFN-α2 and/or IFN-ω (Table 1 and table S3). We have shown that auto-Abs neutralizing type I IFN (100 pg/ml) in plasma diluted 1:10, corresponding to the neutralization of IFN (1 ng/ml) in vivo, can account for at least 18% of deaths and more than 20% of critical cases in the elderly >80 years of age. It is tempting to speculate that an even greater proportion of life-threatening COVID-19 cases are due to auto-Abs neutralizing lower, physiological concentrations of type I IFNs. In vitro, concentrations of type I IFN as low as 100 pg/ml can impair SARS-CoV-2 replication in epithelial cells (Fig. 2A). Moreover, the levels of type I IFN detected in the blood of patients with acute and benign SARS-CoV-2 infections are in the range of 1 to 100 pg/ml (*32*, *33*).

Our findings have immediate clinical applications. First, it is quick and easy to test for auto-Abs against type I IFNs in patients infected with SARS-CoV-2. Screening for these antibodies is even possible in the general population before infection. The type I IFN–neutralizing activity of these antibodies is a better readout than their mere detection, which can be falsely negative. Tests should be performed for auto-Abs against at least three individual IFNs: IFN-α2, IFN-ω, and IFN-β. Particular attention should be paid to elderly individuals and patients with known autoimmune or genetic conditions associated with auto-Abs against type I IFNs (*17*–*20*, *22*, *23*, *26*–*29*). Second, patients with auto-Abs against type I IFN should be vaccinated against COVID-19 as a priority. Third, live-attenuated vaccines, including YFV-17D and vaccines using the YFV-17D backbone against SARS-CoV-2, should not be given to patients with auto-Abs (*31*, *43*). Fourth, these patients appeared to be healthy before SARS-CoV-2 infection, but they should also be carefully followed for other viral illnesses as exemplified by adverse reactions to YFV-17D (*31*). Fifth, in cases of SARS-CoV-2 infection in unvaccinated individuals with auto-Abs

against type I IFNs, the patients should be hospitalized for prompt management. Early treatment with mAbs (*44*, *45*) can be administered in patients without symptoms of severe COVID-19 pneumonia, and IFN-β can be administered in the absence of both pneumonia and auto-Abs against IFN-β (*36*, *37*). Rescue treatment by plasma exchange is another therapeutic option in patients who already have pneumonia (*46*).

Sixth, blood products, especially plasma, should be screened for anti-IFN auto-Abs and any products containing such antibodies should be excluded from donation (*13*). Plasma from donors convalescing from COVID-19 should be tested for such auto-Abs (*13*). Seventh, given the documented innocuity and potential efficacy of a single injection, early therapy with IFN-β may be considered for the contacts of contagious individuals or during the first week after infection, even in the absence of, or before the documentation of auto-Abs against type I IFNs in elderly patients who have a higher risk of critical pneumonia and auto-Abs against IFN-α2 and IFN-ω but not IFN-β (*47*). Another possibility would be the administration of mAbs that can neutralize SARS-CoV-2 (*44*, *45*). Last, it will be important to decipher the mechanism underlying the development of these auto-Abs, which may differ in patients over and under 65 years of age. Overall, our findings show that auto-Abs neutralizing concentrations of type I IFN lower than previously reported (*9*, *11*–*16*), but still higher than physiological concentrations, are common in the elderly population. Their prevalence increases with age in the uninfected general population, reaching more than 4% of individuals after the age of 70 years. They underlie about 20% of cases of critical COVID-19 pneumonia in patients over the age of 80 years and about 20% of total COVID-19 deaths. We previously reported that they can underlie severe adverse reactions to the live-attenuated vaccine against YFV (*31*). It is tempting to speculate that they may also underlie other severe viral diseases, especially in the elderly.

MATERIALS AND METHODS

Study design

We enrolled, from 38 countries across all continents, 3595 patients with proven critical COVID-19, 623 patients with severe COVID-19, 1639 asymptomatic or paucisymptomatic individuals with proven COVID-19, and 34,159 healthy controls in this study. We collected plasma or serum samples for all these individuals to test by immunoassay for the presence of IgG auto-Abs to type I IFNs. All individuals were recruited according to protocols approved by local Institutional Review Boards (IRBs).

COVID-19 classification

The severity of COVID-19 was assessed for each patient as follows (*7*, *9*): "Critical COVID-19 pneumonia" was defined as pneumonia developing in patients with critical disease, whether pulmonary, with high-flow oxygen, mechanical ventilation (continuous positive airway pressure, bilevel positive airway pressure, and intubation), septic shock, or with damage to any other organ requiring admission to the intensive care unit. "Severe COVID-19" was defined as pneumonia developing in patients requiring low-flow oxygen (<6 liters/min). The controls were individuals infected with SARS-CoV-2 (as demonstrated by a positive PCR and/or serological test and/or displaying typical symptoms, such as anosmia/ageusia after exposure to a confirmed COVID-19 case) who remained asymptomatic or developed mild, self-healing, ambulatory disease with no evidence of pneumonia.

Detection of anti-cytokine auto-Abs

Gyros

Cytokines, recombinant human (rh)IFN-α2 (Miltenyi Biotec, reference number 130-108-984) or rhIFN-ω (Merck, reference number SRP3061), were first biotinylated with EZ-Link Sulfo-NHS-LC-Biotin (Thermo Fisher Scientific, catalog number A39257), according to the manufacturer's instructions, with a biotin-to-protein molar ratio of 1:12. The detection reagent contained a secondary antibody [Alexa Fluor 647 goat anti-human IgG (Thermo Fisher Scientific, reference number A21445)] diluted in Rexxip F (Gyros Protein Technologies, reference number P0004825; 1:500 dilution of the 2 mg/ml stock to yield a final concentration of 4 μg/ml). Buffer phosphate-buffered saline, 0.01% Tween 20 (PBS-T) and Gyros Wash buffer (Gyros Protein Technologies, reference number P0020087) were prepared according to the manufacturer's instructions. Plasma or serum samples were then diluted 1:100 in 0.01% PBS-T and tested with the Bioaffy 1000 CD (Gyros Protein Technologies, reference number P0004253) and the Gyrolab xPand (Gyros Protein Technologies, reference number P0020520). Cleaning cycles were performed in 20% ethanol.

Multiplex particle-based assay

Serum/plasma samples were screened for auto-Abs against IFN-α2 and IFN-ω in a multiplex particle-based assay in which magnetic beads with differential fluorescence were covalently coupled to recombinant human proteins (2.5 μg per reaction). Beads were combined and incubated with 1:100 diluted serum/plasma samples for 30 min. Each sample was tested once. The beads were then washed and incubated with phycoerythrin (PE)–labeled goat anti-human IgG (1 μg/ml) for an additional 30 min. They were then washed again and used for a multiplex assay on a Bio-Plex X200 instrument.

Enzyme-linked immunosorbent assays

ELISA was performed as previously described. Briefly, 96-well ELISA plates (MaxiSorp, Thermo Fisher Scientific) were coated by incubation overnight at 4°C with rhIFN-α2 (2 μg/ml; Miltenyi Biotec, reference number 130-108-984) and rhIFN-ω (Merck, reference number SRP3061). Plates were then washed (PBS, 0.005% Tween 20), blocked by incubation with 5% nonfat milk powder in the same buffer, washed, and incubated with 1:50 dilutions of plasma from the patients or controls for 2 hours at room temperature (or with specific mAbs as positive controls). Each sample was tested once. Plates were thoroughly washed. Horseradish peroxidase–conjugated Fc-specific IgG fractions from polyclonal goat antiserum against human IgG, IgM, or IgA (Nordic Immunological Laboratories) were added to a final concentration of 2 μg/ml. Plates were incubated for 1 hour at room temperature and washed. Substrate was added, and the optical density was measured. A similar protocol was used to test for antibodies against 12 subtypes of IFN-α, except that the plates were coated with cytokines from PBL Assay Science (catalog no. 11002-1), or IFN-β (Miltenyi Biotech, reference number 130-107-888).

Functional evaluation of anti-cytokine auto-Abs

Luciferase reporter assays

The blocking activity of anti–IFN-α2 and anti–IFN-ω auto-Abs was determined with a reporter luciferase activity. Briefly, 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, reference

number 6365779001) for 24 hours. Cells in Dulbecco's modified Eagle medium (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 IFN-α2 (Miltenyi Biotec, reference number 130-108-984) and IFN-ω (Merck, reference number SRP3061) at 10 ng/ml or 100 pg/ml or IFN-β (Miltenyi Biotech, reference number 130-107-888) at 10 ng/ml for 16 hours at 37°C. Each sample was tested once for each cytokine and dose. Last, cells were lysed for 20 min at room temperature, and luciferase levels were measured with the Dual-Luciferase Reporter 1000 Assay System (Promega, reference number E1980) according to the manufacturer's protocol. Luminescence intensity was measured with a VICTOR-X Multilabel Plate Reader (PerkinElmer Life Sciences, USA). 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. A similar protocol was used to test for auto-Abs against 12 subtypes of IFN-α, except that we used cytokines from PBL Assay Science (catalog no. 11002-1) at 1 ng/ml for stimulation.

pSTAT1 induction in PBMC

The blocking activity of anti–IFN-α2 and anti–IFN-ω auto-Abs was determined by assessing STAT1 phosphorylation in healthy control cells after stimulation with the appropriate cytokines in the presence of 10% healthy control or patient serum/plasma. Surface-stained healthy control peripheral blood mononuclear cells (PBMCs) (350,000 per reaction) were cultured in serum-free RPMI 1640 medium with 10% healthy control or patient serum/plasma and were either left unstimulated or were stimulated with IFN-α2 or IFN-ω (10 ng/ml) for 15 min at 37°C. Each sample was tested once. Cells were fixed, permeabilized, and stained for intranuclear pSTAT1 (Y701). Cells were acquired on a BD LSRFortessa cytometer with gating on $CD14^+$ monocytes, and the data were analyzed with FlowJo software.

Luciferase-based immunoprecipitation assay

Levels of auto-Abs against IFN-α subtypes were measured in LIPS, as previously described (*9*). IFNA1, IFNA2, IFNA8, and IFNA21 sequences were inserted into a modified pPK-CMV-F4 fusion vector (PromoCell GmbH, Germany), in which the firefly luciferase replaced the NanoLuc luciferase (Promega, USA). The resulting constructs were used to transfect HEK293 cells, and the IFNA-luciferase fusion proteins were collected in the tissue culture supernatant. For auto-Ab screening, we combined 2×10^6 luminescence units (LU) of IFNA1, IFNA2, IFNA8, and IFNA21 in a single IP reaction mixture (pool 1) and IFNA4, IFNA5, IFNA6, and IFNA7 in another IP reaction mixture (pool 2). Serum samples were incubated with Protein G agarose beads (Exalpha Biologicals, USA) at room temperature for 1 hour in a 96-well microfilter plate (Merck Millipore, Germany), and we then added 2×10^6 LU of antigen and incubated for another hour. Each sample was tested once. The plate was washed with a vacuum system, and Nano-Glo Luciferase Assay Reagent (Promega, USA) was added. Luminescence intensity was measured with a VICTOR X Multilabel Plate Reader (PerkinElmer Life Sciences, USA). The results are expressed in arbitrary units as a fold-difference relative to the mean of the negative control samples.

IgG purification

We demonstrated that the IFN-α2– or IFN-ω–neutralizing activity observed was due to auto-Abs and not another plasma factor by depleting IgG from the plasma with a protein G buffer (Pierce Protein G IgG Binding Buffer, 21011) and column (NAb Protein G Spin Columns, 89953). All buffers were homemade: 0.1 M glycine (pH 2.7) and 1.5 M tris (pH 8). Total plasma was loaded onto the column. Each sample was tested once. Purified IgG were then concentrated [Pierce Protein Concentrators polyethersulfone (PES), 50K molecular weight cut-off (MWCO), 88504]. Without eluting the IgG, the flow-through fraction (IgG depleted) was then collected and compared to total plasma in the luciferase neutralization assay.

Statistical analysis

OR and *P* values for the effect of auto-Abs neutralizing each type I IFN on critical or severe COVID-19, using asymptomatic/mild patients or the general population as controls and adjusted on age in years and sex, were estimated by means of Firth's bias-corrected logistic regression (*48*, *49*) as implemented in the "logistf" R package (https://rdrr.io/cran/logistf/). Effect of age (quantitative in years or binary ± 65 years) and sex on the presence of neutralizing auto-Abs in each cohort (critical, severe, deceased, and general population) was tested by multivariable Firth's bias-corrected logistic regression. The SE of the prevalence of neutralizing auto-Abs to each type I IFN per age groups and sex was estimated using the Agresti-Coull approximation (*50*).

Schematic representation

Schematic representations (Fig. 1B) were created with BioRender.com.

SARS-CoV-2 experiment

SARS-CoV-2 strain USA-WA1/2020 was obtained from BEI Resources and amplified in Caco-2 cells at 37°C. Viral titers were measured on Huh-7.5 hepatoma cells in a standard plaque assay. Caco-2 (*Homo sapiens*, sex: male, colon epithelial) and Huh-7.5 cells (*H. sapiens*, sex: male, liver epithelial) were cultured in DMEM supplemented with 1% nonessential amino acids and 10% fetal bovine serum at 37°C under an atmosphere containing 5% CO_2. Both cell lines have been tested negative for contamination with mycoplasma. SARS-CoV-2 experiments were performed as follows: Huh-7.5 cells were used to seed 96-well plates at a density of 7.5×10^3 cells per well. The following day, plasma samples or a commercial anti–IFN-α2 antibody (catalog number 21100-1; R&D Systems) was diluted to 1% and incubated with 5 pM (~100 pg/ml) or 20 pM (~400 pg/ml) recombinant IFN-α2 (catalog number 11101-2, R&D systems) for 1 hour at 37°C (dilutions: plasma samples = 1:100 and anti–IFN-α2 antibody = 1:1000). Molar ratio was calculated according to the manufacturer's datasheet and with http://molbiol.ru/eng/scripts/01_04.html. After this incubation period, the cell culture medium was removed from the 96-well plates by aspiration and replaced with the plasma/anti–IFN-α2 antibody and IFN-α2 mixture. Each sample was tested once in triplicate. The plates were incubated overnight, and the plasma/anti–IFN-α2 antibody plus IFN-α2 mixture was removed by aspiration. The cells were washed once with PBS to remove potential anti–SARS-CoV-2–neutralizing antibodies, and fresh medium was then added. Cells were then infected with SARS-CoV-2 by directly adding the virus to the wells. Cells infected at a multiplicity of infection of 0.05 plaque-forming units per cell and incubated at 33°C for 48 hours. The cells were fixed with 7% formaldehyde, stained

for SARS-CoV-2 with an anti-N antibody (catalog no. GTX135357, GeneTex), imaged, and analyzed as previously described (*9*).

SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S6
Tables S1 to S6

View/request a protocol for this paper from *Bio-protocol*.

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