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The risk of COVID-19 death is much greater and age dependent with type I IFN autoantibodies

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection fatality rate (IFR) doubles with every 5 y of age from childhood onward. Circulating autoantibodies neutralizing IFN-α, IFN-ω, and/or IFN-β are found in ∼20% of deceased patients across age groups, and in ∼1% of individuals aged <70 y and in >4% of those >70 y old in the general population. With a sample of 1,261 unvaccinated deceased patients and 34,159 individuals of the general population sampled before the pandemic, we estimated both IFR and relative risk of death (RRD) across age groups for individuals carrying autoantibodies neutralizing type I IFNs, relative to noncarriers. The RRD associated with any combination of autoantibodies was higher in subjects under 70 y old. For autoantibodies neutralizing IFN-α2 or IFN-ω, the RRDs were 17.0 (95% CI: 11.7 to 24.7) and 5.8 (4.5 to 7.4) for individuals <70 y and ≥70 y old, respectively, whereas, for autoantibodies neutralizing both molecules, the RRDs were 188.3 (44.8 to 774.4) and 7.2 (5.0 to 10.3), respectively. In contrast, IFRs increased with age, ranging from 0.17% (0.12 to 0.31) for individuals <40 y old to 26.7% (20.3 to 35.2) for those ≥80 y old for autoantibodies neutralizing IFN-α2 or IFN-ω, and from 0.84% (0.31 to 8.28) to 40.5% (27.82 to 61.20) for autoantibodies neutralizing both. Autoantibodies against type I IFNs increase IFRs, and are associated with high RRDs, especially when neutralizing both IFN-α2 and IFN-ω. Remarkably, IFRs increase with age, whereas RRDs decrease with age. Autoimmunity to type I IFNs is a strong and common predictor of COVID-19 death.

COVID-19 | type I IFNs | autoantibodies | relative risk | infection fatality rate

Significance

There is growing evidence that preexisting autoantibodies neutralizing type I interferons (IFNs) are strong determinants of life-threatening COVID-19 pneumonia. It is important to estimate their quantitative impact on COVID-19 mortality upon SARS-CoV-2 infection, by age and sex, as both the prevalence of these autoantibodies and the risk of COVID-19 death increase with age and are higher in men. Using an unvaccinated sample of 1,261 deceased patients and 34,159 individuals from the general population, we found that autoantibodies against type I IFNs strongly increased the SARS-CoV-2 infection fatality rate at all ages, in both men and women. Autoantibodies against type I IFNs are strong and common predictors of life-threatening COVID-19. Testing for these autoantibodies should be considered in the general population.

There have already been more than 250 million severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and at least 5 million deaths from COVID-19 worldwide. Interindividual clinical variability in the course of infection with SARS-CoV-2 is immense, ranging from silent infection in about 40% of cases to acute respiratory distress syndrome in ∼3% of cases (1–5). Death occurs in ∼1% of cases (6). Age is the strongest epidemiological predictor of COVID-19 death, with the risk of death doubling every 5 y of age from childhood onward (6, 7). Men are also at greater risk of death than women (5, 8). Based on previously identified inborn errors of type I interferon (IFN) immunity (9), the COVID Human Genetic Effort (10) has shown that type I IFN immunity is essential for protective immunity to respiratory infection with SARS-CoV-2 (11–14). We have reported that inborn errors of Toll-like receptor 3 (TLR3)-dependent type I IFN immunity can underlie life-threatening COVID-19 pneumonia in a small subset of patients (14). Biochemically deleterious mutations of eight genes were found in 23 patients with critical COVID-19 (3.5% of 659 patients), including 18 patients under 60 y old. Remarkably, four unrelated patients, aged 25 y to 50 y, had autosomal recessive (AR) deficiencies of IFNAR1 or IRF7, including three homozygotes (two for *IFNAR1* and one for *IRF7*) and one compound heterozygote (for *IRF7*). Three other patients with AR IFNAR1 or TBK1 deficiency were independently reported (15–17). The penetrance of those defects is unknown, but it is probably higher for AR than for autosomal dominant disorders. We then reported that X-linked recessive TLR7 deficiency accounted for 1.8% of cases of life-threatening COVID-19 in men under 60 y old (13, 18). The penetrance of this disorder is apparently high but incomplete, especially in children. Deficiencies of IFNAR1 and IRF7 blunt type I IFN immunity across cell types, whereas defects of the TLR3 and TLR7 pathway preferentially affect respiratory epithelial cells and plasmacytoid dendritic cells, respectively (13, 19).

We have also reported the presence of autoantibodies (auto-Abs) neutralizing high concentrations (10 ng/mL, with plasma diluted 1/10) of IFN-α2 and/or IFN-ω in about 10% of patients with critical COVID-19 pneumonia but not in individuals with asymptomatic or mild infection (12). This finding has already been replicated in 14 other cohorts (20–35). We then detected auto-Abs neutralizing lower, more physiological concentrations (100 pg/mL, with plasma diluted 1/10) of IFN-α2 and/or IFN-ω in 13.6% of patients with life-threatening COVID-19, and 18% of deceased patients

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Table 1. Lines of evidence suggesting that auto-Abs against type I IFNs are strong determinants of the risk of life-threatening COVID-19

Evidence	Examples	References
Auto-Abs against type I IFNs are present before SARS-CoV-2 infection	In patients for whom a sample collected before the COVID-19 pandemic was available, the auto-Abs were found to preexist infection.	(36)
	These auto-Abs are found in the uninfected general population, and their prevalence increases after the age of 65 y.	(11)
Auto-Abs are associated with COVID-19 severity	Patients with inborn errors underlying these auto-Abs from infancy onward (e.g., APS-1) have a very high risk of developing critical COVID-19 pneumonia.	(36)
	The population of patients with critical disease includes a higher proportion of individuals producing these auto-Abs than the population of patients with silent or mild infection (ORs depending on the nature, number, and concentrations of type I IFN neutralized).	(11)
	The results concerning the proportions of critical cases with auto-Abs against type I IFNs have already been replicated in >15 different cities (Americas, Europe, Asia).	(20, 23–35)
Auto-Abs against type I IFNs neutralize host antiviral activity	These auto-Abs neutralize the antiviral activity of type I IFNs against SARS-CoV-2 in vitro.	(12)
	These auto-Abs are found in vivo in the blood of SARS-CoV-2-infected patients, where they neutralize type I IFN.	(37)
	These auto-Abs are found in vivo in the respiratory tract of patients, where they neutralize type I IFN.	(38–40)
	A key virulence factor of SARS-CoV-2 in vitro is its capacity to impair type I IFN immunity.	(41)
	Animals with type I IFN deficiency develop critical disease, including animals treated with mAbs that neutralize type I IFNs.	(42)
Auto-Abs against cytokines are clinical phenocopies of the corresponding inborn errors	Patients with auto-Abs against type I IFNs are phenocopies of IFNAR1$^{-/-}$, IFNAR2$^{-/-}$, and IRF7$^{-/-}$ patients with critical COVID-19 pneumonia.	(14)
	Patients with auto-Abs against IL-6, IL-17, GM-CSF, and type II IFN are phenocopies of the corresponding inborn errors and underlie staphylococcal disease, mucocutaneous candidiasis, nocardiosis, and mycobacterial diseases, respectively.	(43–51)

(11). The proportion of male patients was greater in patients with auto-Abs than in patients without auto-Abs (11, 12). In addition, 1.3% of patients with critical COVID-19 had auto-Abs neutralizing IFN-β (10 ng/mL, with plasma diluted 1/10), most without auto-Abs neutralizing IFN-α2 or IFN-ω. The prevalence of auto-Abs neutralizing IFN-α2 and/or IFN-ω in the general population increased with age, from 0.18% for 10 ng/mL and 1% for 100 pg/mL in individuals between 18 y and 69 y old to 3.4% for 10 ng/mL and 6.3% for 100 pg/mL for individuals over 80 y old (11). The prevalence of auto-Abs against IFN-β did not increase with age. The crude odds ratios (ORs) for critical COVID-19 as opposed to asymptomatic or mild infection in auto-Ab carriers relative to noncarriers ranged from 3 to 67, depending on the type I IFNs recognized and the concentrations neutralized (11). At least 12 lines of evidence strongly suggest that auto-Abs against type I IFNs are strong determinants of COVID-19 death (Table 1). The specific impact of these auto-Abs on COVID-19 mortality according to age and sex remains unknown and is of major interest (52, 53), as both the prevalence of these auto-Abs and the risk of death increase with age and are higher in men. Here, using data reported by Bastard et al. (11), we estimated the relative risk of COVID-19 death (RRD) for type I IFN auto-Ab carriers relative to noncarriers and the corresponding SARS-CoV-2 infection fatality rate (IFR), by sex and age category.

Results

Patients and Controls. We estimated the RRD of individuals carrying auto-Abs neutralizing type I IFNs relative to noncarriers by Firth's logistic regression, using large samples of 1,261 patients who died from COVID-19 and 34,159 individuals from the general population from whom samples were collected before the pandemic. In this study design, in which controls are sampled from the baseline population regardless of disease status, the ORs obtained by logistic regression approximate the relative risks (RRs) in the absence of the assumption of rare disease (54) (*SI Appendix*, *Supplementary Materials and Methods*). We confirmed that this statement remains valid in our study design, using Firth's logistic regression by a simulation study (*SI Appendix*, *Supplementary Materials and Methods* and Fig. S1). For auto-Abs neutralizing low concentrations (100 pg/mL) of IFN-α2 and/or IFN-ω, we used 1,121 patients who died from COVID-19, and 10,778 individuals from the general population (Table 2). Assessments of auto-Abs neutralizing high concentrations (10 ng/mL) of IFN-α2 and/or IFN-ω were available for 1,094 deceased patients, and 34,159 individuals from the general population (Table 2). We also had assessments of auto-Abs neutralizing 10 ng/mL of IFN-β for a subsample of 636 deceased patients, and 9,126 individuals from the general population (Table 2). RRDs were estimated by means of Firth's

Table 2. Characteristics of the general population cohort and of the cohort of patients who died from COVID-19

Characteristics	Neutralization 100 pg/mL		Neutralization 10 ng/mL	
	General population (n = 10,778)	Deceased patients (n = 1,121)	General population (n = 34,159)	Deceased patients (n = 1,094)
Male – no. (percent)	5,429 (50.4)*	821 (73.2)	17,859 (52.3)	805 (73.5)
Mean age ± SD* – years	62.3 ± 17.2	70.7 ± 13.0	52.7 ± 18.2	70.6 ± 13.1
Age distribution – no. (percent)				
20 y to 39 y	1,251 (11.6)	17 (1.5)	9,102 (26.6)	15 (1.4)
40 y to 49 y	1,459 (13.5)	43 (3.8)	5,403 (15.8)	47 (4.3)
50 y to 59 y	1,736 (16.1)	144 (12.8)	6,414 (18.9)	152 (13.9)
60 y to 69 y	2,475 (23.0)	307 (27.4)	6,881 (20.1)	289 (26.4)
70 y to 79 y	1,790 (16.6)	307 (27.4)	3,721 (10.9)	296 (27.1)
≥80 y	2,067 (19.2)	303 (27.0)	2,638 (7.7)	295 (27.0)
Auto-Ab – no. of carriers (percent)				
IFN-α2 and IFN-ω	65 (0.6)	102 (9.1)	45 (0.1)	75 (6.8)
IFN-α2 or IFN-ω	246 (2.3)	203 (18.1)	181 (0.5)	130 (11.9)
IFN-α2	151 (1.4)	140 (12.5)	117 (0.3)	118 (10.8)
IFN-ω	160 (1.5)	165 (14.7)	109 (0.3)	87 (8.0)
IFN-β[†]	NA	NA	24 (0.3)	6 (0.9)

NA, not available.
*Age is given in years and corresponds to age at the time of recruitment for members of the general population cohort (controls) and age at death for COVID-19 patients.
[†]IFN-β neutralization experiments were performed only for a concentration of 10 ng/mL, on 9,126 individuals (49.5% male, mean age 60.6 y) from the general population and 636 COVID-19 patients (71.1% male, mean age 72.9 y).

bias-corrected logistic regression, considering death as a binary outcome and adjusting for sex and age in six classes (20 y to 39 y, 40 y to 49 y, 50 y to 59 y, 60 y to 69 y, 70 y to 79 y, and ≥80 y). For assessment of the effect of age and sex on RRD, we added interaction terms between auto-Abs and age, and auto-Abs and sex terms to the logistic model (*Materials and Methods* and *SI Appendix, Supplementary Materials and Methods*).

RRD for Carriers of Auto-Abs Neutralizing Low Concentrations of Type I IFNs. We first estimated the RRD for individuals carrying auto-Abs neutralizing low concentrations of IFN-α2 or IFN-ω. As expected, increasing age and maleness were highly significantly associated with greater risk of COVID-19 death (P values $\leq 10^{-16}$; *SI Appendix*, Table S1). Different age classes were used to test the interaction with the presence of auto-Abs, and the best fit was obtained with a two-age class model (20 y to 69 y and ≥70 y; *SI Appendix*, Table S2) with a significant effect of the interaction term between auto-Abs and age (P value $= 4 \times 10^{-6}$). The RRD associated with auto-Abs did not vary significantly with sex (P value = 0.81). These interaction results are fully consistent with the distribution of RRD according to age (Fig. 1*A*) and sex (Fig. 1*B*), with a clear decrease in RRD after the age of 70 y, and no sex effect. Overall, the RRD for individuals carrying auto-Abs neutralizing IFN-α2 or IFN-ω decreased from 17.0 (95% CI: 11.7 to 24.7) before the age of 70 y to 5.8 (4.5 to 7.4) for individuals ≥70 y old (Fig. 2*A* and *SI Appendix*, Table S3). We then applied the same strategy to other combinations of auto-Abs neutralizing low concentrations of IFN, and observed similar age effects on RRDs (*SI Appendix*, Table S1). The presence of auto-Abs neutralizing both IFN-α2 and IFN-ω was associated with the highest RRD, estimated at 188.3 (45.8 to 774.4) for individuals under the age of 70 y and 7.2 (5.0 to 10.3) for those over 70 y old (Fig. 2*A* and *SI Appendix*, Table S3). We also estimated the population attributable fraction (PAF), to assess the proportion of COVID-19 deaths attributable to auto-Abs (*SI Appendix, Supplemental Materials and Methods*). Given the high RRD estimated for all combinations of auto-Abs neutralizing low concentrations of type I IFNs, the PAF was very close to the prevalence of these auto-Abs in deceased patients (*SI Appendix*, Table S3).

RRD for Carriers of Auto-Abs Neutralizing High Concentrations of Type I IFNs. We then estimated the RRD for the presence versus the absence of auto-Abs neutralizing high concentrations (10 ng/mL) of type I IFN. The effect of age on RRD was similar to that observed with auto-Abs neutralizing low concentrations of type I IFN, with the use of two age classes providing the best fit (*SI Appendix*, Tables S2 and S4), and a decrease of RRD with age (Fig. 2*B* and *SI Appendix*, Table S5). The RRD for carriers of IFN-α2 or IFN-ω auto-Abs decreased from 62.4 (38.4 to 101.3) before the age of 70 y to 6.8 (5.1 to 9.2) after the age of 70 y, whereas carriers of auto-Abs against both IFN-α2 and IFN-ω had the highest RRD, estimated at 156.5 (57.8 to 423.4) and 12.9 (8.4 to 19.9) for subjects <70 y and ≥70 y old, respectively (Fig. 2*B* and *SI Appendix*, Table S5). Individuals carrying auto-Abs neutralizing high concentrations of IFN-α2 and/or IFN-ω had a significantly higher RRD than individuals carrying only auto-Abs neutralizing low concentrations (*SI Appendix, Supplemental Materials and Methods*). This finding, consistent with the higher proportion of auto-Abs neutralizing high concentrations in deceased patients than in the general population (*SI Appendix*, Fig S2), suggests a more deleterious impact of auto-Abs neutralizing high concentrations of IFN-α2 and/or IFN-ω on COVID-19 outcomes. Finally, auto-Abs neutralizing high doses of IFN-β had the lowest RRD before 70 y (7.0 [2.2 to 22.4]), with no significant age-dependent association (P value = 0.37). The PAF for auto-Abs neutralizing high concentrations of type I IFNs was also

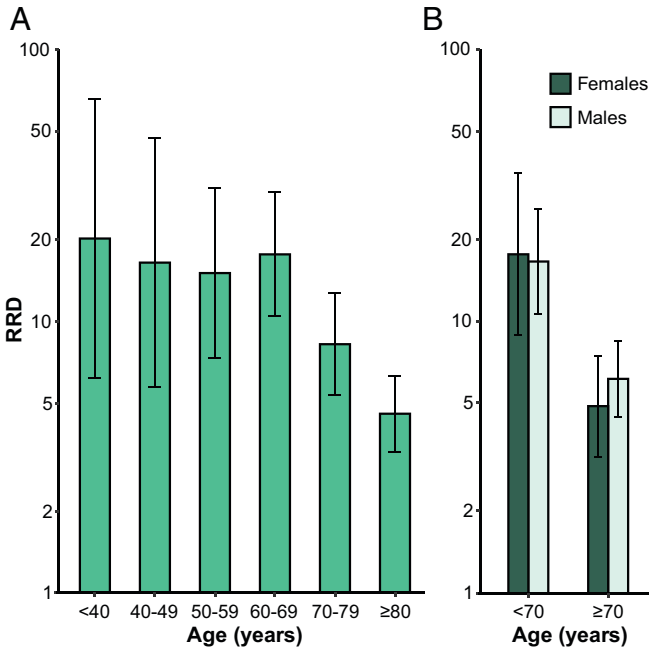

Fig. 1. RRDs for individuals with auto-Abs neutralizing low concentrations of IFN-α2 or IFN-ω relative to individuals without such auto-Abs, by age and sex. RRDs are displayed on a logarithmic scale (*A*) for six age classes and (*B*) for male and female subjects under and over the age of 70 y. Vertical bars represent the 95% CI.

close to the prevalence of these auto-Abs in deceased patients (*SI Appendix*, Table S5).

IFR in Individuals Carrying Auto-Abs Neutralizing Low Concentrations of Type I IFNs. We then estimated the IFR in SARS-CoV-2–infected individuals carrying auto-Abs neutralizing

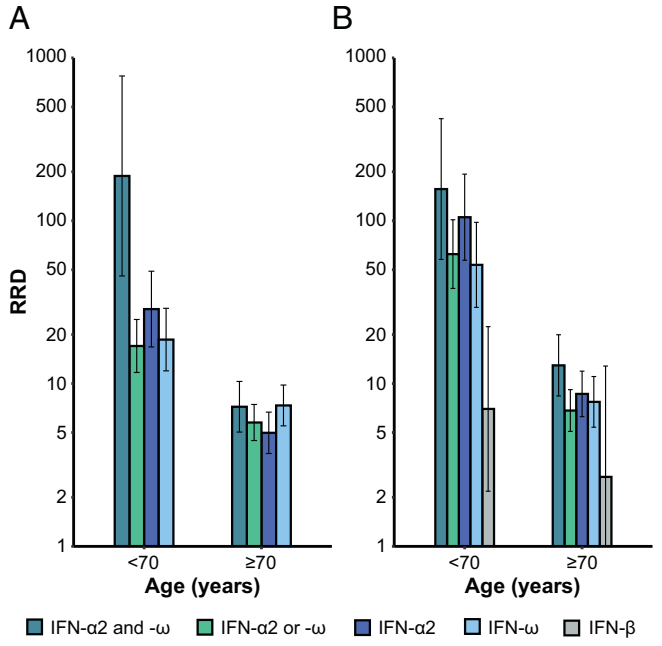

Fig. 2. RRDs for individuals with auto-Abs neutralizing different combinations of type I IFNs relative to individuals without such auto-Abs, by age. RRDs are displayed on a logarithmic scale for individuals under and over 70 y of age with (*A*) auto-Abs neutralizing low concentrations of IFN-α2 and IFN-ω, IFN-α2 or IFN-ω, IFN-α2, and IFN-ω and (*B*) auto-Abs neutralizing high concentrations of IFN-α2 and IFN-ω, IFN-α2 or IFN-ω, IFN-α2, IFN-ω, and IFN-β, relative to individuals without such combinations of auto-Abs. Vertical bars represent the 95% CI.

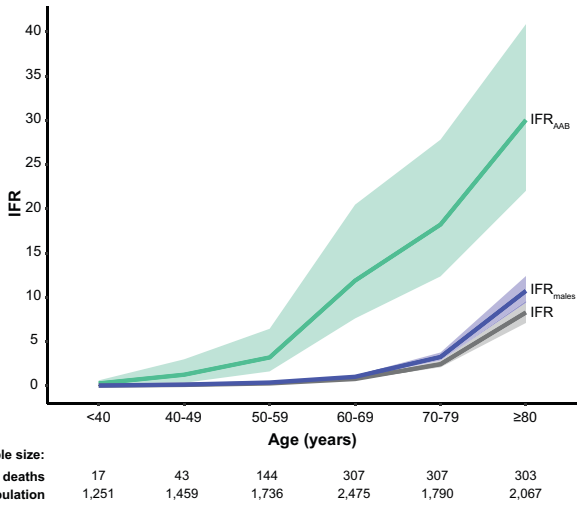

Fig. 3. SARS-CoV-2 IFRs by age. IFRs are provided for the general population for both sexes (gray) and for males only (blue), from the data of O'Driscoll et al. (6); IFR_{AAB} (green) are shown for individuals carrying auto-Abs neutralizing low concentrations of IFN-α2 or IFN-ω. Auto-Abs against type I IFNs are associated with high RRDs and strongly increase the IFR, to a much greater extent than being male, and, by inference, than other common classical risk factors providing ORs of death similar to that for being male (around two), such as certain comorbid conditions, or the most significant common genetic variant on chromosome 3 (5).

low concentrations of type I IFNs (IFR_{AAB}). According to Bayes' theorem, IFR_{AAB} can be expressed as a function of the age-dependent prevalence of auto-Abs in deceased patients and in the general population together with the reported age-specific IFR (6) (*SI Appendix*). For all combinations of auto-Abs, the IFR_{AAB} was much higher than the overall IFR. Fig. 3 illustrates this much higher IFR for carriers of auto-Abs neutralizing low concentrations of IFN-α2 or IFN-ω; it exceeded 1% and 10% for subjects over the ages of 40 y and 60 y, respectively. Considering other combinations of auto-Abs, the highest IFR_{AAB} was observed for carriers of auto-Abs neutralizing both IFN-α2 and IFN-ω, reaching 40.5% (27.8 to 61.2) in individuals over 80 y old (Fig. 4*A* and *SI Appendix*, Table S6). IFR_{AAB} values were similar for all other combinations of auto-Abs. For example, the IFR_{AAB} for individuals carrying auto-Abs neutralizing either IFN-α2 or IFN-ω ranged from 0.17% (0.12 to 0.31) in individuals under 40 y old to 26.7% (20.3 to 35.2) in individuals over 80 y old. An exception was noted for the IFR_{AAB} of carriers of anti-IFN-α2 auto-Abs, which was 1.8 to 2.6 times higher than that for carriers of auto-Abs neutralizing IFN-α2 or IFN-ω in subjects under 60 y old. The IFR_{AAB} was also generally higher in male subjects than in female subjects, particularly in individuals carrying auto-Abs neutralizing both IFN-α2 and IFN-ω (~2.7 times higher) (*SI Appendix*, Fig. S3).

IFR in Individuals Carrying Auto-Abs Neutralizing High Concentrations of Type I IFNs. The age-, sex-, and type I IFN–dependent patterns of IFR_{AAB} observed for carriers of auto-Abs neutralizing high concentrations of IFN-α2 and/or IFN-ω were similar to those previously obtained for carriers of auto-Abs neutralizing low concentrations of these molecules, but with higher values. For example, IFR_{AAB} ranged from 3.1% (1.3 to 20.8) before 40 y of age to 68.7% (42.5 to 95.8) in those over 80 y old for carriers of auto-Abs neutralizing high concentrations of both IFN-α2 and IFN-ω (Fig. 4*B* and *SI Appendix*, Table S7). IFR_{AAB} values were ~5 times higher in male than in female subjects, across all age groups and auto-

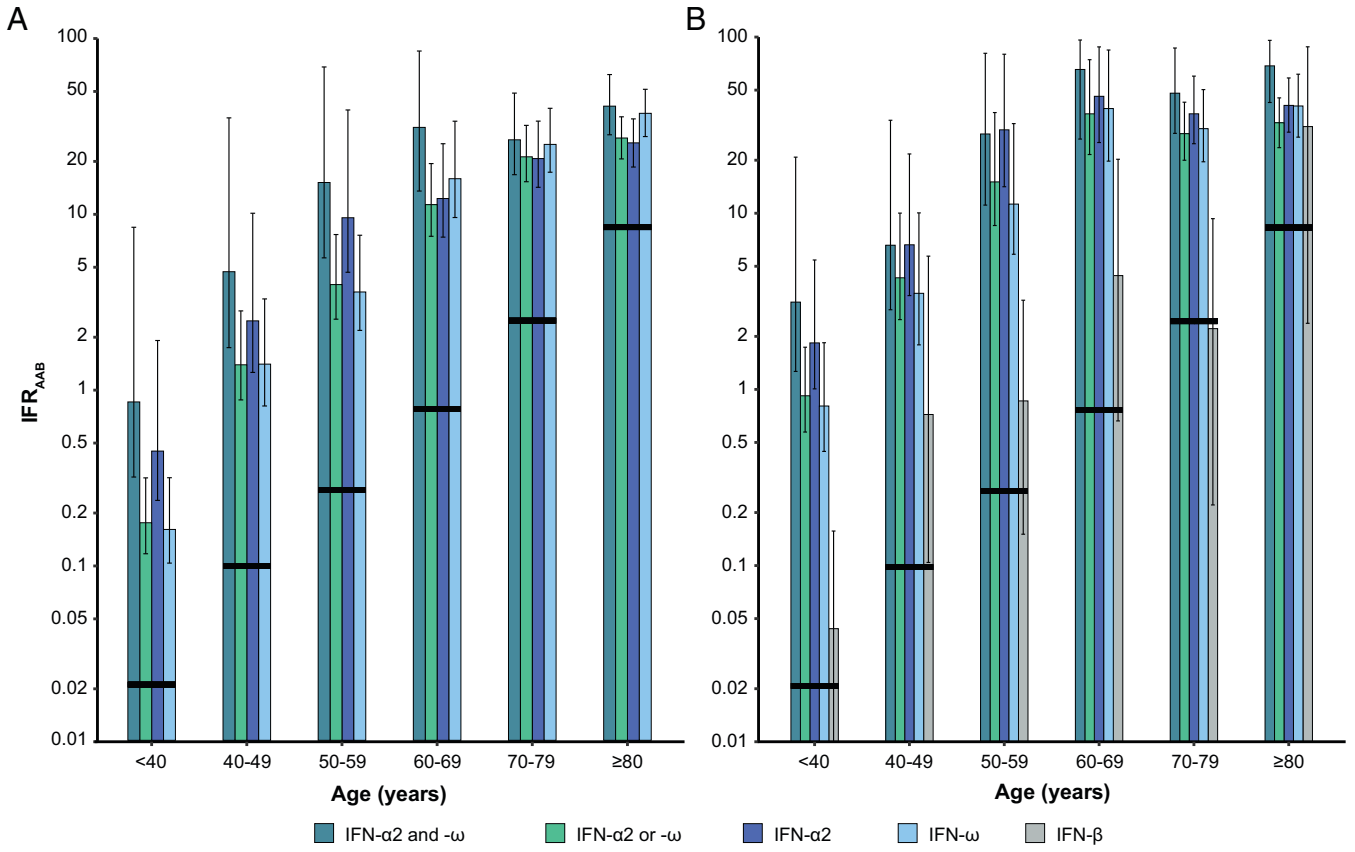

Fig. 4. SARS-CoV-2 IFRs for carriers of various combinations of neutralizing auto-Abs, by age. IFR_{AAB} values (percent) are displayed, on a logarithmic scale, by age, for individuals with (*A*) auto-Abs neutralizing low concentrations of IFN-α2 and IFN-ω, IFN-α2 or IFN-ω, IFN-α2, and IFN-ω and (*B*) auto-Abs neutralizing high concentrations of IFN-α2 and IFN-ω, IFN-α2 or IFN-ω, IFN-α2, IFN-ω, and IFN-β. Vertical bars represent the 95% CI. Horizontal black lines represent the IFR provided by O'Driscoll et al. (6).

Abs combinations (*SI Appendix*, Fig. S4). For carriers of auto-Abs neutralizing IFN-β (tested only at high concentration), IFR_{AAB} was lower (by a factor of 6 to 71) than for individuals under the age of 80 y with auto-Abs neutralizing IFN-α2 and/or IFN-ω. It ranged from 0.04% (0.01 to 0.16) for individuals under the age of 40 y to 2.2% (0.2 to 9.3) for the 70- to 79-y age group. In the oldest age class, IFR_{AAB} was 31.0% (2.4 to 88.1), similar to that for carriers of auto-Abs against IFN-α2 or IFN-ω, albeit with a large confidence interval.

Discussion

In this study, we took advantage of our previous data (11) to estimate RRDs associated with auto-Abs across age groups. We also confirmed, by a simulation study, that, in our design, ORs obtained by Firth's logistic regression were reliable estimates of RR. In addition, we used IFR values previously reported for the general population (6) to estimate IFR_{AAB} under the plausible hypothesis that the prevalence of auto-Abs in the general population is a reliable estimation of the prevalence of auto-Abs in infected individuals (*SI Appendix*, *Supplemental Materials and Methods*). We report high RRDs for carriers of auto-Abs neutralizing type I IFNs, ranging from 2.6 for auto-Abs neutralizing IFN-β (high concentration) in subjects over 70 y old to >150 for auto-Abs neutralizing both IFN-α2 and IFN-ω in subjects under 70 y old. For all types of auto-Abs, RRDs were 3 to 26 times higher in subjects under 70 y old than in older individuals. This is consistent with the increasing prevalence of auto-Abs in the general population with age (~1% under 70 y of age and >4% over 70 y of age), whereas the proportion of deceased patients with these auto-Abs is stable across age categories (~15 to 20%). The lower RRD observed in the elderly may be partly explained epidemiologically, by the larger contribution of other mortality risk factors, such as comorbid conditions, which become more frequent with increasing age. At the cellular level, aging is associated with immunosenescence, which may contribute to a defective innate and adaptive response to SARS-CoV-2 infection, thereby conferring a predisposition to severe COVID-19 (55). At the molecular level, global type I IFN immunity in the blood (plasmacytoid dendritic cells) and respiratory tract (respiratory epithelial cells) has been shown to decline with age (56–59). These epidemiological, cellular, and molecular factors probably overlap. Thus, despite their increasing prevalence with age, auto-Abs against type I IFNs make a decreasing contribution to the risk of COVID-19 death with age, due to the progressive development of additional age-dependent risk factors, including other mechanisms of type I IFN deficiency. However, for the very same reasons, IFR_{AAB} increases dramatically with age in patients with auto-Abs, reaching 68.7% for carriers of auto-Abs neutralizing high concentrations of both IFN-α2 and IFN-ω.

RRD and IFR_{AAB} varied considerably with the IFNs recognized and the concentrations neutralized by auto-Abs. For combinations involving auto-Abs against IFN-α2 and/or IFN-ω, the neutralization of low concentrations was associated with a lower RRD and a lower IFR_{AAB} than the neutralization of high concentrations, suggesting that residual type I IFN activity may be beneficial in at least some patients. Blood IFN-α concentrations

during acute asymptomatic or paucisymptomatic SARS-CoV-2 infection typically range from 1 pg/mL to 100 pg/mL (11). In addition, the presence of auto-Abs neutralizing both IFN-α2 and IFN-ω was associated with the highest RRD and IFR_{AAB} values. Interestingly, IFN-α2 and IFN-ω are encoded by two genes, *IFNA2* and *IFNW1*, that have been shown to have evolved under strong selective constraints (60), consistent with their neutralization being harmful to the host. In addition, patients with auto-Abs against IFN-α2 have been shown to neutralize all 13 IFN-α subtypes (11, 12), rendering any potential IFN-α redundancy inoperative (11, 12). Accordingly, the IFR_{AAB} values for carriers of auto-Abs against IFN-α2 were higher than those for carriers of auto-Abs against IFN-ω in subjects under 60 y of age. In older age groups, this difference tended to disappear, consistent with the lower impact of auto-Abs in the elderly, as discussed above. Finally, auto-Abs neutralizing IFN-β were less common, and associated with lower RRD and IFR_{AAB} values (by about one order of magnitude) than auto-Abs against IFN-α2 and/or IFN-ω, in all age groups except the over-80s. This less deleterious effect of auto-Abs neutralizing IFN-β is consistent with a mouse study showing that the blockade of IFN-β alone does not alter the early dissemination of lymphocytic choriomeningitis virus (61). Overall, auto-Abs against type I IFNs are associated with very high RRD and IFR values, and the magnitude of this effect appears to be much larger than that of other known common risk factors apart from age, such as maleness (Fig. 4), comorbidities, or the most significant common genetic variant on chromosome 3, all of which have been associated with life-threatening COVID-19 with ORs of about two (5).

Despite the lower prevalence of these auto-Abs in younger than in older individuals, the much higher IFR_{AAB} observed in individuals with these auto-Abs suggests that the testing of infected individuals in all age groups is warranted. Particular attention should be paid to patients, especially children, with known autoimmune or genetic conditions associated with the production of auto-Abs against type I IFNs. Early treatments could be provided (62), including monoclonal antibodies (63), new antiviral drugs, and/or IFN-β in the absence of auto-Abs against IFN-β (64, 65). Rescue treatment by plasma exchange is a therapeutic option in patients who already have pneumonia (36). A screening of uninfected elderly people could be considered, given that these auto-Abs are found in 4% of individuals over 70 y old. Carriers of auto-Abs should be vaccinated against SARS-CoV-2 as a priority, and should benefit from a booster, whatever their age, and, ideally, from a monitoring of their antibody response to the vaccine. They should not receive live-attenuated vaccines, including the yellow fever vaccine (YFV-17D) and anti-SARS-CoV-2 vaccines based on the YFV-17D backbone (66). In cases of SARS-CoV-2 infection, vaccinated patients should be closely monitored. As SARS-CoV-2 vaccination coverage increases and mortality due to COVID-19 decreases over time, it will be important to reevaluate the risk of fatal COVID-19 in vaccinated individuals with and without auto-Abs. It is currently unclear whether these auto-Abs impair antibody responses to vaccines, and whether a vaccine-triggered antibody response can overcome type I IFN deficiency in response to large or even medium-sized viral inocula. Finally, further investigations are required to determine the contribution of these auto-Abs to other severe viral diseases, and to elucidate the mechanisms underlying their development, which may be age dependent. In the meantime, auto-Abs against type I IFNs should be considered as a leading common predictor of life-threatening COVID-19, after age, as their detection appears to have a much greater predictive value for death, and, by inference, hospitalization and critical COVID-19, than sex, comorbidities, and common genetic variants (Fig. 3).

Materials and Methods

Study Design. We enrolled 1,261 patients aged 20 y to 99 y old who died from COVID-19 pneumonia before SARS-CoV-2 vaccines became available, and 34,159 controls from the adult general population from whom samples were collected before the COVID-19 pandemic, as previously described (11). The experiments involving human subjects were performed in accordance with institutional, local, and national ethical guidelines. Approval was obtained 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 number 2010-A00634-35), and the Rockefeller University Institutional Review Board in New York (protocol JCA-0700). Participants were consented prior to sampling and collection of clinical data. Auto-Ab determinations were performed as described by Bastard et al. (11, 66), and were classified as neutralizing high concentrations (10 ng/mL) of IFN-α2, IFN-ω, or IFN-β, or low concentrations (100 pg/mL) of IFN-α2 or IFN-ω (*SI Appendix, Supplemental Materials and Methods*).

RRDs and IFRs for Carriers of Neutralizing Autoantibodies. We estimated the RRD in individuals carrying auto-Abs neutralizing type I IFNs relative to non-carriers, using large samples of patients who died from COVID-19 and of individuals from the general population. For each combination of auto-Abs, a Firth's bias-corrected logistic regression model, including auto-Ab status, sex, and age, was fitted (*SI Appendix*, Table S1). For assessments of the effect of age and sex on the RRD due to auto-Abs, we added interaction terms between auto-Abs and sex, and auto-Abs and age (*SI Appendix, Supplemental Materials and Methods*). A similar Firth's logistic regression model was used in the subsample of carriers of auto-Abs, to assess the deleteriousness of auto-Abs neutralizing high concentrations relative to those neutralizing low concentrations of type I IFNs (*SI Appendix, Supplemental Materials and Methods*). From the RRD, we calculated the PAF to assess the proportion of COVID-19 deaths attributable to auto-Abs. The PAF can be estimated as follows: P(auto-Abs/death) * (1 − 1/RRD) (67), where P(auto-Abs/death) is the prevalence of auto-Abs in deceased patients.

Our goal was also to estimate the fatality rate upon infection with SARS-CoV-2 (IFR) in unvaccinated subjects carrying auto-Abs against type I IFNs across age groups and sexes. To this end, we used the fatality rate upon infection with SARS-CoV-2 in the general unvaccinated population provided by O'Driscoll et al. (6). We estimated the IFR for carriers of neutralizing auto-Abs infected with SARS-CoV-2 (IFR_{AAB}) following Bayes' theorem, and using the age-dependent prevalence of auto-Abs in deceased patients and in the general population together with the reported age-specific IFR (6) as detailed in *SI Appendix, Supplemental Materials and Methods*.

Data Availability. All the data are available in the manuscript or in the supporting information. Plasma, cells, and genomic DNA are available from J.-L.C. under a material transfer agreement (MTA) with The Rockefeller University or the Imagine Institute. Huh-7.5 cells are available on request from C.M.R. under an MTA with The Rockefeller University and Apath LLC. The materials and reagents used are almost exclusively commercially available and nonproprietary. Materials derived from human samples may be made available on request, subject to any underlying restrictions concerning such samples.

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The authors declare a competing interest. J.-L.C. is an inventor on patent application PCT/US2021/042741, filed 22 July 2021, submitted by The Rockefeller University, which covers diagnosis of, susceptibility to, and treatment of viral disease and viral vaccines, including COVID-19 and vaccine-associated diseases. M.C.N. is an inventor on patent application PCT/US2021/070472 submitted by The Rockefeller University that covers neutralizing anti-SARS-CoV-2 antibodies and methods of the use thereof. M.C.N. reports being on the Scientific Advisory Board of Celldex and Frontier Biotechnologies. R.P.L. reports being a non-executive director of Roche.

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