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-ω2 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.

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 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.
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-Abs carriers relative to noncarriers ranged from 3 to 67, depending on the nature, number, and concentrations of type I IFN neutralized. 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).

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 before SARS-CoV-2 infection fatality rate (IFR), by sex and age category.

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. These auto-Abs are found in the uninfected general population, and their prevalence increases after the age of 65 y. 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. 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). 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). | (36) |
| Auto-Abs are associated with COVID-19 severity | These auto-Abs neutralize the antiviral activity of type I IFNs against SARS-CoV-2 in vitro. These auto-Abs are found in vivo in the blood of SARS-CoV-2-infected patients, where they neutralize type I IFN. These auto-Abs are found in vivo in the respiratory tract of patients, where they neutralize type I IFN. A key virulence factor of SARS-CoV-2 in vitro is its capacity to impair type I IFN immunity. Animals with type I IFN deficiency develop critical disease, including animals treated with mAbs that neutralize type I IFNs. Patients with auto-Abs against type I IFNs are phenocopies of the corresponding inborn errors from COVID-19 pneumonia. 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. | (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. These auto-Abs are found in vivo in the blood of SARS-CoV-2-infected patients, where they neutralize type I IFN. These auto-Abs are found in vivo in the respiratory tract of patients, where they neutralize type I IFN. A key virulence factor of SARS-CoV-2 in vitro is its capacity to impair type I IFN immunity. Animals with type I IFN deficiency develop critical disease, including animals treated with mAbs that neutralize type I IFNs. Patients with auto-Abs against type I IFNs are phenocopies of the corresponding inborn errors from COVID-19 pneumonia. 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. | (12) |
| Auto-Abs against cytokines are clinical phenocopies of the corresponding inborn errors | These auto-Abs neutralize the antiviral activity of type I IFNs against SARS-CoV-2 in vitro. These auto-Abs are found in vivo in the blood of SARS-CoV-2-infected patients, where they neutralize type I IFN. These auto-Abs are found in vivo in the respiratory tract of patients, where they neutralize type I IFN. A key virulence factor of SARS-CoV-2 in vitro is its capacity to impair type I IFN immunity. Animals with type I IFN deficiency develop critical disease, including animals treated with mAbs that neutralize type I IFNs. Patients with auto-Abs against type I IFNs are phenocopies of the corresponding inborn errors from COVID-19 pneumonia. 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. | (36) |

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-Abs 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-Abs carriers relative to noncarriers and the corresponding SARS-CoV-2 infection fatality rate (IFR), by sex and age category.
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 ≤ 10⁻⁶; 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 × 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. 1A) and sex (Fig. 1B), 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. 2A 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 RRRDs (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. 2A 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, Supplementary 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. 2B 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. 2B 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, Supplementary 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
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 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. 4A 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. 4B and SI Appendix, Table S7). IFR_AAB values were ~5 times higher in male than in female subjects, across all age groups and auto-

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**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.

**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 IFN-β, 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).
Abs combinations (SI Appendix, Fig. S4). For carriers of auto-Abs neutralizing IFN-β (tested only at high concentration), IFRAAB 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, IFRAAB 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 IFRAAB 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, IFRAAB 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 IFRAAB 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 IFRAAB 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

Fig. 4. SARS-CoV-2 IFRs for carriers of various combinations of neutralizing auto-Abs, by age. IFRAAB 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).
during acute asymptomatic or paucisymptomatic SARS-CoV-2 infection typically range from 1 pg/mL to 100 pg/mL (11). 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 IRAAB 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 IRAAB 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-RBC 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/RRD) 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.

**ACKNOWLEDGMENTS.** We thank the patients and their families for placing their trust in us. We thank the members of both branches of the Laboratory of Human Genetics of Infectious Diseases. We thank Y. Nemirovskaya, M. Woollett, D. Liu, S. Bouchent, C. Rivalain, M. Chrabieh, and L. Lorenzo for administrative assistance. We also thank the staff of the Imagine facilities: C. Bureau, L. Colonna, S. Paillet, N. Ghouas, and M. Sy. We are also grateful to the legal team and technology transfer staff of the Imagine Institute: M. Pilorges, R. Marlanges, E. Rubino, W. Loewen, B. Beudin, and N. Wuytens. We thank all the staff of the Imagine Institute, Necker Hospital, and Necker sorting center for help. We thank S. Nagashima (Department of Epidemiology, Infectious Disease Control and Prevention, Graduate School of Biomedical and Health Sciences, Hiroshima...
University, Hiroshima, Japan). The Laboratory of Human Genetics of Infectious Diseases is supported by the Howard Hughes Medical Institute; The Rockefeller University; the St. Giles Foundation; the NIH (Grants RO1AI08364 and RO1AI163029); the National Center for Advancing Translational Sciences; NIH Clinical and Translational Science Awards program (Grant UL1 TR001866); a Fast Grant from Emergent Ventures; Mercatus Center at George Mason University; the Yale Center for Mendelian Genomics and the Genome Sequencing Coordinating Center funded by the National Human Genome Research Institute (Grants UM1HG006504 and U24HG008956); the Yale High Performance Computing Center (Grant S1000D18521); the Fisher Center for Alzheimer’s Research Foundation; the Meyer Foundation; the JPB Foundation; the French National Research Agency (ANR) under the “Investments for the Future” program (Grant ANR-10 IAUH-01); the Integrative Biology of Emerging Infectious Diseases Laboratory of Excellence (Grant ANR-10 LABX-62-IBIED); the French Federation for Medical Research (FRM) (Grant EQQ20190300777); the French Agency for Research on AIDS and Viral Hepatitis (ANRS) Nord-Sud (Grant ANRS-COV05); the ANR GENIVIR (Grant ANR-20 CE93-003), AABFNCOV (Grant ANR-20-C101-0001), CIVIRGEN (Grant ANR-19 CE15 0099-01), and GenMiS-C (Grant ANR 21 COVR-0039) projects; the Square Foundation; Grandir-Fonds de solidarité pour l’Enfance; le Fondation du Souffle; the SCOR Corporation for Science; The French Ministry of Higher Education, Research, and Innovation (Grant MESR-COVID-19); Institut National de la Santé et de la Recherche Médicale (INSERM), REACTing-INSERM; and the University Paris Cité. P. Bastard was supported by the FRM Award (EA20170638020). P. Bastard, J.R., and T.L.V. were supported by the MD-PhD program of the Imagine Institute (with the support of Fondation Bettencourt Schueller). Work at the Neurometabolic lab received funding from Centre for Biomedical Research on Rare Diseases (CIBERER) (Grant ACCI20-767) and the European Union’s Horizon 2020 research and innovation program under grant agreement S241100 (EASI Genomics). Work in the Laboratory of Virology and Infectious Disease was supported by the NIH (Grants P01AI138398-51, 2U19AI111825, and R01AI091707-05S), a George Mason University Fast Grant, and the G. Harold and Leila Y. Mathers Charitable Foundation. The Infanta Leonor University Hospital supported the research of the Department of Internal Medicine and Allergology. The French COVID Cohort study group was sponsored by INSERM and supported by the REACTing consortium and by a grant from the French Ministry of Health (Grant PHRC 20-0424). The Cov-Contact Cohort was supported by the REACTing consortium, the French Ministry of Health, and the European Commission (Grant RECOVER WP 6). This work was also partly supported by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases and the National Institute of Dental and Craniofacial Research, NIH (Grants ZIA A0010270 to L.D.N. and ZIAA001265 to H.C.S.). This program is supported by the Agence Nationale de la Recherche (Grant ANR-10-LABX-69-01). K.K.’s group was supported by the Estonian Research Council, through Grants PRG117 and PRG377. R.H. was supported by an Al Jallia Foundation Seed Grant (Grant ALF20219), Dubai, United Arab Emirates, and a COVID-19 research grant (Grant CoV19-0307) from the University of Sharjah, United Arab Emirates. S.G.T. is supported by Investigator and Program Grants awarded by the National Health and Medical Research Council of Australia and a University of New South Wales COVID Rapid Response Initiative Grant. L.I. reports funding from Regioni Lombardia, Italy (project “Risposta immune in pazienti con COVID-19 e co-morbidità”). This research was partially supported by the Instituto de Saludos Carlos III Grant P171006060 cofinanced by the European Regional Development Fund (ERD/FEDER), C.R.G. and colleagues from the Canarian Health System Sequencing Hub were supported by the Instituto de Salud Carlos III (Grants COV20_0133 and COV20_0134), the Spanish Ministry for Science and Innovation (RTC-2017-44711-AEI/FEDER, European Union), Fundación DISA (Grants OA18/017 and OA20/024), and Cabildo Insular de Tenerife (Grants CIGEIU0002191440 and “Apuestas científicas del ITER para colaborar en la lucha contra la COVID-19”). T.H.M. was supported by grants from the Novo Nordisk Foundation (Grants NN2000C064890 and NN21CO067157). C.M.B. is supported by a Michael Smith Foundation for Health Research Health Professional-Investigator Award. P.O.H. and L. Hammarsröm were funded by the European Union’s Horizon 2020 research and innovation program (Antibody Therapy Against Coronavirus consortium, Grant 101003650). Work at Y.-L.L.’s laboratory in the University of Hong Kong (HKU) was supported for the Society for the Relief of Disabled Children. MBSPhD study of D.L. in HKU was supported by the Croucher Foundation. J.L.F. was supported in part by the Evaluation-Orientación de la Coopéración Scientifique (ECOS) Nord - Coopération Scientifique France-Colombie (ECOS-Nord/Columbian administrative department of Science, Technology and Innovation [COLCIENCIASColumbian Ministry of National Education [MEN])Columbian Institute of Educational Credit and Technical Studies Abroad [ICETEX, Grant 806-2018] and Colciencias Contract 713-2016 [Code 1115744556333]). A. Kloczer was, in part, supported by Grants N2U05-05-00282 and NV18-05-00162 issued by the Czech Health Research Council and Ministry of Health, Czech Republic. L.P. was funded by Program Project COVID-19 OSR-UnSR and Ministero della Salute (Grant COVID-2020-12371617). I.M. is a Senior Clinical Investigator at the Research Foundation-Flanders and is supported by the CSL Behring Chair of Primary Immunodeficiencies (PID); by the Katholieke Universiteit Leuven C1 Grant C16/18/007; by a Flanders Institute for Biotechnology-Grand Challenges - PID grant; by the FWO Grants GOCS817N, GOBS5120N, and GOE8420N; and by the Jeffrey Modell Foundation. I.M. has received funding from the European Union’s Horizon 2020 research and innovation program (Grant Agreement 948959). E.A. received funding from the Hel- lenic Foundation for Research and Innovation (Grant INTERFLU 1574). M. Vidigal received funding from the São Paulo Research Foundation (Grant 2020/9702-1) and JBS SA (Grant 69004). The NH-COVAIR study group consortium was supported by a grant from the Meath Foundation.
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