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Supplementary Information for

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

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This PDF file includes:

Supplementary Information Text

Supplementary Materials and Methods

Autoantibodies neutralizing type-I IFN. Auto-Ab determinations were performed as described by Bastard *et al*.(1, 2). Auto-Ab titers were determined by ELISA (manual or automated). The blocking activity of anti-IFN-α2, anti-IFN-ω and anti-IFN-β auto-Abs was determined on the basis of 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 the *Renilla* luciferase for normalization (pRL-SV40). Cells were either left unstimulated or were stimulated with IFN-α2 and IFN-ω at a concentration of 10 ng/mL ('high' *i.e*. supraphysiological concentration) or 100 pg/mL ('low', *i.e.* more physiological concentration), or with IFN-β at a concentration of 10 ng/mL ('high concentration') for 16 hours at 37°C. We have already shown that auto-Abs neutralizing IFN-α2 are also able to neutralize most of the other 12 subtypes of IFN-α(1).

Relative risks of fatal COVID-19. We estimated the relative risk of death (RRD) in patients carrying auto-Abs neutralizing IFN-α2 and/or IFN-ω, or auto-Abs neutralizing IFN-β relative to patients without such auto-Abs, using large samples of patients who died from COVID-19 and of individuals from the general population. In this study design, in which controls are sampled from the baseline at-risk population regardless of disease status, odds ratios (ORs) provide an approximation for relative risks (RRs) in the absence of the assumption of a rare disease(3). All analyses were performed with Firth's bias-corrected logistic regression (4, 5). This method provides bias-reduction for small sample size, rare events, and yields finite and consistent estimates even in case of separation that may for example occur when a given combination of auto-Abs are observed in deceased patients and not in the general population for a given age class of a given gender. For each combination of auto-Abs, a Firth's logistic regression model, including auto-Ab status, sex and age in six classes (20-39, 40-49, 50-59, 60-69, 70-79, ≥80 years, Table S1), was fitted with the logistf package of R software (https://CRAN.R-project.org/package=logistf). For assessments of the effect of age and sex on the RRD due to auto-Abs, we added first order auto-Abs*sex and auto-Abs*age interaction terms to the Firth logistic regression model. For the auto-Abs*age interaction term, age was considered in either six (as defined above) or two (20-69 and ≥70 years) classes, and the model providing the best fit was selected based on the Akaïke information criterion for Firth's penalized partial likelihood (AICF). Nagashima and Sato used the AICF only in Cox regression models(6). We therefore adapted the AICF for use in logistic regression models by fixing the coefficients obtained with our Firth logistic regression models to a classic logistic regression framework with the fix.coef function implemented in R and extracting the resulting AICF (Table S2). *P* values were obtained in penalized likelihood-ratio tests.

We further investigated whether the risk of COVID-19 death was significantly higher for carriers of auto-Abs neutralizing high concentrations (10 ng/mL) of type I IFNs than for carriers of auto-Abs neutralizing low concentrations (100 pg/mL). For each combination of auto-Abs, we selected deceased individuals and individuals from the general population carrying auto-Abs neutralizing low concentrations of the given combination. In these subsamples of auto-Ab carriers, we tested for an association between auto-Abs neutralizing high concentrations of type I IFNs and death, by Firth's logistic regression, as described above. Analyses were systematically adjusted for age and sex and included an auto-Abs*age interaction term. Given the small sample size, we considered only two classes for age (20-69 and ≥70 years) (Fig. S2).

Simulation study. We assessed the validity of the RR approximation based on the OR obtained by Firth's logistic regression in our case-cohort design by simulation studies. We simulated a general population aged 20 to 100 years with equal number of individuals in the age classes 20-39, 40-49, 50-59, 60-69, 70-79, ≥80 years. We randomly assigned auto-Ab status to each individual with a probability equal to the estimated prevalence of auto-Abs for the corresponding age class in the general population. We used estimates of the prevalence of auto-Abs neutralizing low concentrations of IFN-α2 or IFN-ω, or of the prevalence of auto-Abs neutralizing low concentrations of IFN-α2 and IFN-ω (as provided in Table S6). We further infected the population and randomly assigned "deceased" status with a probability depending on auto-Abs status, age class, the age-

specific RRD for auto-Ab carriers, the age-specific prevalence of auto-Abs in the general population and the age-specific infection fatality rate (IFR) in the general population. For each specific age class, we defined:

$$P(Death/\text{ auto-Abs}) = RRD \times P(Death/\overline{auto\text{-}Abs}), \text{and}$$

$$P(Death/\overline{auto\text{-}Abs}) = \frac{IFR}{1 - P(auto\text{-}Abs) + RRD \times P(auto\text{-}Abs)}$$

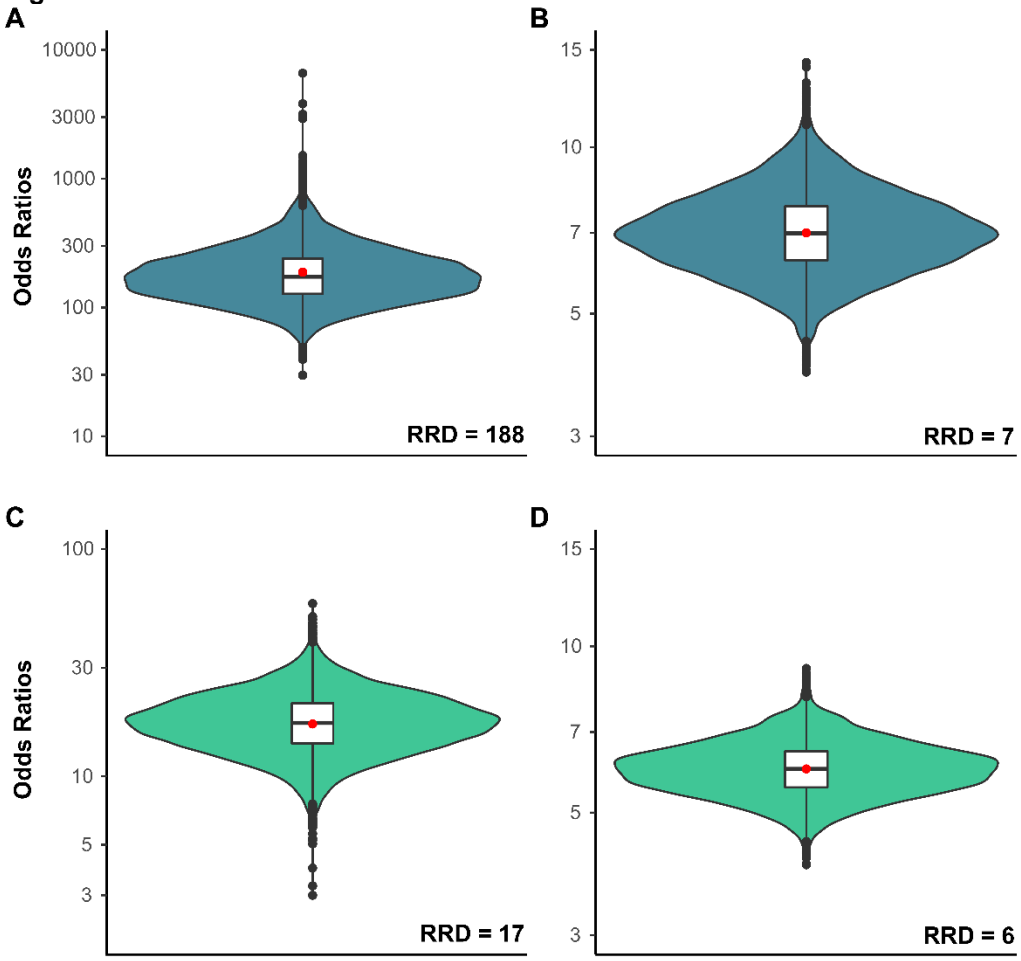
IFR and P(auto-Abs) were taken from Table S6, according to the age of the individual. RRDs for individuals <70 years and ≥70 years were taken from Table S3. We randomly sampled 1,200 deceased individuals. From an independent general population simulated with the same parameters, we randomly sampled 10,000 individuals (corresponding to a general population sampled before the pandemic). We performed Firth's logistic regression on the simulated samples of the 1,200 deceased individuals and the 10,000 individuals from the general population using the same covariates as described above. We generated a total of 10,000 replicates for each combination of auto-Abs. The results are presented in Fig. S1. They confirm that the OR estimated by the age-adjusted Firth's logistic regression model in our design is a valid estimator of the RRD.

IFR for carriers of neutralizing autoantibodies. We estimated the IFR for carriers of neutralizing auto-Abs (IFR_{AAB}) infected with SARS-CoV-2, using Bayes' theorem, as follows:

$$IFR_{AAB} = P(Death/auto\text{-}Abs) = \frac{P(Death) \times P(auto\text{-}Abs/Death)}{P(auto\text{-}Abs)}$$

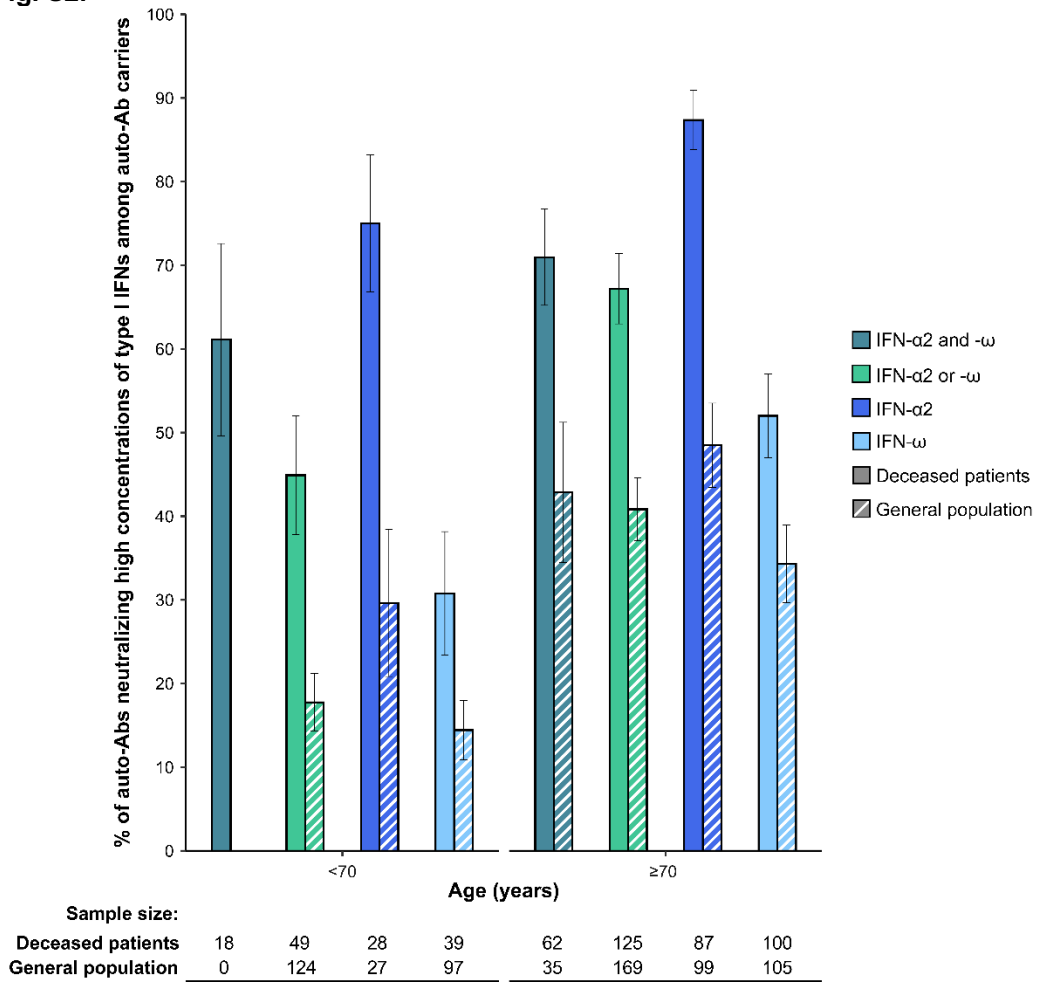
Where P(Death) is the general SARS-CoV-2 IFR as estimated by O'Driscoll *et al.*(7), P(auto-Abs/Death) is the prevalence of auto-Abs in deceased patients, and P(auto-Abs) is the prevalence of neutralizing auto-Abs in our general population sample. This later prevalence is a reasonable estimation of the prevalence of auto-Abs in infected individuals (regardless of their COVID-19 phenotypes) with respect to the reported prevalence of auto-Abs in asymptomatic and pauci-symptomatic SARS-CoV-2 infected subjects(1) which represents the large majority of infected individuals. IFR_{AAB} was then calculated for each auto-Ab combination and by age class. The IFR_{AAB} and P(auto-Abs) were estimated for the six age classes defined above, but P(auto-Abs/Death) was estimated for two age classes only (20-69 and ≥70 years) (Table S6, Table S7). Indeed, consistent with our RRD estimations for fatal COVID-19 in patients carrying auto-Abs *versus* non-carriers, the best-fit model for the effect of age on the prevalence of auto-Abs in deceased patients was obtained with the two age classes 20-69 and ≥70 years. The prevalence of neutralizing auto-Abs in the general population were estimated by Agresti-Coull adjustment, to avoid null values(8). The confidence intervals of the IFR_{AAB} were estimated by Monte-Carlo simulation. We estimated the empirical distribution of IFR_{AAB}, by randomly drawing values for IFR, P(auto-Abs/Death) and P(auto-Abs) based on their observed means and variances, assuming a normal distribution, and recomputing IFR_{AAB}. We simulated 10,000 replicates for which IFR_{AAB} (%) lay within the (0, 100] interval, and determined empirical 95% confidence intervals.

Fig. S1.



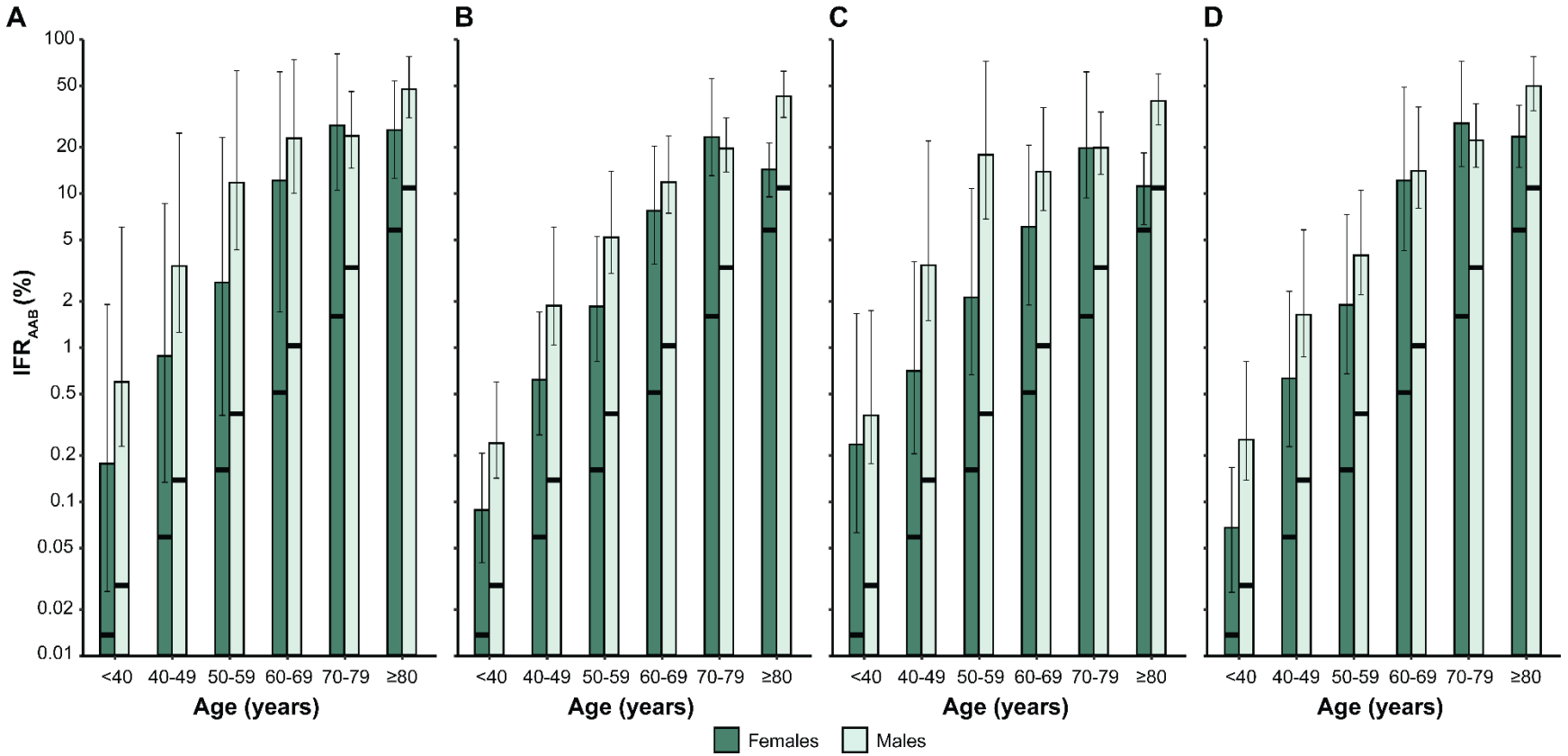
Violin plots of odds ratios obtained in the simulation study with the age-dependent prevalence of auto-Abs and RRD parameters, as estimated in our study. ORs were obtained by Firth's logistic regression analysis of 10,000 replicates of simulated deceased patients and individuals from the general population carrying auto-Abs neutralizing low concentrations of (1) IFN-α2 and IFN-ω with an RRD fixed at 188 in individuals <70 years of age (A), and with an RRD fixed at 7 in individuals ≥70 years of age (B), or (2) IFN-α2 or IFN-ω with an RRD fixed at 17 in individuals <70 years of age (C), and with an RRD fixed at 6 in individuals ≥70 years of age (D). Boxplots show the minimum and maximum simulated OR values, median, first and third quartiles on a logarithmic scale. The red dots represent the fixed RRD.

Fig. S2.



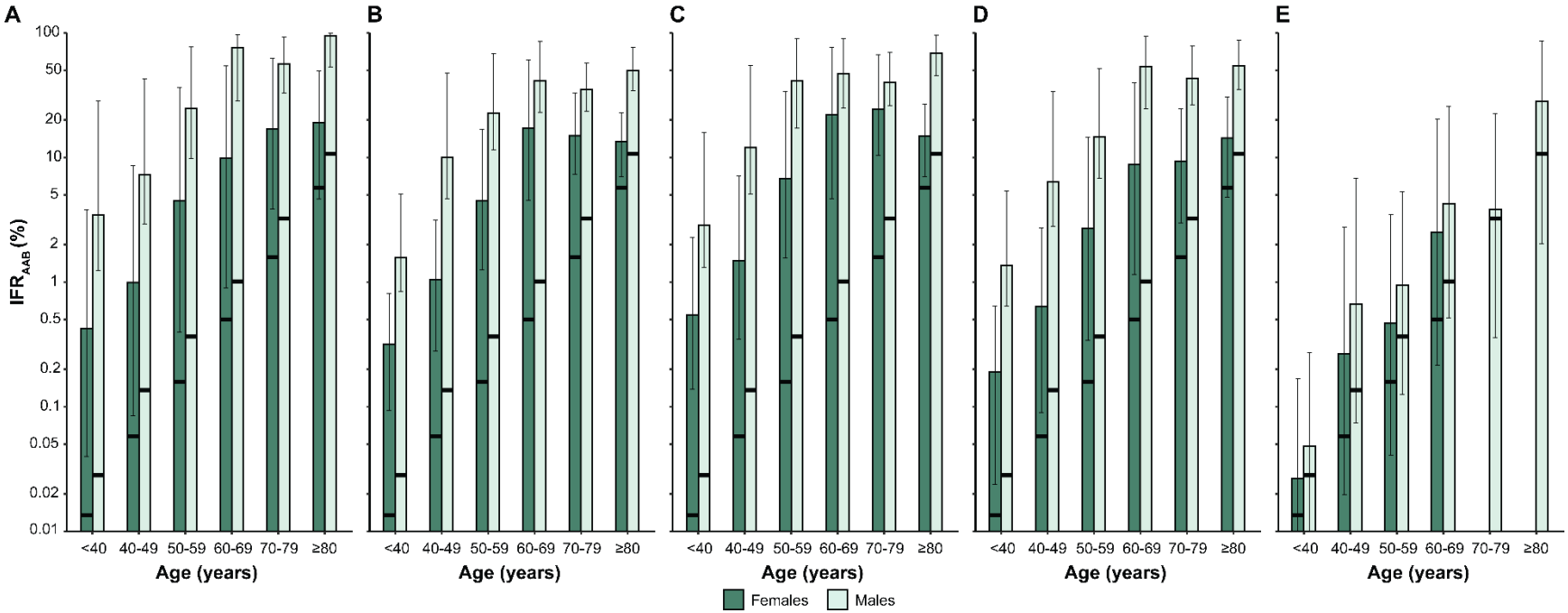
Percentage of carriers of various combinations of auto-Abs neutralizing high concentrations of type I IFNs among all carriers of the same combinations of auto-Abs, by age. The analysis was restricted to auto-Ab carriers among deceased patients (plain bars) and in the general population (hatched bars). Auto-Abs neutralizing high concentrations of type I IFNs also neutralize low concentrations of type I IFNs. By fitting Firth's logistic regression models, we confirmed that the risk of death was significantly higher for individuals carrying auto-Abs neutralizing high concentrations than for those carrying auto-Abs neutralizing only low concentrations of type I IFNs, with P values of 0.05, 2.4×10^{-8}, 7.7×10^{-7} and 5.5×10^{-5} for auto-Abs neutralizing IFN-α and -ω, IFN-α or -ω, IFN-α, and IFN-ω, respectively.

Fig. S3.



SARS-CoV-2 infection fatality rates for carriers of various combinations of auto-Abs (IFR$_{AAB}$) neutralizing low IFN concentrations, by age and sex. IFR$_{AAB}$ are displayed, by age and sex, for individuals with auto Abs neutralizing low concentrations of (A) IFN α2 and IFN ω, (B) IFN α2 or IFN ω, (C) IFN α2, and (D) IFN ω. Vertical bars represent the 95% CI. Horizontal black lines represent the IFR reported by O'Driscoll et al. (7)

Fig. S4.



SARS-CoV-2 infection fatality rates for carriers of various combinations of auto-Abs (IFR$_{AAB}$) neutralizing high IFN concentrations, by age and sex. IFR$_{AAB}$ are displayed, by age and sex, for individuals with auto Abs neutralizing high concentrations of (A) IFN α2 and IFN ω, (B) IFN α2 or IFN ω, (C) IFN α2, (D) IFN ω and (E) IFN-β. Vertical bars represent the 95% CI. Horizontal black lines represent the IFR reported by O'Driscoll et al. (7) No woman over the age of 70 years carrying auto-Abs neutralizing IFN-β was identified among the patients who had died from COVID-19.

Table S1. Best fitting model for multivariate analysis according to various combinations of auto-Abs neutralizing low concentrations of type I IFNs

Covariate		IFN-α2 and IFN-ω			IFN-α2 or IFN-ω			IFN-α2			IFN-ω		
		β (SE)	RRD	*P* value	β (SE)	RRD	*P* value	β (SE)	RRD	*P* value	β (SE)	RRD	*P* value
Sex	**Female *vs.* Male**	-0.90 (0.07)	0.41	$<10^{-16}$	-0.93 (0.07)	0.40	$<10^{-16}$	-0.92 (0.07)	0.40	$<10^{-16}$	-0.92 (0.07)	0.40	$<10^{-16}$
Age (years)	**20-39 years**	ref	ref	-	ref	ref	-	ref	ref	-	ref	ref	-
	40-49 years	0.82 (0.30)	2.27	0.0041	0.83 (0.29)	2.29	0.0029	0.77 (0.29)	2.17	0.0056	0.84 (0.29)	2.31	0.0027
	50-59 years	1.82 (0.27)	6.16	10^{-16}	1.84 (0.26)	6.28	$<10^{-16}$	1.79 (0.26)	6.02	10^{-16}	1.82 (0.26)	6.19	$<10^{-16}$
	60-69 years	2.21 (0.26)	9.15	$<10^{-16}$	2.21 (0.25)	9.09	$<10^{-16}$	2.14 (0.25)	8.52	$<10^{-16}$	2.24 (0.25)	9.36	$<10^{-16}$
	70-79 years	2.51 (0.26)	12.27	$<10^{-16}$	2.54 (0.26)	12.70	$<10^{-16}$	2.48 (0.24)	11.98	$<10^{-16}$	2.53 (0.26)	12.50	$<10^{-16}$
	≥80 years	2.32 (0.26)	10.22	$<10^{-16}$	2.30 (0.26)	9.97	$<10^{-16}$	2.27 (0.25)	9.72	$<10^{-16}$	2.31 (0.26)	10.10	$<10^{-16}$
auto-Abs	**yes *vs.* no**	5.25 (0.71)	189.68[a]	$<10^{-16}$	2.82 (0.19)	16.71[a]	$<10^{-16}$	3.32 (0.27)	27.78[a]	$<10^{-16}$	2.92 (0.22)	18.57[a]	$<10^{-16}$
auto-Abs*Age[a]	**≥70 *vs.* <70**	-3.30 (0.73)	7.03[b]	8×10^{-10}	-1.05 (0.23)	5.85[b]	4×10^{-6}	-1.72 (0.31)	4.96[b]	6×10^{-9}	-0.92 (0.27)	7.41[b]	0.0005

Age-stratified analysis using Firth's logistic regression model integrating sex and auto-Abs*Age (<70 and ≥70 years) as covariates.

β, Relative risks of COVID-19 death (RRD) and *P* values for each covariate are displayed. Male sex, and <40 years age-class were used as reference.

NA: not applicable; SE: standard error, ref: reference.

[a]RRD for <70y.o. individuals displaying auto-Abs neutralizing IFN relative to those who do not as reference, computed as $\exp(\beta_{auto\text{-}Abs})$.

[b]RRD for individuals ≥70 y.o. individuals displaying auto-Abs neutralizing IFN relative to those who do not as reference, the interaction term 'auto-Abs*Age' was calculated as follows: $\exp(\beta_{auto\text{-}Abs} + \beta_{auto\text{-}Abs*Age})$.

Table S2. Model selection for the age effect of type I IFN auto-Abs on RRD based on the Aikake Information Criterion for Firth's penalized partial likelihood (AICF)

Neutralized IFN	Dose	AICF.6[a]	AICF.2[b]
IFN-α2 and -ω	100 pg/mL	680.92	**676.69**
IFN-α2 or -ω		1063.74	**1060.59**
IFN-α2		844.08	**840.37**
IFN-ω		939.02	**934.72**
IFN-α2 and -ω	10 ng/mL	533.82	**533.10**
IFN-α2 or -ω		796.76	**791.93**
IFN-α2		747.42	**742.17**
IFN-ω		595.11	**595.65**
IFN-β		69.91	**71.71**

The age effect of type I IFN auto-Abs on RRD was estimated through the interaction term auto-Abs*age with age considered in two (Age.2) or six (Age.6) classes.

Age.2 corresponds to [20, 70) and ≥70 years old classes; Age.6 corresponds to 20-39, 40-49, 50-59, 60-69, 70-79, ≥80 years old classes.

The best fitting models were selected according to the smallest AICF values, and are shown in bold. When ΔAICF < 2, we chose the most parsimonious model, thus displaying the smaller number of parameters (i.e. with 2 age classes only), as usually done.

[a]AICF obtained using the following logistic model: Death ~ auto-Abs status + Sex + Age.6 + auto-Abs*Age.6.

[b]AICF obtained using the following logistic model: Death ~ auto-Abs status + Sex + Age.6 + auto-Abs*Age.2.

Table S3. Relative risks of COVID-19 death (RRDs) associated with auto-Abs neutralizing low concentrations of various combinations of type I IFNs, by age

IFN neutralized	Age class	*P* value	RRD	RRD lower limit of 95% CI	RRD upper limit of 95% CI	P(auto-Abs/Death)[a] (%)	PAF[b] (%)
IFN-α2 and -ω	20-69 years	$<10^{-16}$	188.32	45.79	774.41	6.46	6.42
	≥70 years	$<10^{-16}$	7.20	5.04	10.30	11.31	9.74
IFN-α2 or -ω	20-69 years	$<10^{-16}$	17.01	11.69	24.75	15.26	14.37
	≥70 years	$<10^{-16}$	5.76	4.47	7.44	20.49	16.94
IFN-α2	20-69 years	$<10^{-16}$	28.66	16.78	48.96	10.18	9.82
	≥70 years	$<10^{-16}$	4.98	3.72	6.68	14.43	11.53
IFN-ω	20-69 years	$<10^{-16}$	18.62	11.97	28.98	11.55	10.93
	≥70 years	$<10^{-16}$	7.34	5.50	9.79	17.38	15.01

Age-stratified analysis with Firth's logistic regression model integrating sex and age classes (20-39, 40-49, 50-59, 60-69 for patients <70 years old; and 70-79 and ≥80 for patients ≥70 years old) as covariates. RRDs are displayed for individuals under and over 70 years of age.
95% CI: 95% confidence interval.
[a]Prevalence of auto-Abs among patients dying from COVID-19
[b]Population attributable fraction, i.e. quantification of the proportion of deaths attributable to auto-Abs against type I IFNs, approximated by P(auto-Abs/Death) * (1-1/RRD), as described by von Cube et al. (7). The higher the RRD, the closer the PAF to the prevalence of auto-Abs in deceased individuals.

Table S4. Best fitting model for multivariate analysis according to various combinations of auto-Abs neutralizing high concentrations of type I IFNs

Covariate		IFN-α2 and IFN-ω			IFN-α2 or IFN-ω			IFN-α2			IFN-ω			IFN-β		
		β (SE)	RRD	*P* value	β (SE)	RRD	*P* value	β (SE)	RRD	*P* value	β (SE)	RRD	*P* value	β (SE)	RRD	*P* value
Sex	**Female *vs* Male**	-0.84 (0.07)	0.43	$<10^{-16}$	-0.86 (0.07)	0.42	$<10^{-16}$	-0.86 (0.07)	0.42	$<10^{-16}$	-0.85 (0.07)	0.43	$<10^{-16}$	-1.07 (0.12)	0.34	$<10^{-16}$
Age (years)	**20-39 years**	ref	ref	-	ref	ref	-	ref	ref	-	ref	ref	-	ref	ref	-
	40-49 years	1.60 (0.29)	4.98	2×10^{-9}	1.63 (0.29)	5.10	10^{-9}	1.61 (0.30)	5.00	2×10^{-9}	1.62 (0.29)	5.07	10^{-9}	0.53 (0.49)	1.70	0.27
	50-59 years	2.55 (0.27)	12.84	$<10^{-16}$	2.60 (0.27)	13.43	$<10^{-16}$	2.59 (0.27)	13.27	$<10^{-16}$	2.57 (0.27)	13.12	$<10^{-16}$	2.06 (0.41)	7.87	6×10^{-11}
	60-69 years	3.09 (0.26)	22.08	$<10^{-16}$	3.12 (0.26)	22.56	$<10^{-16}$	3.10 (0.26)	22.14	$<10^{-16}$	3.12 (0.26)	22.66	$<10^{-16}$	2.56 (0.40)	12.88	$<10^{-16}$
	70-79 years	3.74 (0.26)	41.93	$<10^{-16}$	3.79 (0.26)	44.47	$<10^{-16}$	3.77 (0.26)	43.45	$<10^{-16}$	3.77 (0.26)	43.38	$<10^{-16}$	3.07 (0.40)	21.56	$<10^{-16}$
	≥80 years	4.11 (0.25)	60.80	$<10^{-16}$	4.12 (0.26)	61.44	$<10^{-16}$	4.10 (0.26)	60.55	$<10^{-16}$	4.13 (0.26)	62.00	$<10^{-16}$	NA	NA	NA
auto-Abs	**yes vs no**	5.05 (0.50)	156.99[a]	$<10^{-16}$	4.11 (0.24)	60.80[a]	$<10^{-16}$	4.63 (0.31)	102.79[a]	$<10^{-16}$	3.96 (0.30)	52.70[a]	$<10^{-16}$	1.93 (0.59)	6.91[a]	0.004
auto-Abs*Age[a]	**<70 vs ≥70**	-2.51 (0.55)	12.68[b]	2×10^{-7}	-2.19 (0.29)	6.81[b]	10^{-14}	-2.48 (0.35)	8.62[b]	5×10^{-14}	-1.94 (0.35)	7.61[b]	4×10^{-8}	-0.84 (1.00)	2.97[b]	0.37

Age-stratified analysis using Firth's logistic regression model integrating sex and auto-Abs*Age (<70 and ≥70 years) as covariates.
β, Relative risks of COVID-19 death (RRD) and P values for each covariate are displayed. Male sex, and <40 years age-classes were used as reference.
NA: not applicable; SE: standard error, ref: reference.
[a]RRD for <70y.o. individuals displaying auto-Abs neutralizing IFN relative to those who do not as reference, computed as $\exp(\beta_{\text{auto-Abs}})$.
[b]RRD for individuals ≥70 y.o. individuals displaying auto-Abs neutralizing IFN relative to those who do not as reference, the interaction term 'auto-Abs*Age' was calculated as follows: $\exp(\beta_{\text{auto-Abs}} + \beta_{\text{auto-Abs*Age}})$.

Table S5. Relative risks of COVID-19 death (RRDs) associated with auto-Abs neutralizing high concentrations of various combinations of type I IFNs, by age

IFN neutralized	Age class	*P* value	RRD	RRD lower limit of 95% CI	RRD upper limit of 95% CI	P(auto-Abs/Death)[a] (%)	PAF[b] (%)
IFN-α2 and -ω	20-69 years	$<10^{-16}$	156.47	57.82	423.37	4.97	4.94
	≥70 years	$<10^{-16}$	12.93	8.39	19.94	8.46	7.81
IFN-α2 or -ω	20-69 years	$<10^{-16}$	62.36	38.37	101.35	9.74	9.59
	≥70 years	$<10^{-16}$	6.83	5.08	9.17	13.71	11.70
IFN-α2	20-69 years	$<10^{-16}$	105.10	57.18	193.20	8.75	8.66
	≥70 years	$<10^{-16}$	8.64	6.26	11.92	12.52	11.07
IFN-ω	20-69 years	$<10^{-16}$	53.58	29.37	97.74	5.96	5.85
	≥70 years	$<10^{-16}$	7.72	5.39	11.04	9.64	8.39
IFN-β	20-69 years	0.004	6.98	2.18	22.36	1.62	1.39
	≥70 years	0.229	2.67	0.56	12.81	0.51	0.32

Age-stratified analysis with Firth's logistic regression model integrating sex and age classes (20-39, 40-49, 50-59, 60-69 for patients <70 years old; and 70-79 and ≥80 for patients ≥70 years old) as covariates. RRDs are displayed for individuals under and over 70 years of age.
95% CI: 95% confidence interval.
[a]Prevalence of auto-Abs in patients dying from COVID-19.
[b]Population attributable fraction, i.e. quantification of the proportion of deaths attributable to auto-Abs against type I IFNs, approximated by P(auto-Abs/Death) * (1-1/RRD), as described by von Cube et al. (7). The higher the RRD, the closer the PAF to the prevalence of auto-Abs in deceased individuals.

Table S6. ***SARS-CoV-2 infection fatality rates for individuals with auto-Abs (IFR_{AAB}) neutralizing low concentration of type I IFNs.***

IFN neutralized	Age group	IFR_{AAB}[a] (%)	IFR_{AAB} lower limit of 95% CI	IFR_{AAB} upper limit of 95% CI	IFR[b] (%)	P(auto-Abs)[c] (%)	P(auto-Abs/Death)[d] (%)
IFN-α2 and IFN-ω	20-39 years	0.84	0.31	8.28	0.02	0.16	6.46
	40-49 years	4.63	1.71	34.71	0.10	0.14	6.46
	50-59 years	14.89	5.55	67.61	0.27	0.11	6.46
	60-69 years	30.64	13.31	83.29	0.77	0.16	6.46
	70-79 years	26.04	16.49	48.01	2.44	1.06	11.31
	≥80 years	40.47	27.82	61.20	8.29	2.32	11.31
IFN-α2 or IFN-ω	20-39 years	0.17	0.12	0.31	0.02	1.83	15.26
	40-49 years	1.37	0.86	2.77	0.10	1.09	15.26
	50-59 years	3.91	2.49	7.53	0.27	1.03	15.26
	60-69 years	11.14	7.36	19.07	0.77	1.05	15.26
	70-79 years	20.85	15.04	31.46	2.44	2.40	20.49
	≥80 years	26.66	20.28	35.20	8.29	6.37	20.49
IFN-α2	20-39 years	0.44	0.23	1.88	0.02	0.48	10.18
	40-49 years	2.43	1.24	9.95	0.10	0.41	10.18
	50-59 years	9.38	4.59	38.49	0.27	0.29	10.18
	60-69 years	12.07	7.28	24.73	0.77	0.65	10.18
	70-79 years	20.36	13.98	33.26	2.44	1.73	14.43
	≥80 years	25.02	18.23	34.25	8.29	4.78	14.43
IFN-ω	20-39 years	0.16	0.10	0.31	0.02	1.51	11.55
	40-49 years	1.38	0.80	3.24	0.10	0.82	11.55
	50-59 years	3.55	2.15	7.46	0.27	0.86	11.55
	60-69 years	15.65	9.41	33.23	0.77	0.56	11.55
	70-79 years	24.52	17.03	39.35	2.44	1.73	17.38
	≥80 years	36.84	27.17	50.46	8.29	3.91	17.38

[a]COVID-19 fatality rate for individuals with auto-Abs.
[b]IFR provided by O'Driscoll *et al.*(7)
[c]Prevalence of auto-Abs in the general population.
[d]Prevalence of auto-Abs in patients dying from COVID-19.
95% CI: 95% confidence interval.

Table S7. SARS-CoV-2 infection fatality rates for individuals with auto-Abs (IFR_{AAB}) neutralizing high concentration of type I IFNs.

IFN neutralized	Age group	IFR_{AAB}[a] (%)	IFR_{AAB} lower limit of 95% CI	IFR_{AAB} upper limit of 95% CI	IFR[b] (%)	P(auto-Abs)[c] (%)	P(auto-Abs/Death)[d] (%)
IFN-α2 and IFN-ω	20-39 years	3.13	1.26	20.82	0.02	0.03	4.97
	40-49 years	6.58	2.83	33.71	0.10	0.07	4.97
	50-59 years	28.18	11.12	80.90	0.27	0.05	4.97
	60-69 years	65.49	26.37	96.22	0.77	0.06	4.97
	70-79 years	48.03	28.40	86.69	2.44	0.43	8.46
	≥80 years	68.65	42.52	95.81	8.29	1.02	8.46
IFN-α2 or IFN-ω	20-39 years	0.92	0.57	1.74	0.02	0.22	9.74
	40-49 years	4.30	2.49	10.02	0.10	0.22	9.74
	50-59 years	15.06	8.52	37.28	0.27	0.17	9.74
	60-69 years	36.67	21.54	74.41	0.77	0.20	9.74
	70-79 years	28.29	19.99	42.69	2.44	1.18	13.71
	≥80 years	32.64	23.56	45.17	8.29	3.48	13.71
IFN-α2	20-39 years	1.84	1.01	5.43	0.02	0.10	8.75
	40-49 years	6.62	3.41	21.70	0.10	0.13	8.75
	50-59 years	29.76	14.14	79.91	0.27	0.08	8.75
	60-69 years	46.10	25.20	87.94	0.77	0.15	8.75
	70-79 years	36.69	24.81	60.02	2.44	0.83	12.52
	≥80 years	40.94	28.85	58.60	8.29	2.54	12.52
IFN-ω	20-39 years	0.80	0.44	1.84	0.02	0.15	5.96
	40-49 years	3.51	1.79	10.05	0.10	0.17	5.96
	50-59 years	11.27	5.85	32.27	0.27	0.14	5.96
	60-69 years	39.29	19.76	84.43	0.77	0.12	5.96
	70-79 years	30.21	19.59	50.32	2.44	0.78	9.64
	≥80 years	40.63	27.03	61.55	8.29	1.97	9.64
IFN-β	20-39 years	0.04	0.01	0.16	0.02	0.77	1.62
	40-49 years	0.72	0.10	5.71	0.10	0.22	1.62
	50-59 years	0.86	0.15	3.21	0.27	0.50	1.62
	60-69 years	4.43	0.66	20.25	0.77	0.28	1.62
	70-79 years	2.21	0.22	9.32	2.44	0.57	0.51
	≥80 years	31.04	2.37	88.06	8.29	0.14	0.51

[a]COVID-19 fatality rate for individuals with auto-Abs

[b]IFR provided by O'Driscoll *et al*. (7)

[c]Prevalence of auto-Abs in the general population

[d]Prevalence of auto-Abs in patients dying from COVID-19.

95% CI: 95% confidence interval.

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