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Title: Age-dependent impact of the major common genetic risk factor for COVID-19 on severity and mortality

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3

Abstract

Background: There is considerable variability in COVID-19 outcomes amongst younger adults—and some of this variation may be due to genetic predisposition. We characterized the clinical implications of the major genetic risk factor for COVID-19 severity, and its age-dependent effect, using individual-level data in a large international multi-centre consortium.

Method: The major common COVID-19 genetic risk factor is a chromosome 3 locus, tagged by the marker rs10490770. We combined individual level data for 13,424 COVID-19 positive patients (N=6,689 hospitalized) from 17 cohorts in nine countries to assess the association of this genetic marker with mortality, COVID-19-related complications and laboratory values. We next examined if the magnitude of these associations varied by age and were independent from known clinical COVID-19 risk factors.

Findings: We found that rs10490770 risk allele carriers experienced an increased risk of all-cause mortality (hazard ratio [HR] 1·4, 95% confidence interval [CI] 1·2–1·6) and COVID-19 related mortality (HR 1·5, 95%CI 1·3–1·8). Risk allele carriers had increased odds of several COVID-19 complications: severe respiratory failure (odds ratio [OR] 2·0, 95%CI 1·6-2·6), venous thromboembolism (OR 1·7, 95%CI 1·2-2·4), and hepatic injury (OR 1·6, 95%CI 1·2-2·0). Risk allele carriers ≤ 60 years had higher odds of death or severe respiratory failure (OR 2·6, 95%CI 1·8-3·9) compared to those > 60 years OR 1·5 (95%CI 1·3-1·9, interaction p-value=0·04). Amongst individuals ≤ 60 years who died or experienced severe respiratory COVID-19 outcome, we found that 31·8% (95%CI 27·6-36·2) were risk variant carriers, compared to 13·9% (95%CI 12·6-15·2%) of those not experiencing these outcomes. Prediction of death or severe respiratory failure among those ≤ 60 years improved when including the risk allele (AUC 0·82 vs 0·84, p=0·016) and the prediction ability of rs10490770 risk allele was similar to, or better than, most established clinical risk factors.

Interpretation: The major common COVID-19 risk locus on chromosome 3 is associated with increased risks of morbidity and mortality—and these are more pronounced amongst individuals ≤ 60 years. The effect on COVID-19 severity was similar to, or larger than most established risk factors, suggesting potential implications for clinical risk management.

Funding: Funding was obtained by each of the participating cohorts individually.

4

Introduction

The COVID-19 pandemic has led to the death of millions of individuals and the largest economic contraction since the Great Depression[1]. The clinical outcomes of COVID-19 are remarkably variable, such that some individuals remain asymptomatic[2], while others develop severe COVID-19 with systemic inflammation, respiratory failure or death. This variability in outcome creates difficulties in clinical management when estimating who is at risk of severe disease and may develop a need for intensive care. Furthermore, recent guidelines suggest risk stratification should be considered when deciding upon prophylactic treatment algorithm and priority for vaccination[3].

Some of this variation in COVID-19 behavior has been attributed to risk factors such as age[4], sex[4], comorbidities[5], socioeconomic factors[6] and genetic variants in the SARS-CoV-2 genome.[7] While the main risk factor for severe outcomes is age, which increases exponentially after age 60[5], some younger individuals experience severe COVID-19 outcomes and death. The early onset of several common diseases such as breast cancers and myocardial infarction, is disproportionally influenced by human genetic factors[8–10] and this may also be the case for COVID-19. Several studies have identified and replicated a major genetic risk locus for severe COVID-19[11–13] in the human genome. This genetic risk locus harbors a cluster of genes on chromosome 3, in which the true causal variant is still unknown. The single nucleotide polymorphism (SNP) rs10490770 serves as a marker for this genetic risk (as well as other SNPs

5

in linkage disequilibrium[14]) and approximately 15% of individuals of European ancestry carry the

C risk allele[15]. However, the clinical relevance of this locus, and its potential age-dependent

impact, is unknown.

We therefore assembled individual-level COVID-19 clinical and human genomic data in a large

international consortium of 17 cohorts in nine countries (Belgium, Brazil, Canada, Germany, Italy,

Norway, Spain, Sweden, and UK) to assess the relationship between the chromosome 3 genetic

risk with COVID-19 severity, complications and mortality. We next tested the age-dependent

effects of this locus on COVID-19 outcomes. Last, in order to assess the relative importance of

this locus, we compared its ability to predict COVID-19 outcomes to that of other established

clinical risk factors.

Methods

Study participants

We gathered clinical and genomic data from 13,424 COVID-19 cases (6,689 of whom were

hospitalized) with genetic information available, harmonizing individual-level data from 17 studies.

COVID-19 cases were defined as individuals having at least one confirmed SARS-CoV-2 viral

nucleic acid amplification test from relevant biologic fluids, or whose SARS-CoV-2 status was

confirmed by ICD-10 codes, using codes U071 and/or U072. We combined data from

6

hospital-based studies which recruited participants after COVID-19 outbreak, and a

population-based biobank in which recruitment was not dependent upon COVID-19 status.

Detailed information for each individual study is described in the online supplement.

Statistical analysis

In order to tag the chromosome 3 locus, we selected the SNP rs10490770, which was most

significantly associated with hospitalization in the COVID-19 genome-wide association study

(GWAS) from the COVID-19 Host Genetics Initiative, since this is the largest genome-wide

association study meta-analysis of COVID-19 severity[13] (cases / controls = 12,888 /

1,295,966). Each participating study performed genotyping and imputation separately

following a recommended quality control pipeline[16]. Detailed methods describing genotyping

and imputation are available in the online supplement. Ancestry was inferred by performing

projection onto the principal component analysis (PCA) space from the 1000G[17] Phase 3

population using HapMap3 SNPs[18] with minor allele frequency > 1% (detailed methods are in

the online supplement) (Supplementary Table 1, Supplementary Figure 1). To test the

association between rs10490770 and all phenotypes above, we applied a dominant model by

grouping participants into two groups according to their genotype at rs10490770 – C is the

allele associated with COVID-19 severity; those with TC genotype or CC genotype were

labeled as carriers and those with TT genotype were labeled as non-carriers. We chose this

model because it had the lowest Akaike Information Criterion (AIC), compared to additive and

recessive models (see the online supplement for detail, Supplementary Table 2), in a logistic

regression for death or severe respiratory failure outcome (defined below). All analyses were

performed separately for each ancestry group. Because the sample size in non-Europeans

was limited, we reported the results from European descent as main analyses, but also

reported the results from non-European ancestry individuals are in the supplement. All

analyses were based on mixed-effects model adjusted for age, sex and the first five genetic

principal components (PCs) as fixed effects and study groups were also included as random

effects to account for the study variability. Five study groups, mostly reflecting the country of

origin of the study, were created by combining small participating studies with few cases and

controls to reduce the risk of collinearity (detail is described in the online supplement). We

further estimated the frequency of rs10490770 risk allele carrier status from the population

frequencies reported in external database (the Genome Aggregation Database v 3·1

[gnomAD[15]]), assuming this variant follows Hardy-Weinberg equilibrium.

Association with mortality

The hazard ratio (HR) for all-cause mortality was estimated by Cox proportional hazard models

using the "coxme v2·2-16" R package. Individuals entered the follow-up when diagnosed with

COVID-19 or if a diagnosis date was missing, the date when they were hospitalized or when

8

their symptoms started. They were considered as an event at the date of death and censored

at the last date of follow-up (details are described in the online supplement). We additionally

performed competing risk analyses to estimate the sub-distribution hazard ratio for COVID-19

related mortality using the "cmprsk v2·2-10" R package, which accounts for the competing risk

of non-COVID-19 related death: i.e. individuals who did not die of COVID-19 but died due to

other causes (e.g. cancer). In the competing risk model, study groups were considered as

fixed effects. Survival analyses were restricted to study participants with available follow-up

and cause of death information (N=9,248). Cause of death was defined by doctor-diagnoses,

medical chart reviews or ICD-10 codes (details are described in the online supplement).

Association with COVID-19 severity and complications

To understand the clinical implications of the chromosome 3 locus, we fit mixed-effects

regression models to assess the association of rs10490770 risk allele [C] carrier status with

three types of COVID-19 outcomes: COVID-19 severity, COVID-19 complications and

laboratory values. To do so, we defined three COVID-19 severity outcomes, with appropriate

control definitions amongst SARS-CoV-2 positive individuals. 1) hospitalization; 2) intensive

care unit (ICU) admission and 3) death or severe respiratory failure. Hospitalization cases

were COVID-19 cases admitted to the hospital, whereas controls were individuals who did not

experience hospitalization. ICU cases were those COVID-19 cases admitted to the ICU and

controls were individuals who did not experience hospitalization. To assess potential selection

bias, we also repeated the analyses using only individuals who were hospitalized. In these

analyses, controls were defined as those who were hospitalized, but not admitted to the ICU.

Death or severe respiratory failure cases were defined as individuals who died or required

respiratory support (intubation, continuous positive airway pressure, Bilevel Positive Airway

Pressure, or continuous external negative pressure, Optiflow/high flow Positive End Expiratory

Pressure Oxygen), had ICD-10 codes for acute respiratory distress syndrome (ARDS) or acute

respiratory failure ("J80", "J9600","J9609","Z991"), or OPCS codes of the use of ventilator

("E851","E852"). Controls for the death or severe respiratory failure cases were defined as

those requiring no oxygen therapy and who were alive.

We next defined five COVID-19 related complications, which were diagnosed at hospital.

These included: 1) Severe respiratory failure**,** which was defined by the use of respiratory

support or individuals with administrative codes for ARDS, respiratory failure or ventilatory

support as described above; 2) Hepatic injury was defined as individuals with at least one of

the following: doctor-diagnosed hepatic complications, highest alanine aminotransferase > 3

times upper limit of normal (ULN), or ICD-10 codes for acute hepatic failure ("K720"); 3)

Cardiovascular complications were defined by at least one of the following: doctor-diagnosed

acute myocardial infarction (AMI) or stroke, highest troponin T or troponin I > ULN, or ICD-10

codes for AMI or stroke ("I21*","I61", "I62", "I63", "I64", "I65" ,"I66*").; 4) Kidney injury was

defined by at least one of the following: doctor-diagnosed acute kidney injury (AKI), highest

creatinine > 1·5 times ULN, or ICD-10 codes for AKI ("N17*"); 5) Venous thromboembolism

(VTE) was defined by at least one of the following: doctor-diagnosed pulmonary embolism

(PE) or deep venous thrombosis (DVT), or ICD-10 codes for PE or DVT ("I26*" ,"I81", "I82*").

Controls for severe respiratory failure were defined as those requiring no oxygen therapy and

who were alive, whereas controls for other complications were defined as those who did not

meet the corresponding case criteria and were alive.

Last we considered the laboratory values of complete blood count and biochemistry tests

available at hospital (Supplementary Table 3). To test the association with the chromosome 3

locus we used the highest or lowest value recorded per individual[19–23]. We selected the lowest

value for lymphocyte counts and otherwise highest value. This is because we were interested

in using these laboratory values as a proxy of COVID-19 severity. Definitions and quality

control of laboratory values and specific codes are described in the online supplement

(Supplementary Figure 2).

Age-dependent associations with COVID-19 severity

We evaluated the age-dependent effects of the risk allele carrier status on COVID-19 three

severity phenotypes by performing two sets of analyses: 1) linear regressions between age at

11

diagnosis and risk allele carrier status amongst severe cases, adjusting for the same

covariates as the main analyses, and 2) adding a carrier status by age interaction term in the

main regression models. Age was not dichotomized in these analyses. We also stratified

participants by age ≤60 or >60 years and repeated the same logistic regressions, as well as we

estimated the frequency of the risk allele carriers in the two age groups. We used 60 years as

a cut-point for age-stratified analyses, because COVID-19 case fatality rates increased

markedly after this age[24,25].

Associations with COVID-19 severity stratified by established clinical risk factors

In order to compare the association of rs10490770 risk allele carrier status with other risk

factors, we similarly stratified participants by BMI ≥30 kg/m^2 (a definition of obesity[26]), smoking

(ever-smoker vs never-smoker), cancer, chronic kidney disease, chronic obstructive

pulmonary disease (COPD), chronic heart failure, transplantation, and diabetes mellitus (DM),

all of which were curated as established clinical risk factors for severe illness of COVID-19

according to the Centre for Disease Control website[26]. All of the eight risk factors were defined

by doctor-diagnoses, medical chart reviews or ICD-10 codes (details are described in the

online supplement). We then tested the difference of the magnitude of the associations of the

risk allele carrier status compared to the eight clinical risk factors. Clinical risk factors stratified

analysis and prediction assessment (described below) were restricted to individuals with

12

complete information for demographics, clinical risk factors and rs10490770 genotype

information (N=7,919). The majority of this subset were from UK Biobank (N=7,461), and only

50 individuals were included from the first discovery GWAS[11].

Risk prediction compared to established clinical risk factors

To better understand the prediction improvement by adding of the chromosome 3 genetic risk

in addition to the eight clinical risk factors, we performed multivariate regressions in individuals

with complete information as described above (N=7,919). We evaluated whether the

rs10490770 risk allele improved the risk prediction discrimination for severe COVID-19

outcomes by calculating the area under receiver operation curve (AUC) and the continuous net

reclassification improvement (NRI) using "pROC v1·16·2" and "PredictABEL v1·2-4" R

packages.

Meta-analyses

As secondary analyses, we meta-analyzed the results with non-European ancestries and two

external cohorts for which we did not have access to individual-level data; FinnGen and

Columbia University COVID-19 Biobank (CUB). This resulted in a total study population of

14,620 individuals with COVID-19. An inverse-variance weighted meta-analyses were

performed under a fixed effect and random effects models using the "meta v4·16-1" R package

13

when the appropriate phenotypes were available and case counts, control counts, and the

rs10490770 risk allele carrier counts were larger than ten in each cohort.

Sensitivity analysis

Adjusting for participating studies may lead to reduced statistical power, given that some studies

had only severe cases or had disproportional case-control ratio. To alleviate the collinearity issue,

we grouped some small studies to account for study variability. This may not fully account for

between study variability. Thus we performed two sets of sensitivity analyses where we included,

1) only five genetic PCs without including the study of origin as random or fixed effects, and 2)

including all participating studies either as fixed or random effects. Next, we performed the same

analyses using UK Biobank (UKB) to provide estimates which are more representative of general

population, since this is not a COVID-19 specific cohort. We also tried binning by different cut-offs

for age-stratified analyses. In order to understand if results could have been influenced by related

individuals within the samples, we selected one individual from a pair of relatives with PI-HAT

(proportion of identity by descent calculated by PLINK[27]) >0·1875 (meaning between second and

third-degree relatives) and repeated the main analyses.

Role of the funding source

14

The funding sources had no role in study design; in the collection, analysis, and interpretation of

data; in the writing of the report; and in the decision to submit the paper for publication.

Results

Study participants

We collected and harmonized individual-level data from 13,424 COVID-19 patients diagnosed

with COVID-19 from February 5th, 2020 to January 2nd, 2021. Table 1 illustrates the

participants' demographic and clinical characteristics. The majority of participants were of

European descent (11,658; 86·8%). However, important numbers of non-European descent

individuals were also included in meta-analyses: 388 (2·9%) were South Asian ancestry and

574 (4·3%) were Admixed-American ancestry. 6,689 were hospitalized, amongst whom 1,622

(25·0%) were admitted to the ICU. 1,223 (21·6%) died following COVID-19 diagnosis and

1,644 (31·9%) met the criteria for severe respiratory failure. Clinical information was obtained

with different degrees of completeness across studies. A detailed description of study-specific

demographic, clinical characteristics and their missingness rates is provided in Supplementary

Table 4.

Table 1. Patients' characteristics

	Hospitalized	Total

15

	(N=6,689)	(N=13,424)
Female	2,650 (39·6%)	6,344 (47·3%)
Age (years)*	64·9 (14·7)	63·8 (12·7)
Ancestry		
European	5,601 (83·7%)	11,658 (86·8%)
South Asian	109 (1·6%)	388 (2·9%)
African	233 (3·5%)	421 (3·1%)
Others	185 (2·8%)	275 (2·0%)
East Asian	59 (0·9%)	108 (0·8%)
Admixed American	502 (7·5%)	574 (4·3%)
ICU admission	1,622 (25·0%)	1,622 (12·4%)
Death Status		
Survived	4,437 (78·4%)	10,951 (90·0%)
Deceased	1,223 (21·6%)	1,223 (10·0%)
Respiratory failure		
Severe respiratory failure	1,644 (32·0%)	1,644 (14·7%)
Oxygen supplementation	1,641 (32·0%)	1,641 (14·6%)
Hepatic injury	447 (10·0%)	447 (4·1%)
Cardiovascular complications	799 (17·1%)	804 (7·5%)
Kidney injury	1,095 (22·5%)	1,097 (9·6%)
Venous thromboembolism	286 (6·9%)	287 (2·7%)

Age*: Mean (SD), % was calculated amongst those with complete information. The missing rates per each study are listed in

Supplementary Table 4.

Risk allele frequency

According to the population frequencies in gnomAD[15], we estimate that 15·6% of individuals of

European descent carry at least one rs10490770 C allele, as well as 10·0% of

Latinx/Admixed-American, 2·4% of African/African-American, 62·0% of South Asians and

16

0·4% of East Asians. In our study the carrier frequency was 16·2% amongst individuals of

European descent in our cohort.

Association with mortality

Risk allele carriers at rs10490770 had a higher HR for all-cause mortality compared to

non-carriers (HR 1·4, 95%CI 1·2–1·6, p=1·1x10^{-4}, dead / alive = 832 / 8,416) over a median

follow-up duration of 45 days (interquartile range [IQR] 21-70 days) (Figure 1A). A competing

risk model to estimate the HR for COVID-19-related death while accounting for

non-COVID-19-related deaths estimated a similar HR for COVID-19 related mortality (HR 1·5,

95%CI 1·3-1·8, p=2·7x10^{-6}, dead / alive = 720 / 8,416) (Figure 1B). The association with

mortality was reduced when the analysis was restricted to hospitalized individuals (HR for

all-cause mortality 1·2, 95%CI 1·0–1·4, p=0·061, dead / alive = 832 / 2,796, and HR for

COVID-19 related mortality 1·3, 95%CI 1·1-1·5, p=4·2x10^{-3}, dead / alive = 720 / 2,796).

Associations with COVID-19 severity

We confirmed that risk allele carrier status at rs10490770 was significantly associated with

hospitalization (OR 1·5, 95%CI 1·3-1·7, p=9·1x10^{-10}, cases / controls = 5,601 / 5,997). A

stronger effect was observed for ICU admission (OR 2·5, 95%CI 1·9-3·2, p=1·9x10^{-12}, cases /

controls = 1,173 / 6,004) and death or severe respiratory failure (OR 1·7, 95%CI 1·5-2·1,

17

p=7·7x10^{-10}, cases / controls = 1,925 / 7,055) (Figure 2, Supplementary Table 5). Restricting

analyses to hospitalized individuals, we observed consistent results, some of which were with

diminished effect sizes (Figure 2, Supplementary Table 5). For instance, a significant reduction

in effect size was observed in OR for ICU admission (OR 1·5, 95%CI 1·3-1·8, p=1·4x10^{-6},

cases / controls = 1,173 / 4,428)

We next explored the association of the rs10490770 risk allele with laboratory values, which

are known to be associated with the severity of COVID-19[19–23]. rs10490770 risk allele carrier

status was associated with the worst value for each of these laboratory values at hospital (e.g.

lactate dehydrogenase: 0·24 SD increase, p=2·8x10^{-6}, D-dimer: 0·15 SD increase, p=3·6x10^{-3}

and interleukin-6: 0·18 SD increase, p=6·3x10^{-3}; Supplementary Figure 3, Supplementary

Table 3).

Associations with COVID-19 complications

Risk allele carrier status at rs10490770 was associated with multiple COVID-19-related severe

complications (Figure 2). These included severe respiratory failure (OR 2·0, 95%CI 1·6-2·6,

p=4·3x10^{-10}, Cases / Controls = 1,234 / 7,055), VTE (OR 1·7, 95%CI 1·3-2·4, p=5·7x10^{-3},

Cases / Controls = 205 / 8,914) and hepatic injury (OR 1·5, 95%CI 1·2-2·0, p=1·9x10^{-3}, Cases

/ Controls = 309 / 9,190). No significant effect was observed for cardiovascular complications

18

(OR 1·2, 95%CI 1·0-1·5, p=0·075, Cases / Controls = 697 / 8,611), although this might be due

to lack of statistical power to detect such effects. Similar results were observed when

restricting to hospitalized patients (Figure 2; Supplementary Table 5), indicating that the effect

of rs10490770 on severe COVID-19 complications was not simply explained by the higher

hospitalization rate among the carriers.

Age-dependent associations with COVID-19 severity

We explored the age-dependent effects of rs10490770 risk allele carrier status on severe

COVID-19 outcomes in individuals of European descent. Amongst severe patients who died or

had severe respiratory failure, rs10490770 risk allele carriers were on average 2·3 (95%CI

1·1-3·5) years younger than non-carriers (p=$2·4x10^{-4}$, N=1,925, Figure 3A; Supplementary

Table 5). Stratifying by age, we found that amongst those who were ≤ 60 years, risk allele

carrier status had markedly increased odds of death or severe respiratory failure (OR 2·6

95%CI 1·8-3·8), whereas risk allele carrier status had more modest effects amongst those >60

years with an OR of 1·5 (95%CI 1·3-1·9, p-value interaction=0·043, Figure 3B, Supplementary

Table 5-6). Amongst all participants ≤ 60 years who died or experienced a severe respiratory

COVID-19 outcome, we found that 31·8% (95%CI 27·6-36·2%) were rs10490770 risk variant

carriers, compared to 13·9% (95%CI 12·6-15·2%) of those who did not experience severe

disease (Table 2). When considering other severity phenotypes, such as hospitalization and

19

ICU admission, we observed that risk allele carriers tend to be younger than non-carriers.

However, we did not detect a different effect in the association between rs10490770 risk allele

carriers and these additional severity phenotypes amongst those who were ≤60 vs >60 years

old. This could be attributed to the heterogeneity of the criteria of hospitalization or ICU

admission, or case-control imbalance in some participating studies.

Table 2 Age and risk allele carrier status by COVID-19 severity outcomes

	Death or severe respiratory failure	COVID positive but no oxygen supplementation	
		Hospitalized only	**All**
All			
carrier	25·1% [23·2; 27·1] (483)	16·2% [14·4; 18] (258)	13·8% [13; 14·6] (974)
non-carrier	74·9% [72·9; 76·8] (1442)	83·8% [82; 85·6] (1,339)	86·2% [85·4; 87] (6,081)
Total	100% (1,925)	100% (1,597)	100% (7,055)
Age ≤ 60 years old			
carrier	31·8% [27·6; 36·2] (143)	14·5% [11·2; 18·5] (51)	13·9% [12·6; 15·2] (366)
non-carrier	68·2% [63·8; 72·4] (307)	85·5% [81·5; 88·8] (301)	86·1% [84·8; 87·4] (2,273)
Total	100% (450)	100% (352)	100% (2,639)
Age > 60 years old			
carrier	23·1% [21; 25·3] (340)	16·6% [14·7; 18·8] (207)	13·8% [12·8; 14·8] (608)
non-carrier	76·9% [74·7; 79] (1,135)	83·4% [81·2; 85·3] (1,038)	86·2% [85·2; 87·2] (3,808)
Total	100% (1,475)	100% (1,245)	100% (4,416)

Frequency of rs10490770 risk variant carriers in individuals of European descent stratified by age and COVID-19 severe

outcomes. [95%CI] (Sample size)

Associations with COVID-19 severity stratified by established clinical risk factors

We studied how the effects of rs10490770 risk allele carrier status on COVID-19 severity

varied by other established clinical risk factors. Amongst individuals with no risk factors (BMI ≥

20

30, smoking, cancer, chronic kidney disease, chronic obstructive pulmonary disease, heart

failure, transplantation, and DM) prior to COVID-19, risk allele carriers had an OR of 1·9 for

death or severe respiratory failure (95%CI 1·1-3·6), whereas risk allele carrier status had more

modest effects amongst those with one medical condition (OR 1·6, 95%CI 1·0-2·4) and more

than one medical conditions (OR 1·4, 95%CI 1·0-1·8) (p-value for interaction=0·087; Figure 3B,

Supplementary Table 7).

Risk prediction compared to established clinical risk factors

We compared the risk discrimination conferred by the rs10490770 risk allele on COVID-19

severity with that observed for other established COVID-19 risk factors. To do so, we used

multivariate regression in individuals of European ancestry with complete ascertainment of

clinical risk factors. rs10490770 risk allele carrier status was independent of other risk factors

(Figure 4A, Supplementary Table 8) when examining the association with death or severe

respiratory failure (OR 2·0, 95%CI 1·7-2·4, p=4·7x10^{-13}, frequency of risk allele carriers 14·6%,

Cases / Controls = 834 / 6,454). The effect sizes were comparable, or larger, than those of

other known risk factors such as DM (OR 1·9, 95%CI 1·6-2·4, p=6·2x10^{-12}, frequency of DM

12·3%). Stronger effects were observed amongst individuals ≤60 years (risk allele carrier

status: OR 4·0, 95%CI 2·6-6·2, p=1·3x10^{-10}, Cases / Controls = 128 / 2,348) relative to DM (OR

2·3, 95%CI 1·3-4·2, p=5·7x10^{-3}, frequency of DM: 5·5%) (Figure 4A, Supplementary Table 8).

21

Consistent with the results from multivariate regression, adding rs10490770 genotype to

non-genetic risk factors improved discrimination for death or severe respiratory failure

amongst ≤ 60 years (AUC: 0·82 vs 0·84, p=0·016 and NRI 0·45, p=6·5x10^{-8}, Table 3), and the

performance of risk discrimination was similar to, or better than, most of established risk

factors included in the study (Figure 4B, Supplementary Table 9).

Table 3: Risk prediction performance for death or severe respiratory failure

Age range	Model	AUC †	AUC p-value*	NRI †	NRI p-value*
All Cases = 834 Controls = 6,454	Baseline	0·77 [0·75; 0·78]	-	-	-
	Baseline and rs10490770	0·78 [0·76; 0·79]	1·8x10^{-4}	0·19 [0·13; 0·25]	2·0x10^{-10}
Age≤60 Cases = 128 Controls = 2,348	Baseline	0·82 [0·78; 0·86]	-	-	-
	Baseline and rs10490770	0·84 [0·81; 0·88]	1·6x10^{-2}	0·45 [0·29; 0·62]	6·5x10^{-8}

Only individuals with complete information of clinical risk factors and genotype were included. Baseline model includes age, sex,

BMI, smoking status (ever-smoker vs never-smoker), cancer, chronic kidney disease, chronic obstructive pulmonary disease

(COPD), chronic heart failure, transplantation, and diabetes mellitus. *p-values were calculated by comparing baseline model and

baseline and rs10490770 model. †: [95%CI]

Meta-analyses

We meta-analyzed the European ancestry results presented above with those of

non-European ancestry participants and two external cohorts. We confirmed similar effects in

the associations with mortality (Supplementary Figure 4), COVID-19 severity (Supplementary

Figure 5), COVID-19 complications (Supplementary Figure 6) and age-dependent effects

(Supplementary Figure 7). Given the small sample size of non-European participants, we

lacked sufficient statistical power to investigate whether the association between rs10490770

risk allele carriers and COVID-19 outcomes was different when comparing individuals of

non-European and European ancestry.

Sensitivity analysis

Last, we performed several sensitivities analyses to evaluate the robustness of our results. First,

we removed the study variables from the covariates and instead included the top five PCs

(Supplementary Table 10-11). Second, we included participating studies themselves either as

fixed or random effects (Supplementary Table 10-11). Third, we restricted to individuals of

European descent from UKB, a cohort which was not developed to study COVID-19 and thus is

less prone to selection bias. These UKB analyses generated similar results (Supplementary

Table 12). Fourth, we explored different cut-offs for age-stratified analyses (Supplementary

Table 13). Last, we excluded related individuals (Supplementary Table 14). All sensitivity

analyses were consistent with the results from the main analyses.

Discussion

Combining individual-level data from 13,424 individuals ascertained for COVID-19 outcomes

from 17 cohorts in nine countries, we found that the major genetic risk factor for severe

COVID-19 on chromosome 3 was strongly associated with COVID-19 related mortality and

clinical complications such as respiratory failure and venous thromboembolism. Effect sizes were

considerably larger in individuals ≤60 years and this genetic risk factor was similar in magnitude,

and often more common, than most established clinical risk factors. These findings suggest that

this genetic variant should be considered in risk stratification for COVID-19 outcomes.

The risk allele is common. We estimated that 15·6% of individuals of European ancestry are risk

allele carriers at rs10490770. Further, 10·0% of Latinx/Admixed Americans, 2·4% of

African/African-American, 62·0% of South Asians and 0·4% of East Asians are risk allele

carriers[15]. Consequently, a large proportion of individuals carry this risk factor.

The effect of carrying the risk allele on COVID-19 severity was stronger in younger individuals.

First, amongst those ≤60 years, the odds of death or severe respiratory failure increased 2·6-fold

for risk allele carriers. We found that 32% of individuals ≤60 years who died, or experienced

severe respiratory failure, were risk allele carriers, compared to 14% of individuals not requiring

supplemental oxygen. Second amongst individuals who died, or experienced severe respiratory

failure, risk allele carriers were on average 2·3 years younger than non-carriers. Last, the risk

discrimination for death and severe respiratory COVID-19 provided by the risk allele was similar

to, or larger than, established clinical risk factors in individuals ≤60 years. Other common

diseases have also demonstrated larger effects of genetic risk factors at younger age[8,9]. Genetic

24

risk factors are often clinically valuable for risk stratification in younger age groups because the frequency of other established risk factors for COVID-19 are often reduced, while the frequency of the genetic variant remains high. Moreover, this specific variant is not associated with any known COVID-19 risk factor and therefore provide orthogonal information compared to existing risk assessment tools.

Our findings suggest potential implications for clinical risk assessments in three situations. Currently, risk factors such as DM are clinically used in triage to decide if COVID-19 patients require further follow-up. Amongst individuals less than 60 years old, this genetic risk factor has considerably larger effect size and is more common than DM. This suggests that genotyping could help to identify individuals who are at risk for COVID-19 severe outcomes and death, allowing for more tailored treatment and clinical observation. Second, amongst very ill individuals less than 60 years, the genetic risk factor is quite common and may help to explain to patients and families why this individual has become severely ill, while others with the same clinical risk factor profile remain healthy. Last, since SARS-CoV-2 will become endemic in the human population, future public health strategies, including vaccines against novel variants of SARS-CoV-2, could be targeted to individuals at higher risk of severe outcomes. The major common genetic risk factor for severe COVID-19 could help to ensure individuals at highest risk are prioritized for vaccine programs, thus reducing the overall burden of the disease.

The biology of how this chromosome 3 genetic risk has an effect on COVID-19 severity is still unknown. This locus on chromosome 3p21 includes the putative SARS-COV-2 coreceptors; *SCL6A20*[28,29], *LZTFL1, FYCO1*[30], and the chemokine receptors; *CCR9*[29], *CXCR6*[31], *XCR1.* There are other flanking genes; *CCR1, CCR2 and CCR3*[32–34], whose involvement in SARS-CoV-2 infection had been suggested and could explain the biology of the striking effect of this genetic risk. Many studies[12,29] had been trying to pinpoint a or a set of causal genes but the consensus had not been built to date.

This study has important limitations. Each cohort has its own selection bias and ascertainment bias. Several studies were enriched for severe patients, whereas UKB is a non-COVID-19 cohort, with evidence of healthy volunteer bias[35]. Nevertheless, it may be less prone to selection bias than the COVID-19 cohorts. Selection bias is inherent to most COVID-19 observational studies[36] and this influences the generalizability of the results outside the study populations. To mitigate against these potential issues, we combined data from observational studies with different ascertainment strategies, including national healthcare systems, studies that were established prior to the COVID-19 pandemic and thus recruitment was not dependent upon COVID-19 status and hospital-based studies. This allowed for an increased representation of individuals with severe COVID-19 outcomes. We also provide analyses

26

restricted to hospitalized patients, which is an ascertained, but clinically-relevant population.

While we included information from participants who were of non-European ancestry, on-going

efforts should enable larger sample sizes in these ancestries to better define the importance of

the chromosome 3 risk locus in these contexts. This further emphasizes the importance of

developing genomics-enabled studies in individuals of non-European ancestry.

In summary, the major genetic COVID-19 risk locus is common and has large effects on

COVID-19 outcomes including mortality. These effects are age-dependent, such that the

magnitude of risk increases in younger individuals. These findings suggest potential

implications of genetic information in clinical risk management.

Figure 1: Associations with mortality

(A) Survival analysis using Cox-proportional hazard model
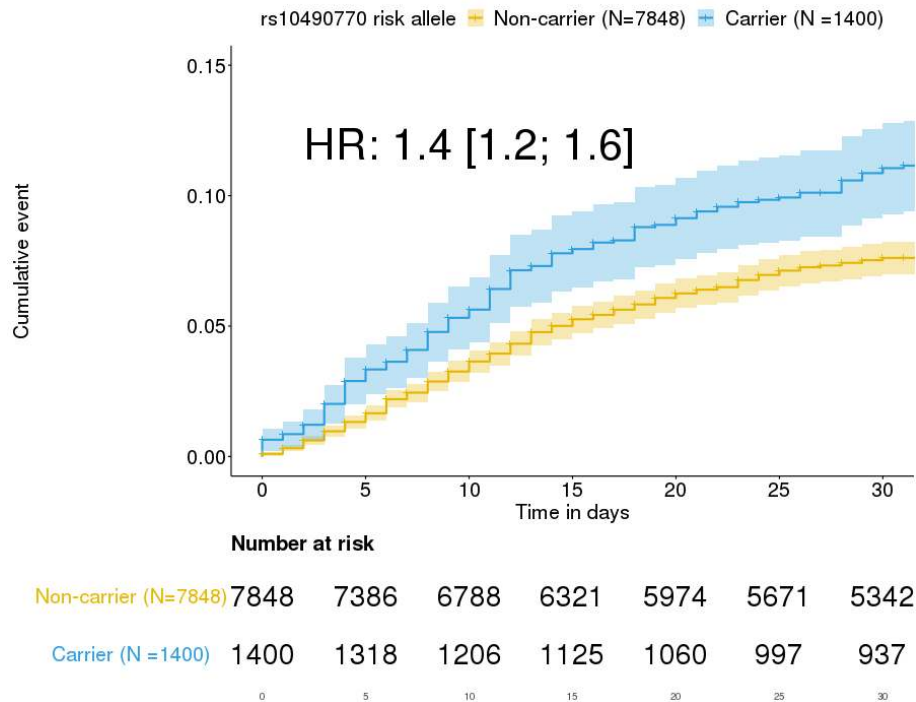
(B) Cumulative incidence curves
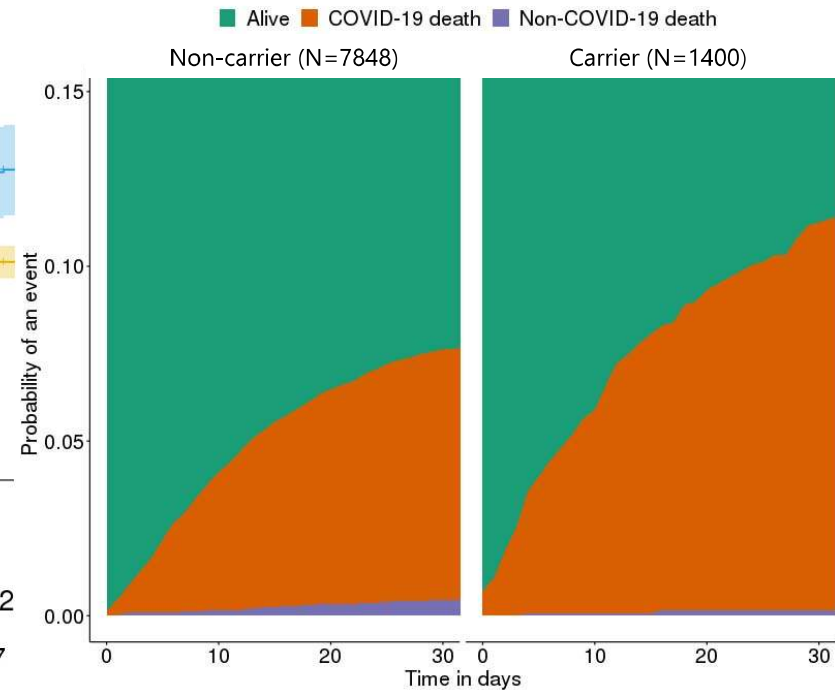
The results described here were restricted to 9,248 COVID-19 patients of European ancestry with available follow-up and cause of death information.

(A) Kaplan-Meier curves stratified by rs10490770 risk allele carrier status. (Carriers: N=1,400 vs non-carriers: N=7,848). Hazard ratios (HR) were calculated by adjusting for age, sex, genetic PCs 1 to 5 as fixed effects, and groups indicating participating studies as random effects.

(B) Cumulative incidence curves for COVID-19 related death and COVID-19 unrelated death amongst the same individuals as (A).

Figure 2: Associations between rs10490770 risk allele carrier status and COVID-19 severity and complications.
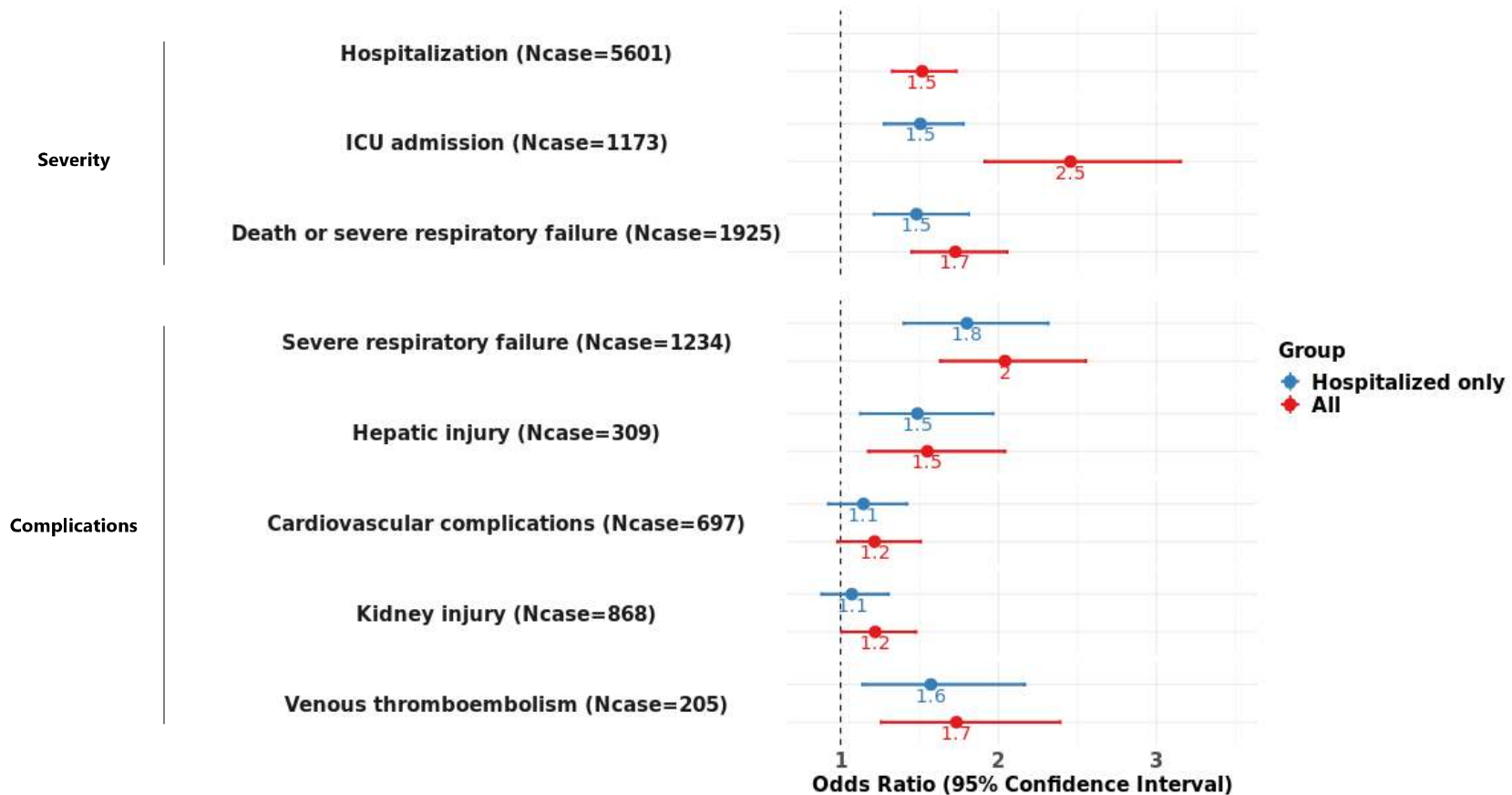
The results described here were restricted to COVID-19 patients of European ancestry. Logistic regressions were fit to assess the associations of rs10490770 risk allele carrier status with COVID-19 severity and complications, adjusting for age, sex, genetic PCs 1 to 5 as fixed effects, and groups indicating participating studies as random effects. Red: All participants (N=11,658) Blue: Hospitalized participants only (N=5,601) The case counts demonstrated here are from the data in all individuals.

Figure 3: Influence of age and clinical risk factors for the effect of rs10490770 risk allele carrier status on death or severe respiratory failure.
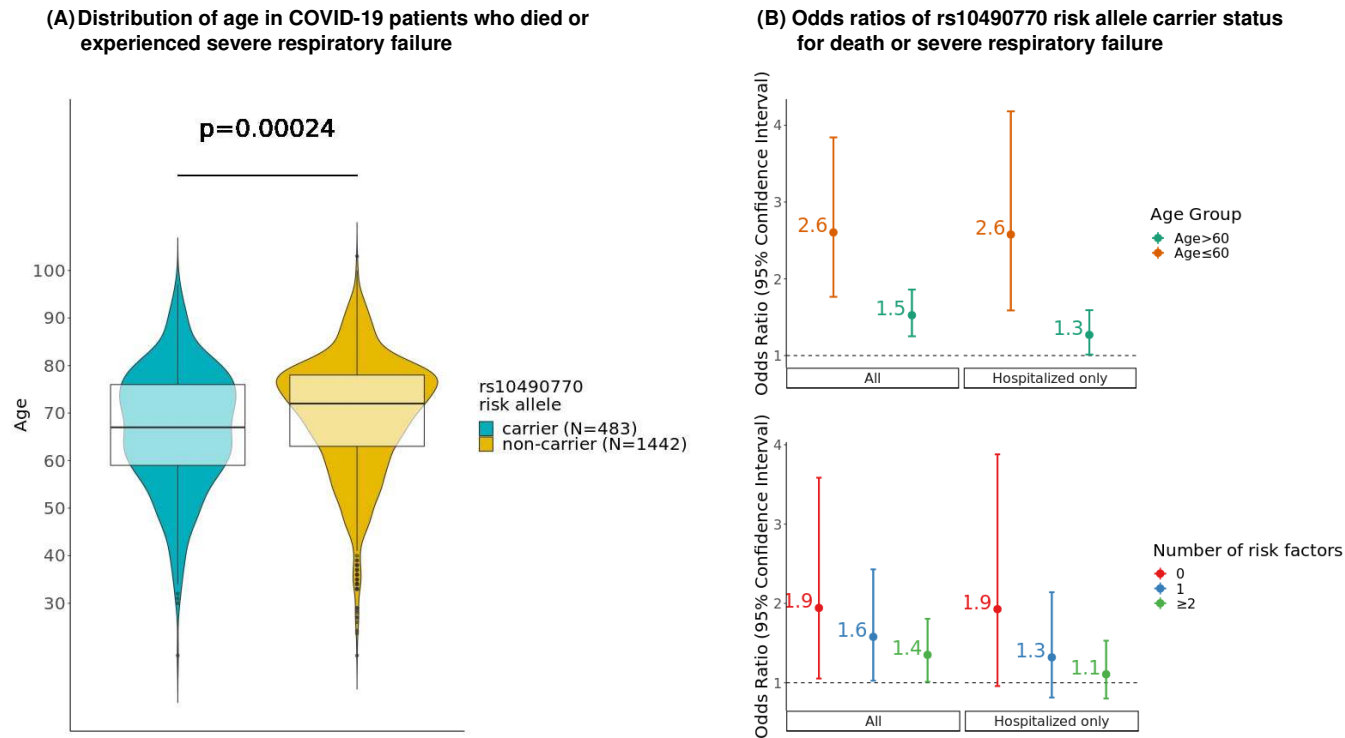
(A) Age distribution in COVID-19 patients of European ancestry who died or experienced severe respiratory failure (N=1,925). Median (IQR) age was 67 (63-78) years in carriers (N=438) and 72 (59-76) years in non-carriers (N=1,442).

(B) Logistic regressions between rs10490770 risk allele carrier status and death or severe respiratory failure. Regressions were performed within subgroups stratified by age (age ≤ 60 years and age > 60 years) (Cases / Controls = 1,925 / 7,055) or by the number of established risk factors (0, 1, or ≥2); BMI≥30, smoking, cancer, chronic kidney disease, chronic obstructive pulmonary disease (COPD), chronic heart failure, transplantation, and diabetes mellitus (Cases / Controls = 834 / 6,454).

Figure 4:   Multivariate regression models and risk prediction estimates of COVID19 death or severe respiratory failure
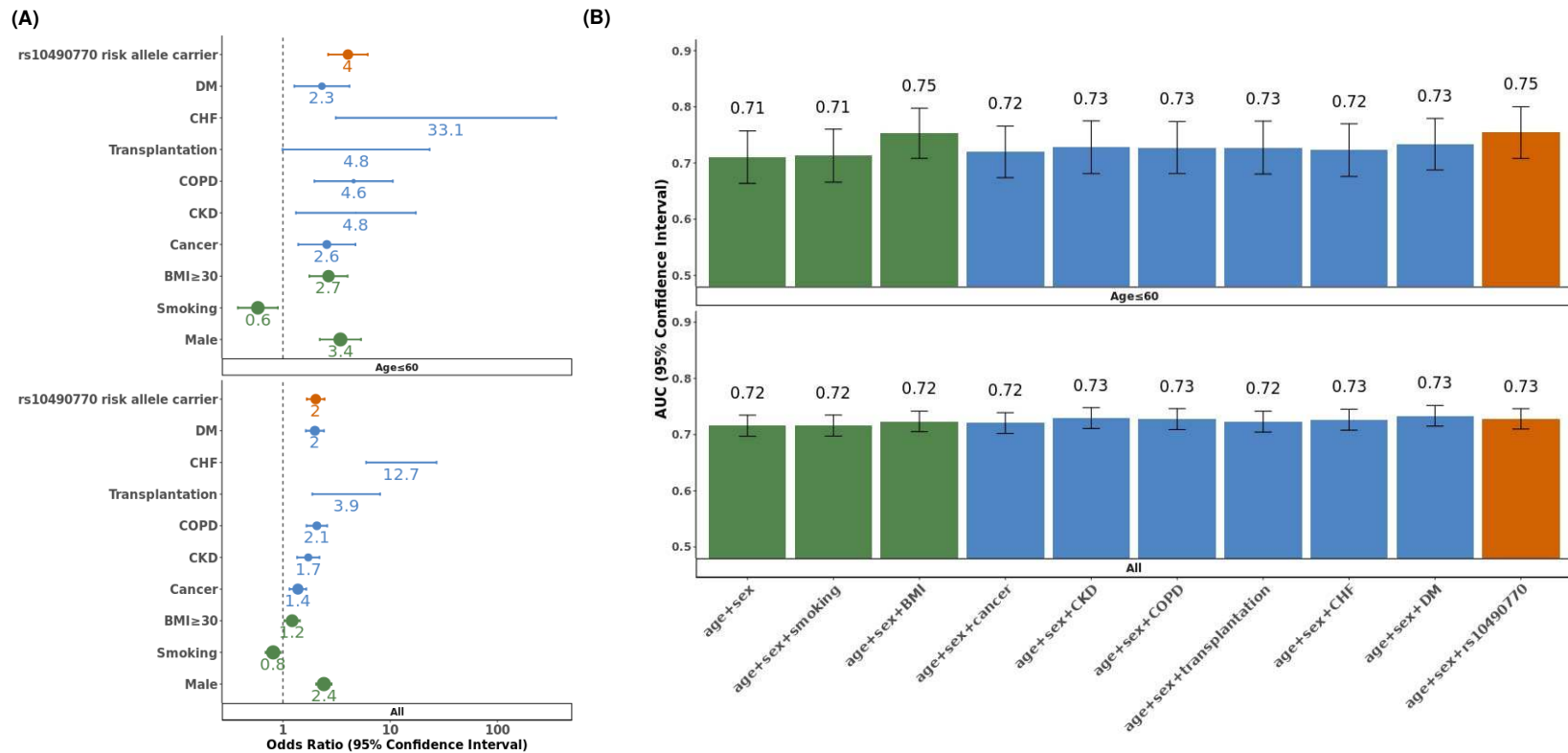
Multivariate regression analyses for death or severe respiratory failure were restricted to European-ancestry individuals with complete information of demographic variables (green), comorbidities (blue) and rs10490770 risk allele status (red). (N=7,288 for all and N = 2,476 for Age ≤ 60), CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, CHF: chronic heart failure, DM: diabetes mellitus.

(A) Forest plots comparing odds ratios from multivariate regression models. The size of each dot represents the frequency of the risk factors.

(B) Comparison of AUCs of predictions for COVID-19 outcomes. rs10490770 risk allele and non-genetic clinical risk factors were included separately in addition to age and sex in multivariate regression models

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Declaration of interests

JBR has served as an advisor to GlaxoSmithKline and Deerfield Capital. DP has served as an advisory board, and has received travel/research grants, speaking and teaching fees for Macopharma, Ortho Clinical Diagnostics, Grifols, Terumo, Immucor, Diamed, and Diatech Pharmacogenetics. THK has served an advisor to Novartis, Gilead, Intercept and Engitix. LV declares following; speaking fees: MSD, Gilead, AlfaSigma, AbbVie, Consulting: Gilead, Pfizer, Astra Zeneca, Novo Nordisk, Intercept pharmaceuticals, Diatech Pharmacogenetics, IONIS; Research grants: Gilead. All other authors declare that there are no conflicts of interest.

Contributors

Conception and design: TN, GBL, BNJ, FG, RF, MRG, KUL, MB, SR, MEAR, ECS, THK, LV, HZ, JBR and AG. Formal analysis: TN, SP, FD, MC, GBL, DMM, BNJ, YB, MN, DE, MMB, KUL, MEAR, LV, HZ, BR and AG. Data curation: TN, FD, MC, GBL, DMM, BNJ, YB, MN, DE, MMB, SR, SA, LR, FF, CDS, FG, IFC, JCH, RF, RA, ACP, LB, JRH, IM, AR, KUL, MB, ECS, JBR and AG. Interpretation of data: TN, GBL, BNJ, SR, RF, MRG, IM, KUL, MEAR, LV, HZ, BR, and AG. Funding acquisition: DMM, SA, FF, CDS, DP, DB, FG, GD, JCH, RF, SD, MRG, JRH, IM, AR, KUL, MB, SR, MEAR, ECS, THK, JBR, and AG. Investigation: TN, GBL, DMM, BNJ, YB, RF, IM, KUL, MEAR, BR and AG. Methodology: TN, GBL, MMB, MEAR, HZ, JBR and AG. Project administration: TN, FD, DMM, SR, CDS, DP, DB, FG, GD, JCH, JB, JRH, IM, KUL, SR, ECS, AF, THK, LV, JBR and AG. Resources: FG, GD, MRG, IM, SR, MEAR, JBR and AG. Supervision: DMM, BNJ, FG, MRG, IM, KUL, SR, MEAR, JBR and AG. Validation: TN, SP, FD, DE, AK, KK, and AG. Visualization: TN and AG. Writing—original draft: TN, JBR and AG. Writing—review and editing: TN, GBL, DMM, BNJ, AP, SR, IFC, JCH, RF, KK, SD, RA, LB, JRH, IM, AR, AMP, KUL, MEAR, THK, LV, HZ, JBR and AG. All authors were involved in further drafts of the manuscript and revised it critically for content. All authors gave final approval of the version to be published. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethical approval

All institutions contributing cohorts to the COVID-19 Host Genetics Initiative received ethics approval from their respective research ethics review boards. Genetic modifiers for COVID-19 related illness (BelCovid_1) was approved by the Erasme Ethics committee (protocol P2020_209). Host genetics and immune response in SARS-Cov-2 infection (BelCovid_2) was approved by the ethics committee of Liege University Hospital (approval number 2020-242). The BoSCO study was approved by Ethics Committee of the Medical Faculty of the University of Bonn. BQC19 received ethical approval from the JGH research ethics board (2020-2137). The BRACOVID study has been approved by the Hospital das Clinicas, Sao Paulo University Medical School and by Brazilian National IRB, CONEP. COMRI and the COVID-19 biobank of the Faculty of Medicine at Technical University Munich received ethical approval from the local research ethics board (TUM 217/20, TUM 221/20S, TUM 440/20S). San Sebastian Hospital and Basque Biobank (COVID19-Host(a)ge_1) was approved by the Euskadi Ethics Committee on April 6, 2020 (approval number PI2020064). The study in Hospital Universitario Valle Hebron and CIberehd del Instituto Carlos III. Barcelona (COVID19-Host(a)ge_2) was approved by Vall d'Hebron Ethical Committee. COVID GWAs, Premed COVID-19 (COVID19-Host(a)ge_3) was approved by COVID GWAs (ethics id: 0886-N-20) and Premed Covid (ethics id: 1954-N-20). Genetics against coronavirus (GENIUS), Humanitas University (COVID19-Host(a)ge_4) was approved by the ethic committee (approval number reference number 316/20). FoGS was approved by the ethics committee (approval number 342_2020). The GEN-COVID is a multicentre academic observational study was approved by the IRB of each participating centre. The INMUNGEN-CoV2 study was reviewed and approved by the Ethical Committee of the Hospital Clinic of Barcelona (CEIm number: Reg.HCB/2020/0357). NorCoV2 was approved by the Regional Committee for Medical and Health Research Ethics in South-Eastern Norway (project no. 132550). SPGRX was reviewed and approved by the Valladolid Ethics Committee (PI-201716) and the Granada Ethics Committee (no number given) on March 24th, 2020 and April 13th, 2020, respectively. SweCovid was approved by the National Ethical Review Agency (EPM; 2020-01623). UK Biobank was approved by the Northwest Multi-Centre Research Ethics Committee and informed consent was obtained from all participants prior to participation. This study was conducted under project ID 27449. FinnGen was approved by HUS coordinating Ethics committee. The Columbia University Biobank was approved by the Columbia University IRB.

Data sharing

The harmonized individual-level data of some participating cohorts from Belgium (BeLCovid_2), Brazil (BRACOVID), Italy (COVID19-Host(a)ge_4, GEN-COVID), Spain (COVID19-Host(a)ge_1,2,3, INMUNGEN-CoV2, SPGRX), and Sweden (SweCovid) is under preparation to be deposited at the European Genome-phenome Archive (EGA). Regarding the data from genetic modifiers for COVID-19 related illness (BelCovid_1),

individual level data were acquired and shared with FIMM during the sanitary crisis under an emergency consent and an ethical approval which were specific to this particular project and do not cover deposition to public repositories. Upon contact with Françoise Wilkin (Françoise.Wilkin@erasme.ulb.ac.be), Isabelle Migeotte (Isabelle.Migeotte@erasme.ulb.ac.be), or Guillaume Smits (Guillaume.Smits@erasme.ulb.ac.be), an institutional data transfer agreement can be established and data shared if the aims of data use are covered by ethical approval and patient consent. The procedure will involve an update to the ethical approval, as well as review by legal departments at both institutions and the process will typically take 2-4 months from initial contact.

Regarding the BoSCO study, individual-level genotype and clinical data for purpose of this study were shared with FIMM under a legal, bilateral agreement and were specific to this particular project. Current participant consents and privacy regulations prohibit deposition of individual level data to public repositories. Upon contact with Kerstin Ludwig (kerstin.ludwig@uni-bonn.de) or Markus M. Nöthen (markus.noethen@uni-bonn.de), an institutional data transfer agreement can be established and data shared if the aims of data use is covered by ethical approvals and patient consent. The procedure will involve review by legal departments at both institutions and the process will typically take about 2 months from initial contact.

The BQC19 is an Open Science biobank. Instructions on how to access data for individuals from the BQC19 at the Jewish General Hospital site are available here: https://www.mcgill.ca/genepi/mcg-covid-19-biobank. Instructions on how to access data from other sites of the BQC19 are available here: https://www.bqc19.ca/en/access-data-samples. For the COMRI cohort, data protection legislation does not allow for deposition of individual level data in public repositories. Upon direct contact with Prof Ulrike Protzer (protzer@tum.de, genetic data) and Dr Christoph Spinner (christoph.spinner@tum.de), an institutional data transfer agreement can be established and data will be shared if the aims of data use are covered by ethical approvals and patient consent. The procedure will involve an update to the ethical approval as well as review by legal departments at both institutions and the process will typically take 2-3 months from initial contact.

Regarding the Fondazione IRCCS Milan data (FOGS study), institutional data privacy regulations prohibit deposition of individual level data to public repositories without a specific consent. Participant written consent also does not cover public sharing of data for use for unknown purposes. Upon contact with professor Luca Valenti (luca.valenti@unimi.it) an institutional data transfer agreement can be established and data shared if the aims of data use are covered by ethical approvals and patient consent. The procedure will involve the request for an amendment to the ethical approvals, as well as review by legal departments at both institutions and the process will typically take 1-2 months from initial contact.

Regarding Norwegian data (NorCoV2), institutional data privacy regulations prohibit deposition of individual level data to public repositories. Participant written consent also does not cover public sharing of data for use for unknown purposes. Upon contact with professor Tom H Karlsen (t.h.karlsen@medisin.uio.no) or professor Johannes R. Hov (j.e.r.hov@medisin.uio.no) an institutional data transfer agreement can be established and data shared if the aims of data use is covered by ethical approvals and patient consent. The procedure will involve an update to the ethical approvals, as well as review by legal departments at both institutions and the process will typically take 1-2 months from initial contact.

The genetic and phenotype datasets from UK Biobank are available via the UK Biobank data access process (see http://www.ukbiobank.ac.uk/register-apply/).

Code availability

All code for data management and analysis is archived online at https://github.com/tomoconaka/COVID19-chr3 for review and reuse.

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