Testing the association between blood type and COVID-19 infection, intubation, and death

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Abstract

The rapid global spread of the novel coronavirus SARS-CoV-2 has strained existing healthcare and testing resources, making the identification and prioritization of individuals most at-risk a critical challenge. A recent study of patients in China discovered an association between ABO blood type and SARS-CoV-2 infection status by comparing COVID-19 patients with the general population. Whether blood type is associated with increased COVID-19 morbidity or mortality remains unknown. We used observational healthcare data on 1559 individuals tested for COVID-19 (682 COV+) with known blood type in the New York Presbyterian (NYP) hospital system to assess the association between ABO+Rh blood type and SARS-CoV-2 infection status, intubation, and death. We found a higher proportion of blood group A and a lower proportion of blood group O among COV+ patients compared to COV-, though in both cases the result is significant only in Rh positive blood types. We show that the effect of blood type is not explained by risk factors we considered (age, sex, hypertension, diabetes mellitus, overweight status, and chronic cardiovascular and lung disorders). In a meta-analysis of NYP data with previously reported data from China, we find significantly increased A and B and significantly decreased O blood groups among COVID-19 patients compared to the general population. Our data do not provide strong evidence of associations between blood group and intubation or death among COVID-19 patients. While our results are based on preliminary observational data collected during the care of patients and should not be used to guide clinical practice, we find further evidence of recently-discovered associations between blood group and SARS-CoV-2 infection status and new evidence of associations between B and Rh blood groups and COVID-19.

Background

The novel Coronavirus disease (COVID-19) has rapidly spread across the globe and has caused over 1,130,000 confirmed infections and over 62,000 deaths worldwide as of April 5, 2020 [1]. A number of risk factors for COVID-19 infection, morbidity, and mortality are known, including age, sex, and a number of chronic conditions and laboratory findings [2]. Recently, a study on COVID-19 patients in Wuhan and Shenzhen, China discovered associations between ABO blood types and infection [3]. Their analysis compared blood groups between hospitalized COVID-19 patients and the general populations of Wuhan and Shenzhen City, as assessed by previously-published samples of healthy individuals. They found that the odds of testing positive for COVID-19 among A blood groups was increased and among O blood groups was decreased relative to the general population. Similarly, previous work has identified associations between ABO blood groups and a number of different infections or disease severity following infections, including SARS-CoV-1 [4], *P. falciparum* [5], *H. pylori* [6], Norwalk virus [7], hepatitis B virus [8], and *N. gonorrhoeae* [9].

Within the United States, New York City has become a major center of the pandemic, with over 64,000 cases and over 2,400 deaths as of April 5, 2020 [10]. We sought to replicate and extend the previous investigation into the association between COVID-19 and blood type using electronic health record data from the New York Presbyterian (NYP) hospital system in New York, USA. We compared both ABO and ABO+Rh blood types, and we investigated three COVID-19 outcomes: infection status, intubation, and death.

Methods

We compared several combinations of blood group definitions (ABO vs ABO+Rh) and COVID-19 outcomes between four pairs of populations: COV+ vs COV-, COV+ vs general population (excluding those tested for COVID-19), COV+/Intubated vs COV+/Not intubated, and COV+/Deceased vs COV+/Alive. For each of the eight test conditions (2 blood group definitions and 4 outcome comparison population pairs), we performed a Pearson's Chi-squared test to test whether blood

group distributions differ between the compared populations. Additionally, we compared each blood group against all others using a 2x2 contingency table to determine effect sizes for each blood group itself. For the one-vs-rest blood group comparisons, we report odds ratios (OR), p-values from Fisher's exact test (two-sided), and odds ratio confidence intervals.

We evaluated the confounding effect of risk factors (age, sex, overweight status, diabetes mellitus, hypertension, pulmonary diseases, and cardiovascular diseases) on associations between blood group and COVID-19 outcomes. Since these analyses were performed at the individual level, we only considered COV+ vs COV-, COV+/Intubated vs COV+/Not intubated, and COV+/Died vs COV+/Alive, leaving out the COV+ vs general population comparison. First, we evaluated associations between risk factors and blood groups using logistic regressions of risk factors on blood groups. Then, we performed two comparisons using three nested logistic regression models on each COVID-19 outcome and analysis of deviance. The first comparison evaluated the predictive performance of risk factors by comparing the fit of a model using risk factors to a null model, using only an intercept term. The second comparison evaluated the additional predictive performance of blood groups beyond risk factors by comparing the fit of a full model (blood group + risk factors) to a nested model using only risk factors. We also performed nested regressions of outcome vs blood group and outcome vs blood group + risk factors to evaluate whether the effects of blood groups are affected by the presence of risk factors, indicating potential conditional independence.

We performed a meta-analysis using our data in combination with data from Wuhan and Shenzhen reported by Zhao et al. [3]. These analyses used a random effects model to create pooled estimates of odds ratios for each ABO blood group in comparisons between COV+ individuals and the general populations of New York, Wuhan, and Shenzhen. We compared the general population blood group distributions between New York and Wuhan and Shenzhen and evaluated the heterogeneity between sites.

Throughout our analysis, individuals with a single positive COVID-19 test were considered COVID+, even if they had previous or subsequent negative COVID-19 tests. Blood group was identified using either a measurement of LOINC code 34474-7, "ABO and Rh group [Type] in Cord blood," or the results of a procedure identified by one of the names listed in Table 4. We excluded individuals with multiple contradictory blood group measurements. The distribution of blood groups in the general population was estimated using blood group lab results on 108,929 individuals recorded in the NYP electronic health record (EHR) system between May 2011 and June 2019, excluding results for any individuals later tested for COVID-19 (regardless of result). Risk factor phenotypes were assigned using diagnosis codes (Table 5).

We considered EHR data up to April 5, 2020. We performed our analyses using the R language, and we used the `meta` package [11] for meta-analysis. While our data from NYP are protected by HIPAA and cannot be released, we have made all code used for our analysis available at https://github.com/zietzm/abo_covid_analysis. The manuscript was written openly on GitHub using the Manubot software [12].

Results

We first determined blood groups for COVID-tested individuals using laboratory measurements recorded in the NYP EHR system. One individual with multiple contradictory blood group measurements was excluded, resulting in 1,559 individuals with known blood groups who received a COVID-19 test (either positive or negative result). Of these, 682 were COV+ (positive in at least one COVID-19 test) and 877 were COV- (negative in all COVID-19 tests administered). Among the COV+ individuals, 179 were intubated and 80 had died, while the remaining individuals had not been intubated and remained alive as of April 5, 2020. We found that 354 tested COV- individuals were intubated during the same time, though we did not include them in any analysis.

For each comparison cohort pair, we performed chi-squared tests using both ABO and ABO+Rh blood types (Tables 1, 6). Since there were no AB-negative individuals testing positive for COVID-19 and only 5 individuals testing negative, we excluded AB-negative from all ABO+Rh analyses. Finally, we conducted individual tests of each blood type against all others (within the same ABO vs ABO+Rh system) for each of the COVID-19 outcomes we considered (Full data in Table 7).

We found associations between COVID-19 status and both ABO (p=0.006) and ABO+Rh (p=0.031) blood groups in a comparison between individuals testing positive vs testing negative (Tables 1, 2). Blood groups A were associated with increased odds of testing positive for COVID-19 (OR 1.338, p=0.009), while O blood groups were associated with decreased odds of testing positive (OR 0.790, p=0.036). While few individuals with AB blood groups were included (21 COV+, 47 COV-), we also found AB blood groups to be associated with decreased odds of testing positive (OR 0.561, p=0.033). When we tested individual ABO+Rh blood groups against all others, we discovered that strong associations are only found in Rh positive blood groups (Tables 2, 7). Finally, we compared the blood group distributions between all individuals tested for COVID-19 with the general population at NYP, finding insufficient evidence to conclude that tested individuals are not drawn from the general population at random (Chi-squared 3.8896, p=0.2736).

Table 1: Summary of chi-squared tests for association between blood type and COVID-19 outcomes. "df" indicates the degrees of freedom; ABO used a 4x2 table for each test, while ABO+Rh used a 6x2 table for each test, resulting in 3 and 5 degrees of freedom, respectively.

Blood group type	Comparison groups	Chi-squared	df	p-value
ABO	COV+ vs general population	5.288	3	0.152
ABO+Rh	COV+ vs general population	9.129	6	0.166
ABO	COV+ vs COV-	12.295	3	**0.006**
ABO+Rh	COV+ vs COV-	13.882	6	**0.031**
ABO	COV+/Intubated vs COV+/Not intubated	3.493	3	0.322
ABO+Rh	COV+/Intubated vs COV+/Not intubated	5.844	6	0.441
ABO	COV+/Died vs COV+/Alive	3.190	3	0.363
ABO+Rh	COV+/Died vs COV+/Alive	7.431	6	0.283

Table 2: Summary of one-vs-rest analysis for a comparison of COV+ vs COV- individuals. Each test compares the listed blood group to all other blood groups (combined) between the COV+ and COV- individuals. OR means odds ratio (COV+ vs COV-), and the 95% CI is a confidence interval on the OR. P-values computed using Fisher's exact test.

Blood group	Blood group type	OR	95% CI	p-value
A	ABO	1.338	1.072 - 1.672	**0.009**
A-negative	ABO+Rh	0.832	0.42 - 1.608	0.641
A-positive	ABO+Rh	1.382	1.099 - 1.737	**0.004**
AB	ABO	0.561	0.315 - 0.969	**0.033**
AB-positive	ABO+Rh	0.628	0.35 - 1.097	0.093
B	ABO	1.117	0.843 - 1.477	0.446
B-negative	ABO+Rh	0.636	0.216 - 1.695	0.381
B-positive	ABO+Rh	1.169	0.874 - 1.563	0.282
O	ABO	0.804	0.654 - 0.987	**0.036**
O-negative	ABO+Rh	1.034	0.548 - 1.93	1.000

Blood group	Blood group type	OR	95% CI	p-value
O-positive	ABO+Rh	0.790	0.642 - 0.971	**0.024**

Multivariate analysis of blood group associations

To evaluate potential confounding due to risk factors, we evaluated the association between risk factors (age, sex, overweight status, diabetes mellitus, hypertension, pulmonary diseases, and cardiovascular diseases) and blood groups. Using logistic regression of risk factors on blood groups, we discovered significant associations between hypertension and O- blood groups, between age and A, A+, AB, AB+, O, and O+ blood groups, between diabetes mellitus and B and A- blood groups, as well as between overweight status and O+ blood groups. A summary of these regressions including coefficients is in Table 10.

Next, we evaluated blood group's effect beyond risk factors on COVID-19 outcomes using logistic regression on outcomes and analysis of deviance. We verified that the risk factors (without blood groups) provide predictive power compared to intercept-only null models (Table 8). Then, we compared models including both risk factors and blood group to those including only risk factors, and we found that only the COVID-19 status outcome (COV+ vs COV-) is significantly better explained by including blood group in addition to risk factors ($p<0.02$ for both ABO and ABO+Rh, Table 8). This result is consistent with our previous analysis (Table 1), where only COV+ vs COV- cohorts showed significant differences in blood group distribution.

We inspected individual blood group coefficients between nested (blood group on outcome) and full (blood group and risk factors on outcome) logistic regression models to evaluate potential conditional independencies between outcomes and blood groups given risk factors (Table 9). For ABO blood groups, we found that coefficients only marginally changed, with some coefficients being more extreme (greater in magnitude and more significant) in full models than in nested models. No ABO+Rh blood groups were significant in either the nested or full models for ABO+Rh, though we found no large coefficient changes between nested and full models. These results provide no evidence for conditional independence between outcomes and blood group given risk factors, indicating we have no evidence that the significant effects of blood group we found are the result of confounding by risk factors.

Meta-analysis

Finally, we compared our data from New York City to the data from Wuhan and Shenzhen presented by Zhao et al. [3] and conducted a meta-analysis using the data they report in combination with our NYP data. Zhao et al. used a random effects model to meta-analyze data between three different hospitals (Wuhan Jinyintan, Renmin Hospital in Wuhan, and Shenzhen Third People's Hospital), comparing each hospital's COV+ blood group distribution to the general population distribution for each city. We performed a similar analysis—including NYP data—to assess the effect of blood type in the combined data from all four sources (full counts in Table 11).

We found that the distribution of blood groups in the general population at NYP differs significantly from both the distributions in Shenzhen (Chi-squared = 2056, p-value < 2.2e-16) and Wuhan (Chi-squared = 583.29, p-value < 2.2e-16) (Table 11). The difference in distributions is reflected in tests of heterogeneity between sites, where we find more heterogeneity between sites in our meta-analysis than Zhao et al.'s meta-analysis (Table 13).

We fit a random effects model for each ABO blood type using data from NYP and the three sources for which Zhao et al. report data. The overall associations between ABO blood groups and COVID-19 status that Zhao et al. identified (significantly increased COV+ odds for blood group A and decreased

COV+ odds for blood group O) are replicated in our meta-analysis (Table 3). Using the additional data from NYP, the pooled association between blood group B becomes larger in effect size and significant at the 5% level (original: OR 1.09, p=0.121; with NYP data: OR 1.25, p=0.0361).

Table 3: Meta-analysis associations for individual ABO blood groups in comparisons of COV+ vs general population using a random effects model. Each blood group was compared against all others using data from NYP, and Zhao et al. (Wuhan Jinyintan, Renmin Hospital in Wuhan, and Shenzhen Third People's Hospital). OR refers to the pooled odds ratio (COV+ vs general population), and the 95% CI is a confidence interval on the OR. P-values are for the pooled association from the random effects model.

Blood group	OR	95% CI	p-value
A	1.1636	1.0155 - 1.3333	**0.0291**
B	1.1101	1.0068 - 1.2240	**0.0361**
AB	1.2519	0.8384 - 1.8694	0.2721
O	0.7252	0.5971 - 0.8807	**0.0012**

Discussion

We stratified by ABO+Rh blood groups in a comparison of COV+ vs COV- individuals and found that A and O associations were only supported by evidence among those with Rh positive blood groups. Negative Rh blood groups are less common in our data, representing only 9.25% of individuals, so the lack of evidence for association with negative blood types could be due to lower sample sizes. However, odds ratios for ABO groups A and O are less extreme than the associated ABO+Rh blood groups (A+, O+), and the corresponding negative blood groups (A-, O-) have (insignificant) odds in the opposite directions as their positive counterparts. Further work is needed to better understand the associations between Rh negative blood groups and COVID-19.

Since both blood groups and risk factors vary across populations, we thought it was important to evaluate the associations we found in a multivariate context as well. Indeed, we found significant associations between risk factors and blood groups. However, the significant associations between blood group and COVID-19 status were reflected in significant reductions in deviance when adding blood group to a regression of risk factors on COVID-19 status. Moreover, the blood group regression coefficients were largely unchanged when risk factors were present or not, indicating that blood groups have an independent effect on COVID-19 status not captured by the risk factors.

Our meta-analysis found large heterogeneity in blood group distributions between Wuhan, Shenzhen, and New York City, consistent with previous work indicating large differences in blood group distributions between the United States and China [13,14]. Overall blood group differences introduced heterogeneity in our meta-analysis comparisons of blood group between COV+ individuals and the general population. Larger sample sizes of COVID-19 patients will allow afford a more detailed picture of the effects of blood type on COVID-19 susceptibility.

The significant associations we found for blood type between COV+ and COV- individuals were far from significant in a comparison between COV+ and the general population at NYP. A possible explanation for this finding is that individuals tested for infection at NYP represent a more homogeneous sub-population of patients at NYP. Increased homogeneity would strengthen the blood-group-COVID-19 association signal as it would reduce the influence of overall population differences in blood-type distribution. We did not find sufficient evidence to conclude that COVID-19-tested individuals have a significantly different blood group distribution than the general population at NYP, though we cannot rule out other differences between tested and general populations that could explain the difference in associations. Moreover, our meta-analysis using COV+ vs general population found significant associations between A, B, and O blood groups, and the NYP data

received 20-30 percent weight for each comparison, indicating a large contribution to the pooled associations. Further work is needed to understand how the population of COVID-tested patients differs from the general population.

We did not identify any significant relationships between blood group and intubation or death due to COVID-19. However, intubation and death due to COVID-19 continue in New York as of April 5, 2020, and individuals currently alive, not intubated, or COV- may reach these outcomes in the future. Our data is preliminary and represents a snapshot of the pandemic in a New York hospital system. When more patients become tested, intubated, and recovered, we will be better able to assess the relationship between blood group and eventual COVID-19 outcomes that may not have occurred at the time of our analysis.

Our study analyzed EHR data collected during the care of patients, not necessarily with research intent. Our sample sizes were relatively small, making explicit stratifications by age, sex, comorbidities, and other risk factors challenging. As an observational study without rigorous corrections for possible confounding, our results should be considered preliminary and should not be taken to inform clinical practice or policy.

Conclusion

In this study we found further evidence for the association between blood group and COVID-19. Using data from NYP, we found the odds of COVID-19 positive vs negative test results were increased in blood groups A and decreased in blood groups O, consistent with previous results from Wuhan and Shenzhen [3]. While Rh negative blood types are rare, we find evidence of association only for Rh positive blood groups. Though few AB individuals were included in our cohort, we discovered a new significant odds decrease for AB blood groups. In a meta-analysis of our data with data from Wuhan and Shenzhen reported by Zhao et al., we found a new significant COVID-19 odds increase for B blood groups compared to the general population. We demonstrated that the associations we found were not explained by confounding due to several known risk factors. Our results replicate previously-discovered associations between A and O blood groups and COVID-19, and we show novel associations between B, AB, and Rh blood groups.

Supplemental information

Table 4: Procedures used by name to identify individual blood group

Procedure name
TYPE AND SCREEN
BLOOD TYPE ABO AND RH
TYPE (ABO CONFIRMATION ONLY)
NEWBORN PANEL (ABO/RH PLUS DAT PLUS AB SCREEN)
CORD BLOOD PANEL (ABO/RH PLUS DAT)
NEWBORN BLOOD TYPE

Table 5: Codes used to define phenotypes. For each code, we used the code and all descendants of the code to define the phenotype, and assigned individuals based on the presence or absence of any code belonging to the phenotype assigned them. Concept IDs are based on OMOP CDM concept IDs.

Risk factor	Concept ID
Hypertension	19829001

Risk factor	Concept ID
Cardiovascular diseases	134057
Diabetes mellitus	201820
Overweight status	437525

Table 6: Counts of individuals by blood group and the three COVID-19 outcomes assessed (test result, intubation, death), and blood groups estimated for the general population using data from 108,929 individuals not tested for COVID-19.

Blood group	COV+	COV-	COV+/ Intubated	COV+/Not intubated	COV+/ Died	COV+/ Alive	General population
A	233	245	62	171	27	206	35643
A-negative	17	26	2	15	1	16	3447
A-positive	216	219	60	156	26	190	32196
AB	21	47	8	13	5	16	4582
AB-negative*	0	5	0	0	0	0	394
AB-positive	21	42	8	13	5	16	4188
B	116	136	35	81	12	104	16229
B-negative	7	14	2	5	0	7	1422
B-positive	109	122	33	76	12	97	14807
O	312	449	74	238	36	276	52406
O-negative	21	26	4	17	0	21	4808
O-positive	291	423	70	221	36	255	47598
Total	682	877	179	503	80	602	108860

* AB-negative was not included in the ABO+Rh analyses as no individuals with that blood type recorded tested positive for COVID-19.

Table 7: Summary of all one-vs-rest analyses conducted. Each individual test compared the listed blood group with all other blood groups between the listed comparison groups. Shown are comparisons between each blood type and all three COVID-19 outcomes investigated.

Blood group	Blood group type	Comparison groups	OR	95% CI	p-value
A	ABO	COV+ vs general population	1.066	0.906 - 1.252	0.437
A-negative	ABO+Rh	COV+ vs general population	0.779	0.45 - 1.258	0.379
A-positive	ABO+Rh	COV+ vs general population	1.098	0.93 - 1.294	0.257
AB	ABO	COV+ vs general population	0.723	0.444 - 1.116	0.151
AB-positive	ABO+Rh	COV+ vs general population	0.791	0.486 - 1.221	0.368
B	ABO	COV+ vs general population	1.170	0.949 - 1.432	0.131

Blood group	Blood group type	Comparison groups	OR	95% CI	p-value
B-negative	ABO+Rh	COV+ vs general population	0.781	0.312 - 1.622	0.733
B-positive	ABO+Rh	COV+ vs general population	1.203	0.971 - 1.48	0.083
O	ABO	COV+ vs general population	0.908	0.778 - 1.059	0.219
O-negative	ABO+Rh	COV+ vs general population	0.685	0.421 - 1.057	0.092
O-positive	ABO+Rh	COV+ vs general population	0.952	0.815 - 1.111	0.536
A	ABO	COV+ vs COV-	1.338	1.072 - 1.672	**0.009**
A-negative	ABO+Rh	COV+ vs COV-	0.832	0.42 - 1.608	0.641
A-positive	ABO+Rh	COV+ vs COV-	1.382	1.099 - 1.737	**0.004**
AB	ABO	COV+ vs COV-	0.561	0.315 - 0.969	**0.033**
AB-positive	ABO+Rh	COV+ vs COV-	0.628	0.35 - 1.097	0.093
B	ABO	COV+ vs COV-	1.117	0.843 - 1.477	0.446
B-negative	ABO+Rh	COV+ vs COV-	0.636	0.216 - 1.695	0.381
B-positive	ABO+Rh	COV+ vs COV-	1.169	0.874 - 1.563	0.282
O	ABO	COV+ vs COV-	0.804	0.654 - 0.987	**0.036**
O-negative	ABO+Rh	COV+ vs COV-	1.034	0.548 - 1.93	1.000
O-positive	ABO+Rh	COV+ vs COV-	0.790	0.642 - 0.971	**0.024**
A	ABO	COV+/Intubated vs COV+/Not intubated	1.029	0.705 - 1.493	0.927
A-negative	ABO+Rh	COV+/Intubated vs COV+/Not intubated	0.368	0.04 - 1.608	0.263
A-positive	ABO+Rh	COV+/Intubated vs COV+/Not intubated	1.121	0.765 - 1.635	0.575
AB	ABO	COV+/Intubated vs COV+/Not intubated	1.762	0.622 - 4.678	0.214
AB-positive	ABO+Rh	COV+/Intubated vs COV+/Not intubated	1.762	0.622 - 4.678	0.214
B	ABO	COV+/Intubated vs COV+/Not intubated	1.266	0.79 - 1.999	0.298

Blood group	Blood group type	Comparison groups	OR	95% CI	p-value
B-negative	ABO+Rh	COV+/Intubated vs COV+/Not intubated	1.125	0.106 - 6.948	1.000
B-positive	ABO+Rh	COV+/Intubated vs COV+/Not intubated	1.269	0.783 - 2.027	0.342
O	ABO	COV+/Intubated vs COV+/Not intubated	0.785	0.547 - 1.124	0.190
O-negative	ABO+Rh	COV+/Intubated vs COV+/Not intubated	0.654	0.158 - 2.042	0.616
O-positive	ABO+Rh	COV+/Intubated vs COV+/Not intubated	0.820	0.569 - 1.177	0.291
A	ABO	COV+/Died vs COV+/Alive	0.979	0.574 - 1.639	1.000
A-negative	ABO+Rh	COV+/Died vs COV+/Alive	0.464	0.011 - 3.067	0.708
A-positive	ABO+Rh	COV+/Died vs COV+/Alive	1.044	0.608 - 1.757	0.898
AB	ABO	COV+/Died vs COV+/Alive	2.437	0.679 - 7.226	0.088
AB-positive	ABO+Rh	COV+/Died vs COV+/Alive	2.437	0.679 - 7.226	0.088
B	ABO	COV+/Died vs COV+/Alive	0.845	0.402 - 1.646	0.751
B-negative	ABO+Rh	COV+/Died vs COV+/Alive	0.000	0 - 5.26	1.000
B-positive	ABO+Rh	COV+/Died vs COV+/Alive	0.919	0.436 - 1.794	0.872
O	ABO	COV+/Died vs COV+/Alive	0.966	0.586 - 1.585	0.906
O-negative	ABO+Rh	COV+/Died vs COV+/Alive	0.000	0 - 1.429	0.158
O-positive	ABO+Rh	COV+/Died vs COV+/Alive	1.113	0.675 - 1.827	0.718

Table 8: Analysis of deviance for comparisons between between null (intercept only), risk factors (RF), and blood groups (ABO and ABO+Rh) on COVID-19 outcomes. The deviance column gives the deviance reduced by the addition of the first term in the comparison. Similarly, DF indicates the degrees of freedom reduced by the addition. For both, the "Resid." column indicates the remaining deviance and degrees of freedom for the full model. P-values are computed using a chi-squared distribution with DF degrees of freedom.

Comparison	Outcome	DF	Resid. DF	Deviance	Resid. Deviance	p-value
Risk factors vs Null	COV+ vs COV-	7	1550	121.851	2013.777	0.000
Risk factors vs Null	COV+/Intubated vs COV+/Not intubated	7	674	12.250	772.893	0.093

Comparison	Outcome	DF	Resid. DF	Deviance	Resid. Deviance	p-value
Risk factors vs Null	COV+/Died vs COV+/Alive	7	674	100.012	393.094	0.000
ABO + Risk factors vs Risk factors	COV+ vs COV-	3	1547	10.752	2003.024	0.013
ABO + Risk factors vs Risk factors	COV+/Intubated vs COV+/Not intubated	3	671	3.021	769.872	0.388
ABO + Risk factors vs Risk factors	COV+/Died vs COV+/Alive	3	671	1.153	391.941	0.764
ABO+Rh + Risk factors vs Risk factors	COV+ vs COV-	7	1543	17.165	1996.612	0.016
ABO+Rh + Risk factors vs Risk factors	COV+/Intubated vs COV+/Not intubated	6	668	5.876	767.017	0.437
ABO+Rh + Risk factors vs Risk factors	COV+/Died vs COV+/Alive	6	668	5.641	387.453	0.465

Table 9: Logistic regression coefficients and coefficient p-values for comparisons between nested (outcome vs blood group) and full (outcome vs blood group + risk factors) models. The outcome here is COV+ vs COV-. Full information for ABO+Rh blood groups are available on GitHub. The coefficients are either changed marginally or more extreme in the full model than the nested model. Were COV+ status conditionally independent of blood type given risk factors, we would expect full model coefficients to be less extreme than in the nested model. AB blood groups were not included because they are mutually exclusive with A, B, and O blood groups.

Blood group	Nested model coefficient	Full model coefficient	Nested model p-value	Full model p-value
A	0.759	0.752	0.006	0.009
B	0.647	0.757	0.026	0.012
O	0.442	0.504	0.105	0.074

Table 10: All associations between risk factors and blood groups where logistic regression coefficient p-values were below 0.1. Full data are available on GitHub.

Blood group	Term	Coefficient	Standard error	p-value
A	age	0.008	0.003	0.005
AB	age	0.014	0.006	0.027
B	diabetes	-0.434	0.195	0.026
O	age	-0.008	0.003	0.003
O	diabetes	0.248	0.142	0.080
A_neg	hypertension	-0.895	0.511	0.080
A_neg	diabetes	0.880	0.442	0.047
A_neg	cv_diseases	0.852	0.507	0.093
A_pos	age	0.009	0.003	0.001
AB_pos	age	0.013	0.006	0.043
B_neg	age	0.018	0.011	0.096
B_pos	diabetes	-0.390	0.200	0.052

Blood group	Term	Coefficient	Standard error	p-value
O_neg	hypertension	2.124	1.043	0.042
O_neg	overweight	-1.359	0.744	0.068
O_pos	age	-0.007	0.003	0.006
O_pos	diabetes	0.279	0.143	0.051
O_pos	overweight	0.355	0.168	0.034

Table 11: Distributions of blood groups between New York City data from the NYP EHR system and individuals from Shenzhen (cases from Shenzhen Third People's Hospital, controls from Shenzhen general population) and Wuhan (cases from Wuhan Jinyintan Hospital and Renmin Hospital of Wuhan University, controls from Wuhan general population). Shenzhen and Wuhan data reported by Zhao et al. [3].

Blood group	NYP general population	NYP COV+	Shenzhen general population	Shenzhen COV+	Wuhan general population	Wuhan Jinyintan COV+	Wuhan Renmin COV+
A	32.7% (35643)	34.2% (233)	28.8% (6728)	28.8% (82)	32.2% (1188)	37.7% (670)	39.8% (45)
AB	4.2% (4582)	3.1% (21)	7.3% (1712)	13.7% (39)	9.1% (336)	10% (178)	13.3% (15)
B	14.9% (16229)	17% (116)	25.1% (5880)	29.1% (83)	24.9% (920)	26.4% (469)	22.1% (25)
O	48.1% (52406)	45.7% (312)	38.8% (9066)	28.4% (81)	33.8% (1250)	25.8% (458)	24.8% (28)

Table 12: Weights for sites in random-effects meta-analyses conducted for each ABO blood group. Each blood group was compared against all others using data from NYP, and Zhao et al. (Wuhan Jinyintan, Renmin Hospital in Wuhan, and Shenzhen Third People's Hospital).

Blood group	Site	OR	95% CI	%Weight
A	NYP	1.0660	0.9095 - 1.2494	31.8
A	Wuhan Jinyintan	1.2790	1.1364 - 1.4395	39.3
A	Wuhan Renmin	1.3959	0.9519 - 2.0472	10.3
A	Shenzhen	1.0001	0.7727 - 1.2945	18.6
B	NYP	1.1698	0.9573 - 1.4294	23.7
B	Wuhan Jinyintan	1.0828	0.9516 - 1.2321	57.1
B	Wuhan Renmin	0.8566	0.5460 - 1.3440	4.7
B	Shenzhen	1.2233	0.9458 - 1.5822	14.4
AB	NYP	0.7230	0.4678 - 1.1176	23.5
AB	Wuhan Jinyintan	1.1139	0.9201 - 1.3487	30.2
AB	Wuhan Renmin	1.5297	0.8783 - 2.6643	20.0
AB	Shenzhen	2.0071	1.4266 - 2.8237	26.3
O	NYP	0.9084	0.7810 - 1.0566	31.1
O	Wuhan Jinyintan	0.6799	0.5993 - 0.7715	32.9
O	Wuhan Renmin	0.6441	0.4179 - 0.9925	13.2
O	Shenzhen	0.6272	0.4842 - 0.8124	22.8

Blood group	Site	OR	95% CI	%Weight

Table 13: Heterogeneity across meta-analysis sites.

Blood group	I-squared	I-squared 95% CI	Q	Q d.f.
A	47.1%	0.0 - 82.4	5.67	3
B	0.0%	0.0 - 79.4	2.23	3
AB	80.6%	48.9 - 92.6	15.43	3
O	72.1%	21.0 - 90.2	10.76	3

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