extracted the data from the electronic patient files. Paul J. Hengeveld, Nathalie I. Bouwer, Anton W. Langerak and Mark-David Levin advised and performed the data analysis. Paul J. Hengeveld wrote the manuscript. All authors critically reviewed and approved the final manuscript.

Conflict of Interest

The authors do not have any conflict of interest to report.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Routine blood analysis, leucocyte differentiation and immunophenotyping.

Fig S2. Survival analysis in COVID-19-positive patients.

Table S1. Baseline clinical characteristics and outcomes.

Table S2. Blood cell- and lymphocyte subset counts of non-critically and critically ill patients with COVID-19.

Table S3. Definitive diagnoses in controls who underwent immunophenotyping.

Data S1. Supplementary methods.

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ABO phenotype and death in critically ill patients with COVID-19

Blood groups are inherited traits that vary across populations, likely due to both founder effects and natural selection.[1] A link between blood groups and susceptibility to infectious disease has been well-described, with notable examples being *H. Pylori* and *Plasmodium falciparum* infection.[1,2] Blood group antigens may influence disease susceptibility by several mechanisms, including serving as receptors or decoys for infectious organisms and modifying immune response in the form of anti-ABO antibodies.[2]

Data on the relationship between blood group and outcomes in patients with coronavirus disease 2019 (COVID-19) are limited. Studies from China[3] and Europe[4] reported that patients with type O blood may be protected from COVID-19 infection, whereas those with type A blood may be at

Table I. Characteristics and outcomes according to ABO phenotype.

Characteristic	All $N = 2033$ (100%)	Type A $N = 666$ (32·7%)	Type B $N = 328$ (16·1%)	Type AB $N = 89$ (4·4%)	Type O $N = 950$ (46·7%)
Age, years, median (IQR)	62 (52–71)	64 (53–72)	63 (54–71)	66 (56–72)	61 (50–70)
Male sex, *n* (%)	1297 (63·8)	417 (62·6)	189 (57·6)	58 (65·2)	633 (66·6)
Race/ethnicity, *n* (%)					
White non-Hispanic	561 (27·6)	253 (38·0)	64 (19·5)	32 (36·0)	212 (22·3)
Black non-Hispanic	645 (31·7)	175 (26·3)	140 (42·7)	21 (23·6)	309 (32·5)
Asian non-Hispanic	114 (5·6)	32 (4·8)	37 (11·3)	11 (12·4)	34 (3·6)
Hispanic	408 (20·1)	120 (18·0)	28 (8·5)	10 (11·2)	250 (26·3)
Body mass index, kg/m^2, median (IQR)	30·2 (26·1–36·1)	29·8 (25·8–36·5)	31·1 (26·2–35·5)	29·3 (25·1–34·4)	30·3 (26·6–36·1)
Co-existing conditions, *n* (%)					
Any	1653 (81·3)	552 (89·9)	285 (86·9)	72 (80·9)	744 (78·3)
Diabetes mellitus	851 (41·9)	278 (41·7)	147 (44·8)	31 (34·8)	395 (41·6)
Hypertension	1258 (61·9)	423 (63·5)	229 (69·8)	55 (61·8)	551 (58·0)
Chronic lung disease	483 (23·8)	164 (24·6)	85 (25·9)	18 (20·2)	216 (22·7)
Current or former smoker	421 (20·7)	139 (20·9)	70 (21·3)	21 (23·6)	191 (20·1)
Coronary artery disease	297 (14·6)	104 (15·6)	52 (15·9)	11 (12·4)	130 (13·7)
Congestive heart failure	204 (10·0)	71 (10·7)	35 (10·7)	7 (7·9)	91 (9·6)
Chronic kidney disease	286 (14·1)	88 (13·2)	50 (15·2)	14 (15·7)	134 (14·1)
ESRD	84 (4·1)	31 (4·7)	15 (4·6)	1 (1·1)	37 (3·9)
Chronic liver disease	80 (3·9)	22 (3·3)	14 (4·3)	4 (4·5)	40 (4·2)
Active malignancy	125 (6·1)	46 (6·9)	20 (6·1)	6 (6·7)	53 (5·6)
Immunodeficiency	33 (1·6)	12 (1·8)	4 (1·2)	0 (0·0)	17 (1·8)
Laboratory values at ICU admission, median (IQR)					
White blood cell count, $\times 10^6$/l	8·4 (6·0–12·0)	8·4 (6·0–12·3)	8·3 (5·9–11·2)	8·2 (6·0–11·9)	8·6 (6·1–12·0)
Lymphocyte count, $\times 10^6$/l	9·6 (6·0–14·6)	9·5 (5·9–14·3)	9·9 (6·0–15·0)	8·6 (5·0–12·1)	9·7 (6·0–15·0)
Haemoglobin, g/l	125 (108–139)	122 (105–137)	124 (107–138)	127 (110–142)	127 (110–141)
Platelet count, $\times$ 10^6/l	211 (162–271)	210 (159–271)	213 (164–273)	204 (153–260)	210 (165–271)
Creatinine, mg/l	11·0 (8·0–17·4)	11·0 (8·1–17·2)	11·4 (8·3–18·0)	11·1 (9·2–19·3)	10·7 (8·0–17·4)
Albumin, g/l	32 (28–36)	32 (28–35)	32 (28–36)	31 (25–34)	32 (28–36)
Total bilirubin, mg/l	0·6 (0·4, 0·8)	6 (4–8)	6 (4–8)	6 (4–9)	6 (4–8)
D-dimer, ng/ml	1400 (730–3690)	1465 (818–3733)	1175 (630–3750)	1170 (527–2856)	1490 (711–3620)
C-reactive protein, mg/l	162 (93–249)	163 (94–245)	154 (99–242)	167 (91–253)	163 (91–254)
Severity of illness on the day of ICU admission					
AKI requiring RRT (ESRD patients excluded), *n* (%)	53 (2·6)	15 (2·3)	11 (3·4)	4 (4·5)	23 (2·4)
Invasive mechanical ventilation, *n* (%)	1438 (70·7)	466 (70·0)	238 (72·6)	71 (79·8)	663 (69·8)
PaO_2:FiO_2, mm Hg, median (IQR)*	127 (86–198)	130 (85–195)	126 (90–220)	117 (87–191)	127 (86–193)
Shock (≥2 vasopressors), *n* (%)	241 (11·9)	85 (12·8)	42 (12·8)	15 (16·9)	99 (10·4)
In-hospital mortality, *n* (%)	799 (39·3)	268 (40·2)	129 (39·3)	41 (46·1)	361 (38·0)

AKI, acute kidney injury; ESRD, end-stage renal disease; ICU, intensive care unit; RRT, renal replacement therapy.

*PaO_2:FiO_2 refers to the ratio of the partial pressure of arterial oxygen (PaO_2) over the fraction of inspired oxygen (FiO_2), and was only assessed in patients receiving invasive mechanical ventilation.

higher risk. Data from a related viral outbreak, the severe acute respiratory syndrome coronavirus (SARS-CoV-1) in 2003, suggested that healthcare workers with type O blood were less likely to contract this disease.[5] *In vitro* experiments revealed that the interaction between the SARS-CoV-1 spike protein and angiotensin converting enzyme 2 (ACE2), necessary for viral uptake, may be mitigated by anti-A antibodies.[6]

To examine the relationship between blood group and clinical outcomes in patients with COVID-19, we studied the distribution and mortality associated with ABO phenotype in a large cohort of critically ill patients. We utilised data from the Study of the Treatment and Outcomes in critically ill Patients with COVID-19 (STOP-COVID), a multicentre cohort study that enrolled consecutive adults (aged ≥18 years) with laboratory confirmed COVID-19 admitted to participating intensive care units (ICUs) at 67 hospitals across the United States. We included patients admitted to ICUs between 4 March and 11 April 2020. We followed patients until the first of hospital discharge, death or 8 May 2020, the date on which the database for the present analysis was locked. All patients who remained hospitalised at the time of analysis had a minimum of 28-days follow-up. The

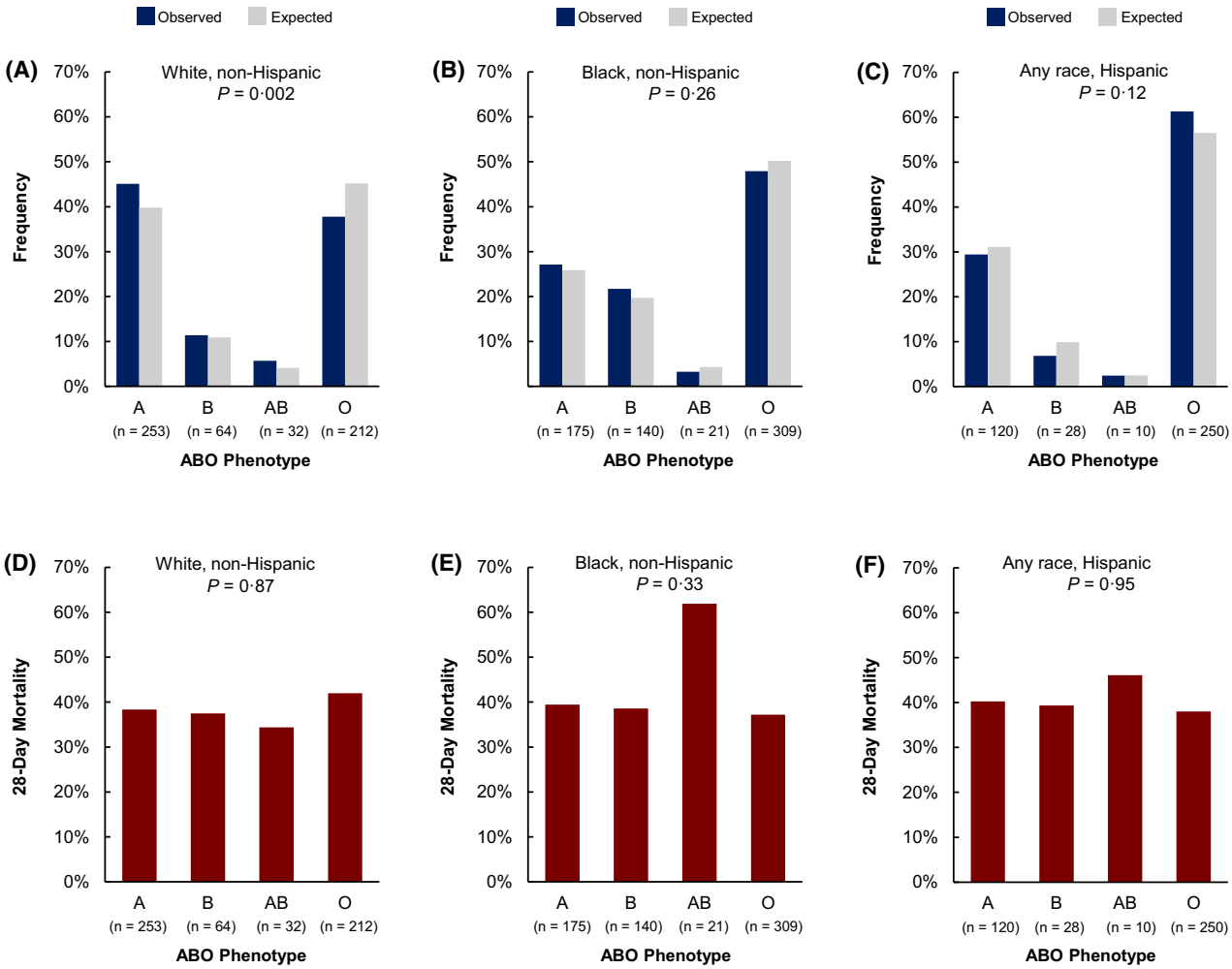

Fig 1. ABO phenotype: distribution and association with mortality. (A) Observed *versus* expected blood group frequency according to race/ethnicity. (B) 28-day mortality according to blood group frequency.

study was approved with a waiver of informed consent by the Institutional Review Board at each participating site.

To examine whether blood type is associated with critical illness in patients with COVID-19, we used a chi-square test to compare the observed *versus* expected distribution of ABO phenotypes. We stratified our analyses by race/ethnicity, as race/ethnicity is an important determinant of ABO phenotype[7] and could also affect hospitalisation for COVID-19. To improve the reliability of our estimates, we limited our analyses to the three most commonly reported categories of race/ethnicity in our cohort: white non-Hispanic; Black non-Hispanic; and Hispanic. Patients missing data on ABO phenotype were excluded. We estimated the expected distribution of ABO phenotype in each of the above race/ethnicity categories using data from 3·1 million blood donors in the United States.[7]

To examine whether ABO phenotype is associated with mortality among critically ill patients with COVID-19, we used a chi-square test to compare the distribution of observed ABO blood phenotypes with 28-day in-hospital mortality, stratified by the above race/ethnicity categories. Patients discharged alive from the hospital prior to 28 days were considered to be alive at 28 days. We tested the validity of this assumption in a random subset of 50 patients discharged prior to 28 days, all of whom remained alive at 28 days according to electronic medical records or follow-up by telephone. Statistical analysis was performed using GraphPad Prism 7 (GraphPad, Inc., San Diego, CA, USA), and Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA).

Among 3239 critically ill patients with COVID-19, 2033 (62·8%) had data available on ABO phenotype and were included in the present analysis. The median (interquartile range) age was 62 (52–71) years, and 1297 (63·8%) were men. Additional characteristics according to ABO phenotype are shown in Table I.

The observed and expected frequencies of ABO phenotypes in white, Black and Hispanic patients are shown in Fig 1. Among white patients, the observed distribution of ABO phenotypes differed from its expected distribution

(Fig 1A). This difference was primarily driven by patients with blood type A being over-represented (45·1% observed vs. 39·8% expected) and patients with blood type O being under-represented (37·8% observed vs. 45·2% expected). Among Black (Fig 1B) and Hispanic patients (Fig 1C) the observed and expected distributions of ABO phenotypes were similar.

A total of 799 of the 2033 patients (39·3%) died within 28 days. The mortality rate was similar across ABO phenotypes in all race/ethnicity categories (Fig 1D–F). Results were qualitatively unchanged when considering Rh phenotype.

In this large nationwide cohort study of critically ill patients with COVID-19, we found significant differences in the observed *versus* expected distribution of ABO phenotypes among white patients, with blood types A and O being over- and under-represented respectively. We found no difference in the observed *versus* expected distribution of ABO phenotypes among Black or Hispanic patients, nor did we find an association between ABO phenotype and 28-day mortality among any of the three examined categories of race/ethnicity.

Our present finding of a higher than expected frequency of blood type A and a lower than expected frequency of blood type O, at least amongst white patients, is consistent with other reports. For instance, in a genome-wide association study of nearly 2000 patients in Italy and Spain, Ellinghaus *et al.*[4] recently identified two gene clusters enriched in patients with COVID-19. One cluster contained genes relevant to both ACE2 functionality and immune response, while the other cluster encoded genes for the ABO blood group. In a meta-analysis of two different case-control cohorts, the authors found that type A blood conferred a higher risk of severe COVID-19, while type O blood afforded protection. Similarly, investigators from both China and the United States reported that patients with type A blood are at increased risk of developing COVID-19, whereas those with type O blood have a lower risk.[3]

The mechanisms responsible for these observations have yet to be elucidated. One theory is that neutralising anti-A antibodies protect against viral entry into lung epithelium, as was hypothesised with SARS-CoV-1;[6] however, if this were the case, we would have expected both type O and type B blood to be under-represented in our present cohort. Alternatively, individuals with type O blood are known to have lower rates of thrombosis and cardiovascular disease, which is attributed to altered glycosyltransferase activity and increased clearance of von Willebrand factor. Thus, patients with type O blood may be less likely to develop COVID-19-related microvascular thrombosis and endothelial dysfunction.[8]

We are unable to provide a discrete biological explanation as to why we found a difference in the incidence of COVID-19-associated critical illness only among white patients, although this finding is consistent with prior reports demonstrating a higher risk of acute respiratory distress syndrome in white patients with type A blood but not in Black patients.[9] We would also note that there is large variation, subjectivity and bias in how race/ethnicity is reported in the USA, and that these results should be interpreted with caution.[10]

Our present study has several strengths. We used granular data from a large number of consecutive critically ill patients from 67 geographically diverse sites across the USA. Furthermore, whereas prior studies in COVID-19 have had limited follow-up, we followed patients until hospital discharge, death or a minimum of 28 days.

We also acknowledge several limitations. As with all observational analyses, we cannot exclude the possibility of residual confounding. Additionally, data on ABO phenotype were missing in approximately one-third of patients. Finally, we were unable to evaluate other blood groups, such as secretor status and Lewis antigens, which are also known to affect host immunity.[1,2]

In conclusion, our present data suggest that type A blood may be a risk factor for COVID-19-related critical illness among white patients, and that type O blood may be protective. Future investigations are needed to determine the mechanisms for these findings.

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Author contributions

Rebecca Karp Leaf and David Leaf wrote the first draft of the manuscript and contributed to concept and design, data analysis, creation of tables and figures, critical revision of the manuscript and final approval; Hanny Al-Samkari contributed to concept and design, data collection, data analysis, creation of tables and figures, critical revision of the manuscript and final approval. Samantha Brenner contributed to the concept and design of the study, revision of the manuscript and final approval. Shruti Gupta contributed to data collection, critical revision of the manuscript and final approval.

Conflict of interest

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Concerns about how to use established minimal residual disease monitoring in the treatment of *NPM1*-mutant acute myeloid leukaemia (AML) following reduced intensity chemotherapy protocols for AML given as a result of the COVID-19 pandemic

In view of the coronavirus disease 2019 (COVID-19) pandemic and the predicted risk of severe infection in immunocompromised patients, chemotherapy protocols for patients with acute myeloid leukaemia (AML) have been modified in some patients to newer, less myelosuppressive regimens than standard induction chemotherapy. However, the modifications to treatment have occurred at such a considerable pace, due to the urgency of the pandemic, that optimal time points for measuring minimal residual disease (MRD) to assess disease response and monitor for relapse have not yet been established for the new regimens. Thus, decisions about duration of therapy and appropriate time points to intensify therapy prove very challenging.

The combination of the B-cell lymphoma 2 (BCL-2) inhibitor venetoclax and the hypomethylating agent azacitidine (Ven-Aza) has recently been introduced as a treatment option for patients with AML during the COVID-19 pandemic, instead of the standard more intensive chemotherapy regimen of daunorubicin and cytarabine. It has been approved by the National Institute for Health and Care Excellence[1] and was introduced in our institution on the 19 March 2020. The use of this combination of drugs in AML is based on evidence that it produces high rates of rapid and durable responses for patients who were not eligible for intensive chemotherapy.[2] In particular, AML with nucleophosmin-1 (*NPM1*) mutations is shown to be particularly responsive to this combination of treatment.[3,4] Moreover, Ven-Aza can be used to treat persistent or rising *NPM1* MRD levels after intensive induction chemotherapy.[5] This combination of drugs is also well tolerated[3,6] and has a lower rate of death than that expected with induction chemotherapy,[7] although to date there has not been a randomised trial to compare Ven-Aza directly with standard induction chemotherapy.