ABO Blood Type A Is Associated With Increased Risk of ARDS in Whites Following Both Major Trauma and Severe Sepsis

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Background: ABO glycosyltransferases catalyze antigen modifications on various glycans and glycoproteins and determine the ABO blood types. Blood type A has been associated with increased risk of vascular diseases and differential circulating levels of proteins related to inflammation and endothelial function. The objective of this study was to determine the association of ABO blood types with ARDS risk in patients with major trauma and severe sepsis.

Methods: We conducted prospective cohort studies in two populations at an urban tertiary referral, level I trauma center. Critically ill patients (n = 732) presenting after major trauma were followed for 5 days for ARDS development. Additionally, 976 medical patients with severe sepsis were followed for 5 days for ARDS. Multivariable logistic regression was used to adjust for confounders.

Results: ARDS developed in 197 of the 732 trauma patients (27%). Blood type A was associated with increased ARDS risk among whites (37% vs 24%; adjusted OR, 1.88; 95% CI, 1.14-3.12; $P = .014$), but not blacks (adjusted OR, 0.61; 95% CI, 0.33-1.13; $P = .114$). ARDS developed in 222 of the 976 patients with severe sepsis (23%). Blood type A was also associated with an increased ARDS risk among whites (31% vs 21%; adjusted OR, 1.67; 95% CI, 1.08-2.59; $P = .021$) but, again, not among blacks (adjusted OR, 1.17; 95% CI, 0.59-2.33; $P = .652$).

Conclusions: Blood type A is associated with an increased risk of ARDS in white patients with major trauma and severe sepsis. These results suggest a role for ABO glycans and glycosyltransferases in ARDS susceptibility.

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Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; ISS = injury severity score; MI = myocardial infarction; vWF = von Willebrand factor

ARDS is a syndrome of inflammation, endothelial dysfunction, alveolar capillary leak, and microthrombosis that occurs after various systemic insults.¹⁻³ ARDS is characterized by diffuse pulmonary edema and severe hypoxemia unrelated to clinical heart failure, affects an estimated 190,000 people in the United States annually, and carries an estimated mortality of 30% to 40%.^{4,5} ARDS develops in only a fraction of patients exposed to predisposing environmental insults, such as sepsis and trauma; therefore, individual risk factors contribute substantially to ARDS susceptibility.⁶⁻⁹

The ABO blood group system was first described > 100 years ago and is the most important blood group

system in transfusion medicine,¹⁰ but it is also believed to carry important functions in various human cells and systems. The ABO gene encodes a family of glycosyltransferases that catalyzes specific antigen modifications on various cell surfaces, including platelets and vascular endothelium, and results in the modified antigens on RBCs that categorize the ABO blood group.¹¹⁻¹³ ABO blood types have been reported to influence susceptibility to infection with malarial parasites, the Norwalk virus, and *Helicobacter pylori* bacteria,¹⁴⁻¹⁵ supporting the hypothesis that historical host-pathogen interactions have resulted in the blood group diversity seen in current populations.¹⁹

Large genome-wide association studies have identified polymorphisms in the *ABO* gene associated with an increased risk for inflammatory vascular diseases, including stroke, acute myocardial infarction (MI), and VTE.²⁰⁻²² Specifically, polymorphisms that result in the A glycosyltransferase or blood type A phenotype are associated with an increased risk of vascular diseases.²³ Additionally, *ABO* variants that define ABO blood types have been reported to be associated with circulating levels of molecules important in ARDS pathogenesis, including von Willebrand factor (vWF), factor VIII, soluble intercellular adhesion molecule-1, and selectins and with angiotensin-converting enzyme activity.²⁴⁻³²

The relationship between the activity of the ABO glycosyltransferases and the development of ARDS is unclear. The aim of this study was to test the global hypotheses that ABO blood types are associated with ARDS risk in two independent populations of patients with ARDS: those with major trauma and those with severe sepsis. Specifically, we hypothesized that blood type A, characterized by the A glycosyltransferase phenotype, is associated with an increased risk of ARDS in these two populations because this blood type was associated with an increased risk of MI and VTE in previous studies.²⁰⁻²³ Conversely, we hypothesize that blood type O, characterized by loss-of-function mutations resulting in a nonfunctional glycosyltransferase, will confer a decreased risk of ARDS. Some of these results have been presented previously in abstract form.^{33,34}

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Study Populations

The study populations comprised two independent cohorts of patients with different ARDS risk factors admitted to the Hospital of the University of Pennsylvania, an urban tertiary referral center and level I trauma center. The trauma cohort, comprising patients admitted through the ED to the surgical ICU, was screened prospectively for enrollment in a cohort study of ARDS after major trauma. Patients were enrolled from 1999 to 2002 and 2005 to 2010. Details of the cohort have been previously described.³⁵⁻³⁷ Subjects were included if they were aged > 13 years and had an injury severity score (ISS) ≥ 16 .³⁸ Subjects were excluded if they were discharged or died within 24 h of admission, had current or past evidence of congestive heart failure, had a recent MI, or suffered severe isolated head trauma. The Institutional Review Board of the University of Pennsylvania approved the study (Protocol #802428) with a waiver of informed consent in accordance with local and national guidelines.

The sepsis cohort enrolled hospitalized medical patients from either the ED or the medical ICU between 2008 and 2012 who met the American College of Chest Physicians consensus definition for severe sepsis.^{39,40} The consensus criteria were (1) two or more systemic inflammatory response syndrome criteria, (2) known or strongly suspected infection, and (3) evidence of organ dysfunction or shock. Exclusion criteria were lack of commitment to life-sustaining measures at time of enrollment, primary reason for admission unrelated to sepsis, and unwillingness to provide consent. The Institutional Review Board of the University of Pennsylvania approved the study (Protocol #808542) with a waiver of timely informed consent. Subjects or their surrogates were approached during their hospital stay for informed consent and could withdraw consent at any time.

Data Collection

Clinical and laboratory data were prospectively collected in both cohorts through chart extraction by trained research personnel and included long-term health information, trauma-related data, physiologic data, and therapies. ABO blood type was determined by standard RBC typing performed for clinical purposes before the receipt of transfused blood products. The ABO blood type was collected from blood bank records, allowing patients to be classified as blood type A, B, AB, and O.

Outcome Definitions

The primary outcome was the development of ARDS within the first 5 days of enrollment. Patients were classified as having ARDS on the basis of the Berlin Definition for mild, moderate, or severe ARDS while intubated and mechanically ventilated,⁴¹ which corresponds to the previous consensus definition for acute lung injury.⁵ The Berlin Definition includes acute onset bilateral infiltrates on chest radiograph consistent with pulmonary edema but not fully explained by cardiac failure or fluid overload and a $\text{Pao}_2/\text{Fio}_2 \leq 300$. Chest radiographs were reviewed by two physician-investigators blinded to all data and each other's interpretations, with adjudication if necessary as we have previously described.⁴² Chest radiographs were considered normal if both radiograph reviewers agreed that bilateral opacities consistent with pulmonary edema were unequivocally present. Patients were then classified using all arterial blood gas and chest radiograph data within a 24-h period for each of the first 5 days after enrollment.

Statistical Analysis

The unadjusted associations of ABO blood type and the development of ARDS were tested separately for each independent

cohort with Pearson χ^2 test. The primary analysis was for the comparison of patients with blood type A with those of all other blood types. The associations of clinical characteristics with ABO blood type and with ARDS risk were tested with Pearson χ^2 , Fisher exact, Student *t*, Wilcoxon rank sum, or Kruskal-Wallis test, as appropriate. Multivariable logistic regression models for the trauma cohort were then constructed, adjusting for the common ARDS risk factors of age, ISS, mechanism of injury (blunt or penetrating trauma), and units of RBCs transfused during resuscitation in the trauma cohort.⁴³ A trauma resuscitation protocol at our institution specified a recommended ratio of blood product transfusions, resulting in the collinearity of these variables in the cohort. Therefore, only RBC transfusion was used in the multivariable models.³⁷ History of diabetes was also included in the multivariable models because diabetes is reported to be protective for ARDS and has been associated with the ABO blood group.^{44,45} Furthermore, additional clinical variables, including alcohol use, abstracted from patients' admission history; history of hypertension; and initial creatinine level were assessed as potential confounders. Additional potential confounders were only included in the final multivariable model if they altered the unadjusted OR for the association between ABO blood type and ARDS by > 10% in bivariate analysis.⁴⁶ We also performed a stratified analysis by mechanism of injury given potential pathophysiologic differences between blunt and penetrating trauma. In the sepsis cohort, multivariable logistic regression models were constructed, adjusting for age, pulmonary vs extrapulmonary source of sepsis, history of diabetes, units of RBCs transfused on hospital days 0 to 3, and the APACHE (Acute Physiology and Chronic Health Evaluation) III score without the blood gas components because they are included in the ARDS outcome. Additional medical history variables, including alcohol use, congestive heart failure, and chronic kidney disease, were considered potential confounders and were included in the final multivariable models if they met the same criteria presented for the trauma cohort. Stratified analyses by reported race was performed given the substantial differences in allele distributions and divergent genetic background between racial groups.⁴⁷ Additionally, effect modification by reported race was evaluated using the likelihood ratio test. Statistical analyses were performed with Stata/IC 12.0 (StataCorp LP).

RESULTS

Major Trauma Cohort

In total, ABO blood type was available in 732 of 768 enrolled trauma subjects (95%) (Fig 1A). Subjects had a median age of 35 years and a median ISS of 24 and were approximately equally split between black and white race. The mechanism of trauma was blunt in 69% of the subjects. Within the first 5 days of admission, ARDS developed in 197 of the 732 subjects (27%; 95% CI, 24%-30%). Baseline characteristics of those with and without ARDS are presented in Table 1. Subjects with ARDS had a higher ISS, were more likely to have a blunt mechanism of injury, and received more transfused units of RBCs and fresh frozen plasma, consistent with previously identified risk factors.^{48,49}

Table 2 provides the frequencies of the ABO blood types separately in white and black subjects. These distributions were not significantly different from the reported distributions by racial groups in the United

States.⁴⁷ The distributions of baseline characteristics of subjects based on ABO blood type are provided in e-Table 1. All clinical variables appeared to be evenly distributed across the blood types with the exception of race, mechanism of trauma, and history of hypertension. White subjects were more likely to experience a blunt trauma mechanism (95%) than black subjects (43%). There were no statistically different distributions of all other clinic variables across blood types. Alcohol use, history of hypertension, and renal impairment as measured by initial creatinine level did not confound the relationship between blood type A and ARDS and, therefore, were not included in the final adjusted models.

Among white subjects, blood type A was associated with increased ARDS risk compared with the non-A blood type (adjusted OR, 1.88; 95% CI, 1.14-3.12; *P* = .014) (Fig 2A, Table 3). Among black subjects, however, blood type A was not associated with increased ARDS risk compared with non-A blood type (adjusted OR, 0.61; 95% CI, 0.33-1.13; *P* = .114) (Fig 2B). A significant effect modification by race was present (*P* = .01). In analyses stratified by mechanism of injury, OR estimates among black subjects were similar for blunt (adjusted OR, 0.58; 95% CI, 0.22-1.49; *P* = .255) and penetrating (adjusted OR, 0.55; 95% CI, 0.23-1.33; *P* = .182) injury. White subjects with blunt trauma had a similar OR to the overall white population (adjusted OR, 1.88; 95% CI, 1.13-3.14; *P* = .016). Among white subjects, insufficient numbers of patients (*n* = 15) suffered primarily penetrating trauma to conduct stratified analyses.

Severe Sepsis Cohort

ABO blood type was available in 973 of 1,062 subjects (92%) enrolled in the severe sepsis cohort (Fig 1B). Subjects had a median age of 59 years and a median APACHE III score of 53. The source of sepsis was pulmonary in 33% of subjects, and 38% met criteria for septic shock. Fifty-seven percent were white, and 37% were black. Within the first 5 days of hospital admission, ARDS developed in 222 of 973 subjects (23%; 95% CI, 20%-26%). Baseline characteristics of subjects with and without ARDS are provided in Table 4. Subjects with ARDS were older and had a higher APACHE III score, more RBC transfusions, more shock, and more frequently a pulmonary source than those without ARDS. The frequency of each ABO blood type among the sepsis cohort is provided in Table 2 and was similar to the reported distributions in the US population.⁴⁷ The distributions of baseline characteristics by ABO blood type are provided in e-Table 2 and were not significantly different by blood type with the exception of race. History of alcohol use, congestive heart failure, and chronic

FIGURE 1. Screening and enrollment. A, Trauma cohort. B, Sepsis cohort.

kidney disease did not confound the relationship between blood type A and ARDS and, therefore, were not included in the final adjusted models.

Table 1—Trauma Cohort Demographics and Clinical Characteristics by ARDS Diagnosis

Clinical Variable	ARDS	Non-ARDS	P Value
Subjects	197 (26.9)	535 (73.1)	...
Demographic			
Race			.634
Black	47	52	
White	51	45	
Asian	2	2	
Other	0	1	
Age	37 (23-50)	34 (24-48)	.800
Male sex	78	77	.739
Severity and mechanism			
Mechanism of trauma			.050
Blunt	74	67	
Penetrating	26	33	
ISS	25 (20-29)	22 (19-29)	< .001
Medical history			
Diabetes	7	5	.165
Alcohol use	14	18	.217
Hypertension	16	15	.774
Initial creatinine level	1.1 (0.9-1.3)	1.1 (0.9-1.3)	.625
Blood transfusions, units			
RBCs	2 (0-7)	0 (0-4)	< .001
Unmatched PRBCs	0 (0-5)	0 (0-2)	.001
Platelets	0 (0-0)	0 (0-0)	.159
FFP	1 (0-4)	0 (0-2)	< .001

Data are presented as No. (%), %, or median (interquartile range). Distributions of continuous variables were compared using Wilcoxon rank sum test, and categorical variables were compared using Pearson χ^2 or Fisher exact test. Blood transfusion data include all blood transfusions received in the ED or operating room before ICU admission. FFP = fresh frozen plasma; ISS = injury severity score; PRBC = packed RBC.

Among white subjects, blood type A was similarly associated with an increased risk of ARDS compared with non-A blood type (adjusted OR, 1.67; 95% CI, 1.08-2.59; $P = .021$) (Fig 3A, Table 5). As in the trauma population, black subjects with severe sepsis demonstrated no association between blood type A and ARDS risk (adjusted OR, 1.17; 95% CI, 0.59-2.33; $P = .652$) (Fig 3B). In the sepsis cohort, statistically significant effect modification by race was not present ($P = .44$).

DISCUSSION

We demonstrate that the ABO blood group is associated with altered risk of ARDS among whites, independent of blood transfusion and other confounding variables, in two independent cohorts of critically ill patients. The increased risk of ARDS among subjects with blood type A is consistent with the risk patterns observed in other inflammatory vascular diseases, including MI and VTE.^{20,21} To our knowledge, the present study is the first to report an association between ABO blood types and ARDS risk, providing evidence for an important role of ABO glycobiology in ARDS pathogenesis. We hypothesized that the ABO antigens play important roles in inflammation, coagulation, and endothelial function, resulting in the altered ARDS risk by ABO blood type.

Several potential mechanisms may explain the increased ARDS risk among patients with blood type A. The ABO glycosyltransferases have been recognized as modifiers of carbohydrate antigens on diverse glycoproteins.¹³ In particular, several previous studies

Table 2—Frequency of ABO Blood Types by Race

Blood Type	Black			White		
	Trauma Cohort	Sepsis Cohort	US Population	Trauma Cohort	Sepsis Cohort	US Population
A	26	28	26	41	39	40
AB	6	5	4	6	5	4
B	21	20	20	10	12	11
O	47	47	50	43	44	45

Data are presented as %. ABO blood types were determined by blood bank RBC testing for clinical purposes and were extracted from the medical chart. The frequencies for the US population are estimated based on previous literature.⁴⁷

demonstrated an association of circulating vWF, a glycoprotein involved in hemostasis and coagulation, with the development of ARDS after various insults.³⁰⁻³² The ABO glycosyltransferase is known to differentially modify oligosaccharide chains of vWF based on ABO blood type, which is believed to alter the metabolism of the vWF molecule by differential cleavage by ADAMTS13, accounting for up to 35% of the variance in vWF levels in healthy control subjects.^{50,51} These effects of ABO glycosyltransferase activity on vWF structure have been hypothesized to

explain some of the association between ABO blood type and vascular diseases⁵² and may explain a portion of associations between ABO blood type and ARDS. Future studies are needed to explore the potential role of vWF metabolism among other biologic pathways in mediating a relationship between blood type A and ARDS risk.

The identified association between the ABO blood group and ARDS is not consistent between white and black subjects, particularly among trauma patients where statistical evidence of effect modification by race was present. There are several potential explanations for this seemingly paradoxical finding. First, the finding may be due to the demographics and exposures of the cohort. Within the trauma cohort, whites nearly universally suffered a blunt mechanism of trauma, whereas blacks suffered both blunt and penetrating mechanisms of trauma. Given the significant differences in injury sustained, there is potentially a divergent gene-environment interaction that may explain some of the different results seen between the racial groups. However, in subgroup analyses among individuals of African descent, the estimates of association were very similar in those who suffered blunt and penetrating trauma, arguing against this explanation for the racial difference. A second possible explanation for the divergent results across racial groups is a significant unidentified genetic or environmental modifier that is different between the races. For example, a nonsense mutation in the secretor gene *FUT2* is known to regulate the expression of ABO antigens in tissues and body fluids other than RBCs and has different distributions among racial groups.^{53,54} Additionally, a polymorphism in the *DARC* gene resulting in a lack of the Duffy glycoprotein on RBCs is nearly exclusively found in individuals of African descent and has been associated with ARDS outcomes.⁵⁵ Genes involved in ABO antigen alterations or affecting overlapping mechanisms in the human body have the potential to alter the ancestry-specific association between ABO blood types and ARDS. Future studies in larger populations may assess these and other important genetic modifiers.

This study has several limitations. First, as is the case for single-center cohort studies, generalizability

FIGURE 2. Frequency of ARDS by ABO blood type in trauma. A, White (n = 335) subjects. B, Black (n = 370) subjects. Numbers at the top of each bar represent the total number of patients with each blood type. P values determined by unadjusted Pearson χ^2 test.

Table 3—Association of Blood Type A With ARDS Risk in Trauma Patients

Population	No.	ARDS, %		Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
		Type A	Non-A Type				
Black	335	18	27	0.60 (0.34-1.07)	.085	0.61 (0.33-1.13)	.114
White	370	37	24	1.87 (1.16-3.01)	.010	1.88 (1.14-3.13)	.014

ORs and *P* values were determined for the comparison of blood type A with all other blood types through logistic regression. Adjusted for age, ISS, mechanism of injury, history of diabetes, and units of PRBCs. See Table 1 legend for expansion of abbreviations.

may be limited. However, the results are consistent with the risk pattern of prior associations of blood type A with other inflammatory vascular syndromes, and the association was similar for two distinct ARDS risk factors. Second, although representing two large cohorts of patients, the analyses were somewhat underpowered to evaluate subgroups stratified by race. This was particularly true for the less common blood types B and AB. Therefore, we may have failed to identify further important associations, and negative results should be interpreted with caution. We were also not able to examine associations among subjects of other racial groups because of small sample sizes. Third, we were able to evaluate for confounding by medical history variables that have the potential to be associated with both ABO blood types and ARDS, including diabetes; however, the medical history variables were

limited to history recorded in the medical record. For example, unrecognized alcohol use and underlying coronary artery disease were not definitively assessed. Additionally, we were unable to assess the effects of ABO blood type on plasma biomarker levels (eg, vWF) because of the unavailability of sufficient banked plasma. Fourth, ascertainment bias may have influenced the findings if the ABO blood types are associated with altered overall risk of sepsis, trauma, or critical illness. However, the frequencies of the blood types in both cohorts are remarkably similar to those in the general US population, making this form of bias unlikely. Finally, complex gene-gene and gene-environment interactions that may affect the association between the ABO blood types and ARDS were

Table 4—Sepsis Cohort Demographics and Clinical Characteristics by ARDS Diagnosis

Clinical Variable	ARDS	Non-ARDS	P Value
Subjects	222 (22.8)	751 (77.2)	...
Demographics			
Race			.006
Black	30	40	
White	61	55	
Asian	3	2	
Other	6	3	
Age	61 (52-69)	58 (47-68)	.008
Male sex	41	43	.546
Severity of illness and source			
APACHE III	54 (38-87)	53 (37-70)	.005
Pulmonary source	54	27	<.001
Shock	72	28	<.001
Medical history			
Diabetes	29	30	.691
Alcohol use	15	22	.014
Heart failure	16	12	.107
CKD	13	18	.043
Blood transfusions			
RBCs, units	0 (0-2)	0 (0-0)	<.001

Data are presented as No. (%), %, or median (interquartile ranges). Distributions of continuous variables were compared using Wilcoxon rank sum test, and categorical variables were compared using Pearson χ^2 or Fisher exact test. Blood transfusion data include all blood transfusions received within the first 3 hospital days. APACHE = Acute Physiology and Chronic Health Evaluation; CKD = chronic kidney disease.

FIGURE 3. Frequency of ARDS by ABO blood type in severe sepsis. A, White (n = 544) subjects. B, Black (n = 341) subjects. Numbers at the top of each bar represent the total number of patients with each blood type. *P* values determined by unadjusted Pearson χ^2 test.

Table 5—Association of Blood Type A With ARDS Risk in Patients With Sepsis

Population	No.	ARDS, %		Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
		Type A	Non-A Type				
Black	358	22	17	1.39 (0.78-2.46)	.266	1.17 (0.59-2.33)	.652
White	544	31	21	1.70 (1.14-2.52)	.009	1.67 (1.08-2.59)	.021

ORs and *P* values were determined for the comparison of blood type A with all other blood types through logistic regression. Adjusted for age, APACHE III score without arterial blood gas components, pulmonary vs extrapulmonary source of sepsis, history of diabetes, and units of PRBCs. See Table 1 and 4 legends for expansion of abbreviations.

not fully evaluated in this study because of sample size limitations.

CONCLUSIONS

Given the increasingly recognized roles of ABO glycosyltransferases in various inflammatory vascular diseases, we hypothesized that the ABO blood types would confer different risks of ARDS among critically ill populations. Blood type A was associated with increased risk of ARDS in critically ill patients with trauma and sepsis. This association identifies a novel mechanistic risk factor for ARDS and implicates ABO glycobiology in the pathogenesis of ARDS.

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Dr J. P. Reilly: contributed to the study design, patient enrollment, data collection, interpretation of results, statistical analysis, writing of the manuscript, and review and editing of the manuscript.

Dr Meyer: contributed to the study design, patient enrollment, data collection, interpretation of results, and review and editing of the manuscript.

Dr Shashaty: contributed to the study design, patient enrollment, data collection, interpretation of results, and review and editing of the manuscript.

Dr Feng: contributed to the study design, interpretation of results, statistical analysis, and review and editing of the manuscript.

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