ABO Blood Type and ARDS

To the Editor:

I read with great interest the article by Reilly et al¹ in a recent issue of CHEST (April 2014). In this article, the authors prospectively studied the association of ABO blood types with ARDS risk in patients with major trauma and severe sepsis. The results were very interesting; however, a few pertinent points should be analyzed before these results are accepted into clinical practice.

First, the authors did not hypothesize that sex may modify the association between ABO blood type and ARDS risk. Previous studies found that women were more likely to develop ARDS compared with men,² whereas sex is not associated with ABO blood type distribution. Thus, it might be reasonable to hypothesize that the effects of ABO blood type on ARDS differ between men and women. Because the authors had these data, more input could have been gained by carrying out additional analysis to investigate whether sex is an effect modifier.

Second, because the study used a prospective study design, which meant that the interested outcome (ARDS) occurred after the exposure, relative risk should have been reported using log-linear regression models rather than the reported OR by logistic regression models.³ Although an OR can be converted to relative risk, it may have been more informative and intuitive to report relative risk for this prospective study.

Last, the author considered diabetes, alcohol use, and chronic heart failure, among others, as potential confounders in the multivariable models. However, several criteria should be met for a variable to be identified as a potential confounder. One of the criteria is that the potential variable should not be in the pathway between exposure (ABO blood type) and outcome (ARDS). If it is in the pathway, this variable should be considered as a mediator, which cannot be adjusted in the models when total effect (direct and indirect effect) of ABO blood type on ARDS is the main research question. In this study, some variables, such as diabetes and chronic heart failure,⁴ may lie in the pathway between ABO blood type and ARDS, so they should not be adjusted in the final analysis. The authors can choose to draw a directed acyclic graph⁵ to select which variables should be included in the models.

I anticipate that the effect of ABO blood type on ARDS would be stronger than reported in the article.

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REFERENCES


Response

To the Editor:

We thank Dr Zhan for his interest in our recent article in CHEST¹ and for providing the opportunity to discuss our findings of an association between ABO blood type A and increased risk of ARDS in the critically ill.¹ First, Dr Zhan’s suggestion that sex may modify the association between ABO blood type and ARDS risk is reasonable because previous research has identified sex differences in the same soluble glycoproteins that are associated with both ABO blood types and ARDS.² However, we did not detect effect modification by sex in either of our populations. Second, we agree that accurate estimations of adjusted relative risks (ARRs) can be obtained given the prospective cohort design of our study. Using postestimation marginal analysis, the adjusted logistic regression

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models can be used to estimate ARRs with accurate CIs.\textsuperscript{3} Based on this approach, the ARRs for the association of blood type A and ARDS among subjects of European descent are 1.52 (95% CI, 1.09-2.13; \( P = .013 \)) in the trauma cohort and 1.40 (95% CI, 1.05-1.85; \( P = .021 \)) in the sepsis cohort. Log-linear regression models, another method of estimating ARRs assuming a Poisson distribution,\textsuperscript{4} result in nearly identical ARR estimates, 1.52 (95% CI, 1.09-2.12; \( P = .014 \)) in the trauma cohort and 1.39 (95% CI, 1.04-1.86; \( P = .027 \)) in the sepsis cohort.

Dr Zhan also raises the concern that diabetes, alcohol use, and chronic heart failure may lie within the causal pathway of the ABO and ARDS relationship and, therefore, should not be included in adjusted analyses. Of these three covariates, we included only diabetes in the final multivariable models, because ABO blood types have been associated with risk of diabetes in prior studies.\textsuperscript{3} Removing diabetes from the logistic regression model does not significantly alter any effect estimates of the association of blood type A and ARDS (ARR 1.53 in trauma, 1.39 in sepsis), suggesting that diabetes is neither a confounder nor a causal mediator. This was also true when all three variables were either included or excluded from multivariable models. Therefore, although ABO blood types have been associated with risk of vascular disease and diabetes,\textsuperscript{5,6} we do not believe the increased risk of ARDS is mediated through these diseases. ARDS develops in the setting of significant environmental insult (eg, trauma or sepsis), resulting in dramatic activation of endothelium and the inflammatory system. Endothelial-derived glycoproteins linked to ABO blood type, including von Willebrand factor, ICAM-1, and the selectins, are released and/or upregulated by critical illness and may provide the mechanistic link between ABO blood type and ARDS.

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