Race, ABO blood group, and venous thromboembolism risk: not black and white

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BACKGROUND: The rate of venous thromboembolism (VTE) has been reported to be higher in blacks compared to whites. Non-O blood groups have also been associated with a significantly higher VTE risk. Given that a higher proportion of blacks have O blood group, one might have expected that black individuals would have fewer VTEs.

STUDY DESIGN AND METHODS: In this study, we analyzed race, sex, age, ABO or Rh blood group, and VTE risk in 60,982 black and white patients admitted over a span of 10 years.

RESULTS: The overall occurrence of VTEs was 7.6%, higher in males (8.7% males vs. 7.2% females), higher in non-O blood groups (8.5% non-O vs. 6.9% O blood group), and increased with age (5.8% <65 years, 11.3% ≥65 years). No difference in VTE rate was noted with Rh antigen positivity. When stratified by age, VTE rate was consistently higher in blacks and non-O blood groups. No difference was detected among the various non-O blood groups. To assess the potential confounder of comorbidities, we stratified patients according to Charlson comorbidity score. In a subgroup of healthy patients with age-independent Charlson comorbidity scores of 0 (n = 28,387), blacks still had an increased VTE risk and this risk was still higher with increasing age and in those with non-O blood groups.

CONCLUSION: We conclude that black race and non-O blood groups have increased VTE risk when stratified for age and that associated comorbidities do not explain these differences.

Venous thromboembolism (VTE) is a complex phenomenon influenced by multiple risk factors, which include cancer, trauma, surgery, prolonged immobility, and certain medical conditions.[1,2] VTE risk is generally acknowledged to increase as age advances.[1,2] Sex associations are less clear: male sex has been shown to be an independent risk factor for VTE in some studies but not in others.[3-8] Even less clear is the issue of increased risk due to race. VTE prevalence has been reported to be higher in blacks compared to whites.[1,3,4,8-12] However, whether increased morbidity in the different at-risk populations accounts for the perceived racial or ethnic differences has not been studied in detail.

While its exact function remains unknown, ABO blood group has been linked, perhaps via von Willebrand factor (VWF), to various medical conditions such as VTE,[13,14] peptic ulcer disease,[15] and pancreatic cancer.[16] Most previous studies have found that individuals with O blood group carry a lower VTE risk compared to other

ABBREVIATIONS: CLG = Clinical Looking Glass; VTE(s) = venous thromboembolism(s).

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non-O blood groups, suggesting that O blood group is protective against VTE.[13,17-21] As O blood group is more prevalent in blacks than in whites,[22] it is paradoxical to find that VTE prevalence has been observed to be higher in blacks than whites. One caveat shared by the majority of previous ABO blood group studies and VTE risk analyses is the fact that these studies were typically limited to whites and included only a small number of blacks, if at all.[10,11,14,17] It is unknown whether the concept of a protective effect of O blood group and its relationship to VWF extends from these studies to the black population, who, despite the increased prevalence of O blood group, have higher baseline Factor (F)VIII and VWF levels than whites.[23]

There is also little known on whether the Rh blood group, which may function as an membrane transport protein with no known interaction with coagulation factors, has any effect on VTE risk.[24] To assess how these factors may affect clinical outcome, we conducted a study to investigate the relative importance of blood group, race, age, sex, and comorbidity on VTE risk.

MATERIALS AND METHODS

Study population

All adult patients (age ≥18 years) who self-identified as non-Hispanic white or non-Hispanic black and had been admitted to Montefiore Medical Center between January 1, 2000, and December 31, 2009, were included in the current study. Other demographic groups, that is, Asian, Hispanic, and those with multiple or unidentified ethnic backgrounds, were excluded.

Data collection

Clinical Looking Glass (CLG) is an interactive software application developed at Montefiore Medical Center that integrates demographic, clinical, and administrative data sets and allows them to be reproduced in a programmable format for statistical access. We utilized CLG to screen the study population defined above for information regarding age, sex, race, and ABO or Rh blood groups. VTE rate was determined using ICD-9 codes either as the primary or secondary diagnosis. We did not differentiate between deep vein thrombosis and pulmonary embolism and they will be referred to collectively as VTE.

Comorbidity information on our population was collected separately using the Charlson comorbidity scoring index.[25] The Charlson index considers 22 disease conditions and scores them according to severity, providing a raw Charlson index. These can be taken into consideration with age-related risk, providing a combined Charlson score index with discrete percent 10-year survival estimates. Patients with a Charlson score of 0 have an estimated 10-year survival of 98.3%, Charlson scores of 1 and 2 have estimated 10-year survivals of 95.9 and 90.2%, respectively; scores of 3 to 5 have estimated 10-year survivals of 77.5, 53.4, and 21.4%, respectively; scores of 6 have an estimated 10-year survival of 2.2%; while scores at least 7 have a less than 1% estimated 10-year survival.

Statistical analysis

Only patients who had ABO or Rh blood group information available were included for further analysis. Data were generated by CLG and transferred to a computer spreadsheet (Microsoft Excel, Microsoft Corp., Redmond, WA). Demographic characteristics, blood group analyses, Charlson comorbidity index, and VTE rates between groups were compared by chi-square analysis of proportions. Two tailed t tests and chi-square analysis were used to assess the effect of age as appropriate. Odds ratios (OR) of VTE for O versus non-O blood groups were estimated with logistic regression models within age-race-sex subgroups. To limit the impact of comorbidity, analyses were repeated in the subgroup of individuals with Charlson comorbidity score of 0 (no comorbidities). Statistical analyses were performed with computer software (SPSS 18, SPSS, Inc., Chicago, IL) and a two-tailed alpha of 0.05 was used to denote significance.

RESULTS

A total of 60,982 non-Hispanic patients were included in the study; 22,088 of these self-identified as white and 38,894 self-identified as black. The main demographic characteristics of the black and white patient sample are detailed in Table 1. In both racial groups, females constituted the majority, although black females were a much larger proportion of their racial cohort than were white females. The black population was significantly younger than the white. Racial distribution of ABO blood group in

TABLE 1. Characteristics of study population

Characteristic	Black	White	p value
Total	38,894	22,088	
Female (%)	71.4	56.3	<0.001
Age (years), mean ± SD	49.4 ± 19.4	62.9 ± 19.4	<0.001
ABO blood group (%)			<0.001
A	25.2	38.1	
B	20.4	13.8	
AB	4.2	5.1	
O	50.2	43.0	
Rh blood group (%)			<0.001
D+	93.5	87.5	
D–	6.5	12.5	

TABLE 2. VTE rate (% of study variable and hazard ratio [HR])

Variable	VTE (%)	HR	p value
Overall	7.7 (4,696/60,982)		
Race			
White	7.80	1.01	0.61
Black	7.70	1.00	
Sex			
Female	7.20	0.93	<0.001
Male	8.70	1.13	
Age group (years)			
18-64	5.80	0.75	<0.001
≥65	11.30	1.47	
ABO blood group			
Non-O	8.50	1.10	<0.001
O	6.90	0.90	

our study was similar to what has been previously reported: blacks have a higher proportion of O and B blood groups, and a lower proportion of A and AB blood groups, than whites.[22] However, our study identified fewer patients with D– blood group than have been previously reported.[22]

A total of 4696 cases of VTE were identified in the study (Table 2), which accounted for 7.7% of total population. Blacks made up 63.8% of the general population and 63.4% of the VTE population. There was no meaningful difference in the overall VTE rate between blacks and whites and between those patients with D+ and those with D– blood group. When groups were stratified by age, however, black race was significantly associated with increased VTE. Overall VTE rate was higher in males than females, increased with age, and was higher in those with non-O blood groups than those with O blood group for both races. The difference in VTE rate among different non-O blood groups was not significant (data not shown) and therefore they will be referred collectively as non-O blood groups for the purpose of comparison.

Because of the wide age and sex disparity, we reanalyzed our data stratified for these factors, as depicted in Fig. 1. Within each matched age-race-sex group, patients with non-O blood groups were significantly associated with a higher VTE rate compared to patients with O blood group (all at $p < 0.001$). When further analyzed for the healthy subgroup of patients (age-independent Charlson index of 0), we found similar trends but significance was achieved only selected populations: male and female blacks younger than 65 (both at $p < 0.001$) and white females younger than 65 ($p = 0.03$). Sex data were less consistent: Male sex was associated with a significantly higher VTE risk only in the younger cohort (Fig. 1).

As expected, VTE rate increased with increasing Charlson scores, regardless of race, sex, or ABO blood group (Table 3). Within each comorbidity group, VTE rate was still higher for those with non-O blood groups.

We performed logistic regression analyses to evaluate the relative contributions of each risk factor. We found

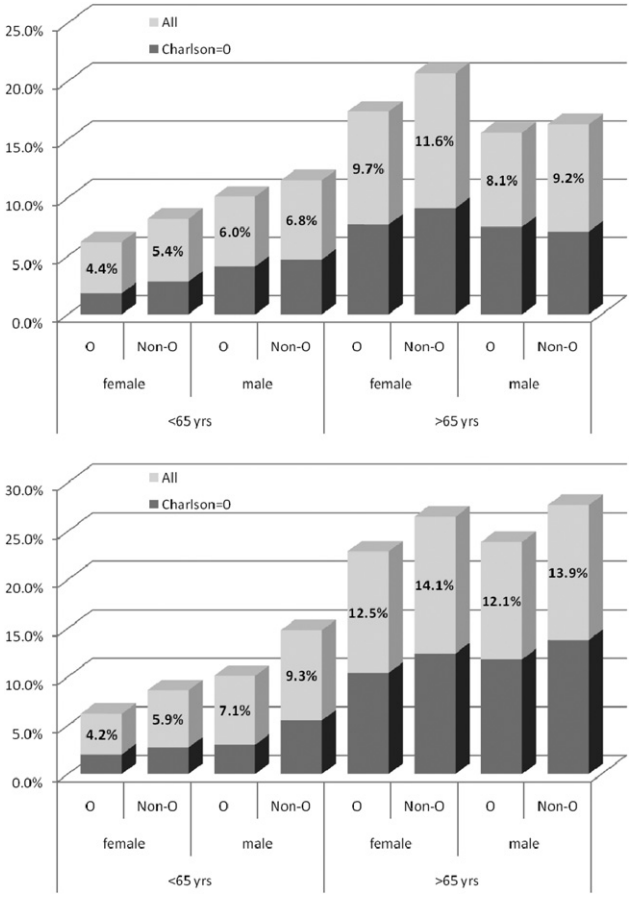

Fig. 1. VTE rates in O and non-O blood groups according to age, sex, and Charlson score. (Top) Whites; (bottom) blacks. All numbered comparisons: $p < 0.001$.

that in patients younger than 65 years, male sex appeared to be the most important risk factor, followed by non-O blood group, while black race appeared to be the least important factor. In contrast, in patients aged 65 years or older, black race appeared to be the most important risk factor, followed by non-O blood group, while male sex appeared to be protective (Table 4).

DISCUSSION

The primary goal of this study was to investigate whether O blood group is protective against VTE in the black population in a role similar to what has been demonstrated for the white population. While the relationship between ABO blood groups and VTE risk has been investigated quite extensively, the role of race remains elusive, as most previous studies have primarily focused on the white population.[13,17-21] Our very large patient population demonstrated that our white and black populations had very different demographics. It is necessary to stratify these groups to ensure that the VTE differences are not secondary to confounding variables such as age, sex, and comor-

TABLE 3. VTE rate according to age-dependent Charlson score

Variable	VTE rate (%)			
	Overall	Charlson ≤2	Charlson 3-5	Charlson ≥6
Race				
White	7.7	4	9.4*	11.4*
Black	7.8	4.4	11.5*	14.9*
Sex				
Female	7.2*	3.7*	11.2*	13.6
Male	8.7*	5.8*	9.5*	12.9
Blood group				
O	6.9*	3.6*	9.6*	12.8
Non-O	8.5*	4.9*	11.3*	13.7

* Significance ($p < 0.01$).

TABLE 4. Logistic regression analysis for VTE risk

Age group	Risk factors	OR	(95% CI)
<65 years	Male sex	1.57	(1.44-1.72)
	Non-O blood group	1.34	(1.23-1.46)
	Black race	1.16	(1.05-1.28)
≥65 years	Black race	1.39	(1.27-1.51)
	Non-O blood group	1.18	(1.08-1.28)
	Male sex	0.88	(0.80-0.96)

bidities. With the advantage of a huge database, we have been able to demonstrate that significant differences in VTE rate for O and non-O blood group hold for the black population and that this is an independent risk factor in blacks.

While there is no conclusive explanation on how ABO blood group influences VTE, there is evidence that the effect may be mediated by ABO blood group antigenic determinants expressed on both the N- and the O-linked carbohydrate structures of VWF that appear to influence clearance rate of VWF.[26,27] As the half-life of VWF is longer in those with non-O blood groups, circulating levels of VWF and FVIII, which are known risk factors for VTE, tend to be higher in those with non-O blood groups than those with O blood group.[28] On the other hand, race also plays a role in determining the level of FVIII: despite a higher proportion of O blood group,[22] blacks generally have a higher level of FVIII and VWF than whites.[29] Since the association of lower FVIII and VWF levels with O blood group may be the mechanism whereby O blood group plays a protective role, we were uncertain whether the protective effect of O blood group would still be present.

The medical and cultural definitions of race are unclear and changing. We chose to use the current recommended definition of self-identification rather than "ancestral" markers since it is uncertain at this juncture whether it is genes,[30-32] phenotype, or associated cultures that underlie putative associations. We found no meaningful difference in the initial crude VTE rate between blacks and whites, but on closer scrutiny, this appears to be due to confounding effects from the different age and sex composition between the white and black populations. The Bronx, as is true of many inner-city areas, retains an elderly white population while becoming home to a newer and mostly younger black population. There was also a higher proportion of females in both groups but especially in the black cohort. This may reflect the greater utilization of medical care by women.[33] We also stratified for Charlson score since we were concerned that differences in obesity, diabetes, and various comorbidities between blacks and whites might confound any observed relationship of race with VTE. By examining VTE rate in a subgroup of patients whose age-independent Charlson score was 0 and was presumed to be otherwise healthy, we tried to control for this to some extent. In this smaller group of patients, we found a trend in VTE rate differences similar to that of the general patient population, suggesting that these differences cannot be explained by comorbidity alone.

Our study finds non-O blood groups are associated with higher VTE risk independent of comorbidity. When examined within black race, we found, similar to what has been reported for whites, that the VTE rate in blacks was consistently higher in those with non-O blood groups than in those with O blood group, suggesting that O blood group may also be protective against VTE in blacks. When further stratified by age and sex, associations with O blood group remained significant, suggesting that O blood group may be a protective factor against VTE independent of age and sex.

As a retrospective study, this study is subject to the usual limitations. Our study focused on an inpatient population and relied on ICD-9 coding diagnoses and we did not differentiate provoked versus idiopathic VTE. Additionally, since this study examined overall rate, we did not include any recurrent VTE after the initial captured VTE. However, these caveats were true for all cohorts analyzed. We did not have access to VWF or FVIII data so we could not examine whether the levels of these factors could account for some of our observations. We provide evidence of associations, not causality. VTE is a complex process influenced and impacted by multiple hereditary and acquired risk factors. Our study provides some insight into how these factors may interact to determine individual risk profile.

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CONFLICT OF INTEREST

The authors declare no conflict of interest or financial involvement in the research, analysis or preparation of this manuscript.

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