Association of ABO Blood Group with Delayed Cerebral Ischemia and Clinical Outcomes Following Aneurysmal Subarachnoid Hemorrhage in Pakistan

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Abstract

Background The ABO blood type, due to its various hemostaseologic properties, has been associated with several vascular diseases, including aneurysmal subarachnoid hemorrhage (aSAH). However, the role of ABO blood type in delayed cerebral ischemia (DCI) onset and other clinical outcomes after aSAH is largely unexplored. This study aimed to investigate the association between ABO blood type and outcomes after aSAH, primarily DCI.

Methods A retrospective analysis was made on the data collected from 175 aSAH patients at a tertiary supraregional neurosurgery department over 5 years. Socio-demographic factors, clinical variables (DCI, mFG, WFNS grade, and Glasgow Outcome Scale at discharge), EVD placement, and aneurysm size were analyzed for their association with ABO blood type.

Keywords
► ABO blood group
► subarachnoid hemorrhage
► cerebral vasospasm
► delayed cerebral ischemia
► Pakistan

Results DCI was reported in 25% of patients with 'O' blood type and 9.6% with 'non-O' blood type. A stepwise logistic regression model showed that after adjusting for BMI, mFG, WFNS grade, and EVD placement, 'O' type blood group was an independent risk factor for DCI, greatly increasing the risk of DCI as compared to 'non-O' type groups (OR = 3.27, 95% CI: 1.21–8.82).

Conclusion This study provides evidence that individuals with 'O' blood type may have a higher risk of DCI onset after aSAH. However, further studies are essential to address the limitations of our work and confirm our findings.

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Introduction

Subarachnoid hemorrhage (SAH) refers to the extravasation of blood into the subarachnoid space between the arachnoid membrane and the pia mater, which normally contains cerebrospinal fluid. In 2010, the crude global incidence of SAH was 6.1 per 100,000 person-years.[1] Even though the mortality rate for SAH has dropped from 50% to 35% over time,[2] it is still considered a life-threatening condition and a neurological emergency.

Ruptured intracranial aneurysms (aSAH) account for approximately 80% of SAH cases.[3] aSAH has a mortality rate of 25 to 50%, and half of those who survive, suffer from long-term neuropsychological effects and decreased quality of life.[4] Cerebral vasospasm after an interventional or surgical procedure to secure the aneurysm leads to delayed cerebral ischemia (DCI), which is the primary source of this morbidity and mortality in patients of aSAH. Risk factors for DCI may include being female, a Hunt and Hess grade of 4 to 5, modified Fisher grade (mFG), and a World Federation of Neurosurgical Societies grade of IV to V.[5,6] Smoking, pre-existing hyperglycemia, pre-existing hydrocephalus, early systematic inflammatory syndrome, a history of diabetes mellitus, and procedure- and patient-related factors such as medication on admission, postoperative steroid use, and patient age have been previously assessed as predictors of vasospasm.[7,8]

In addition to these factors, the ABO blood group system may also have a role in the onset of DCI. Ever since ABO blood groups were discovered in the early 1900s, various associations between blood type and diseases such as cancer, cardiovascular diseases, hematologic disorders, metabolic disorders, cognitive disorders, and circulatory diseases have been found,[9] and this is attributed to the variation in hemostaseologic properties of all four blood group subtypes. Plasma vWF levels are approximately 25% lower in O individuals than non-O individuals,[10] which may lead to excessive bleeding as vWF is crucial for the action of coagulation factor VII. Data also show that SAH, followed by vasospasm, resulted in a 40% decrease in NO secretion by eNOS.[11] NO works essentially as a vasodilator relaxing the smooth muscle and inhibiting platelet aggregation, and is, therefore, significant for maintaining the cerebrovascular tone. A possible relationship between endothelial ABO antigen and eNOS includes a genetic linkage with other genes regulating vasoconstriction, vasodilation, or a direct association of blood type antigen and vascular reactivity may also exist.[12,13]

The role of the ABO blood group as a risk factor for hemorrhage has been demonstrated by prior studies.[14] Previously, the AB blood type has been positively associated with a higher risk of ischemic stroke.[15] Similarly, the blood group AB has been documented to have a higher presence in non-aneurysmal SAH than aSAH (OR 2.45) within an ethnically German cohort.[16] However, there is disagreement in the scarce literature evaluating the role of the ABO blood group in DCI and clinical outcomes following aSAH, with one study demonstrating no link,[17] and two others studies showing patients with blood group O[18] and those with blood group A[19] to have a higher incidence of DCI.[18,19] A large difference between these studies and possibly the reported results may be a geographic or ethnic variation amongst the cohorts of these two studies, the first being White German,[17] and another being a Hispanic and African American urban minority in New York.[18] Similarly, the which showed a higher incidence of DCI following aSAH in patients with blood group A was carried out in England.[19] Our study then aimed to add to this debate and explore whether an association exists and if yes, what is the association between the ABO blood group and the development of DCI and subsequent functional outcomes after aSAH.

Materials and Methods

Study Design and Participants

This study was conducted at the Department of Neurosurgery, Allama Iqbal Medical College, Jinnah Hospital Lahore, Pakistan. Ethical approval for this study was obtained from our institutional review board. A retrospective analysis was made on data collected from consecutive patients presenting with aSAH at a tertiary supraregional neurosurgery department over 5 years. All patients were operated on by the senior author (Ashraf, N). The participants were divided into two groups according to their ABO blood group type: "O" type and "non-O" type.

The main inclusion criteria were all patients over the age of 18 years with aSAH. In addition, patients with non-aneurysmal etiology and incomplete follow-up or clinical information were excluded from the study.

Variables and Outcomes

The key exposure was ABO blood group type classified into either "O" type or "non-O" type, similar to Unda et al.[18] Other variables included in our study were patient demographics (gender, age, BMI, hypertension, and smoking status), clinical variables (DCI, mFG, WFNS grade, and Glasgow Outcome Scale at discharge), EVD placement, and size of the aneurysm (< 5 mm or > 5 mm). All patients underwent neurosurgical clipping as a treatment modality. Forty-six of the aneurysms were part of the posterior circulation, and the rest were part of the anterior circulation. Posterior circulation aneurysms were excluded as they were transferred to another unit for endovascular treatment; thus, we did not have their data. After an aSAH diagnosis, DSA was performed on all patients. All patients were assessed at hospital discharge.

The primary outcome of our study was the development of DCI. The clinical manifestation of vasospasm is referred to as DCI, which is defined as and accepted to be, the presence of a focal neurological impairment and/or a decrease in consciousness lasting for at least an hour with no other apparent cause.[18–20] All patients with clinically suspected vasospasm underwent CT head. The formal definition for clinical deterioration has been previously defined as "the occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its components [eye, motor on either side, verbal]). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes

through clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies."[20]

All patients had clinical and neurological examinations performed by the neurosurgical team throughout their stay and at discharge. Functional outcome at discharge, as measured by GOS was our secondary outcome. GOS 4 to 5 was taken as a "good outcome," and GOS 1 to 3 was taken as a "bad outcome."

Statistical Analysis

Analysis was conducted using SPSS version 26.0 (IBM SPSS Statistics, New York, United States). Descriptive statistics were calculated for all variables included in our study. Associations of the variables with the ABO blood group type and DCI were explored by Pearson's chi-square test (or Fisher's exact test if necessary) for categorical variables and Student's t-test for continuous variables. Chi-square continuity correction was applied where appropriate. Any variable found to be significantly associated with both ABO group type and DCI ($p < 0.05$) was included as a potential confounder in the multivariable logistic regression model used to calculate the effect of ABO type on the development of DCI. Moreover, all variables found to be significantly associated with DCI ($p < 0.05$) were also chosen to be included in the model to identify independent predictors of outcome (DCI). Forward selection was used to arrive at the final stepwise logistic regression. A variable was only included in the model if it improved the model checked by the Akaike information criterion (AIC),[21] and if the Omnibus likelihood ratio test was significant. Odds ratio (OR) and 95% confidence intervals (CIs) were calculated. A p-value less than 0.05 was considered significant.

Results

Participants and Descriptive Data

A total of 175 patients were included in our study. There was an approximately equal number of males and females. The majority of patients were nonsmokers (including former smokers) (59.4%), hypertensive (59.4%), and the mean age was 53.59 years (SD 11.26) and a mean BMI of 28.77 kg/m^2. The frequency distribution of "O" type and "non-O" type blood groups was 34.3% and 65.7%, respectively. Fifty-one patients (29.1%) needed EVD placement, and 26 patients (14.9%) suffered from DCI in our study (►Table 1).

Association of Demographic and Clinical Variables with ABO Type Groups

►Table 2 shows the distribution of variables across the "O" type and "non-O" type groups. The mean BMI was significantly higher in the "non-O" type group (29.07 ± 2.24) than in the "O" type group (28.20 ± 2.28). In addition, the "O" type group had a significantly higher incidence of DCI (25.0%) as compared with the "non-O" type group (9.6%). No other variables had any significant association with the ABO type groups.

Association of Demographic and Clinical Variables with DCI

►Table 3 shows that the mean BMI was significantly lower in the patients that suffered DCI. A significantly larger propor-

tion of patients with DCI had higher grades on the modified Fisher scale (grades 3–4) and WFNS scale (grades 3–5) than those who did not suffer from DCI. In addition, there was a significantly higher number of EVD placements in patients with DCI (61.5%) than in those who did not (23.5%). The rest of the variables did not show any statistically significant results.

ABO Type Blood Group as a Risk Factor for DCI

A stepwise logistic regression model showed that after adjusting for BMI, mFG, WFNS grade, and EVD placement, "O" type blood group was an independent risk factor for DCI, greatly increasing the risk of DCI as compared to "non-O" type groups, OR = 3.27, 95% CI: 1.21–8.82, (►Table 4). In addition, BMI was a potential confounder (►Tables 2 and 3), and the rest of the variables included in the multivariable analysis were significant predictors of DCI (►Table 3).

Discussion

This study explored the relationship between ABO blood type and the onset of DCI, linking DCI onset significantly and positively with the presence of "O" blood type. Our study population had 34.3% individuals with "O" blood type and 65.7% with "non-O" blood type. It is also important to state that there were no statistically significant differences among baseline characteristics between "O" and "non-O" patients except for BMI.

After adjusting the BMI, mFG, WFNS grade, and EVDs by regression, ABO blood type was an important independent predictor for DCI. According to a retrospective analysis by Dubinski et al,[16] AB blood type is more frequent in non-aneurysmal subarachnoid hemorrhages than in aneurysmal etiology patients.[16] However, the same authors also found no significant influence of ABO blood type on cerebral vasospasm onset, SAH-associated intracerebral hemorrhage, or delayed infarction.[17] But their results were suggestive of a potential clinically relevant association of the ABO blood group and hence warranted further investigation. A study carried out by Richards et al[19] demonstrates that blood group A patients have a significantly higher risk of developing DCI following aSAH, and a suggested trend of patients with non-O blood type at a higher risk of developing DCI as well.[19] However, Unda et al's[18] study conflicted with this, demonstrating that O blood type significantly increases the risk of DCI onset with an odds ratio 2.5 times higher relative to non-O blood group patients.[18] However, this finding was in an ethnic minority of Hispanics and African Americans living in New York.[18] Unda et al[18] also document non-statistically significant poorer functional outcomes in those with O blood group.[18] Our study also documents a 3.15 increase in the odds of developing DCI for those with 'O' blood group.

Important differences to consider include that the study by Unda et al[18] was from New York and had only 11.3% Caucasians, with mainly a cohort of Hispanic patients. Richards et al.[19] had an 87.4% Caucasian population from England, whilst our cohort was entirely Pakistani patients. Literature has shown that racial differences can be

Table 1 Demographic and clinical characteristics of patients after aSAH

Parameter	Count ($n = 175$)	n (%)
Gender		
Male	86	49.1
Female	89	50.9
Age (mean and SD)	53.59 (mean)	11.26 (SD)
BMI (mean and SD)	28.77 (mean)	2.29 (SD)
ABO type blood group		
"O" type	60	34.3
"Non-O" type	115	65.7
Smoker		
Current	71	40.6
Non-smoker (including former)	104	59.4
Hypertension		
Yes	104	59.4
No	71	40.6
Delayed cerebral ischemia (DCI)		
No	149	85.1
Yes	26	14.9
Modified Fisher grade (mFG)		
Grade 0–2	54	30.9
Grade 3–4	121	69.1
WFNS grade		
Grade 1–2	120	68.6
Grade 3–5	55	31.4
Outcome at discharge (Glasgow Outcome Scale)		
GOS 4–5 (good outcome)	122	69.7
GOS 1–3 (bad outcome)	53	30.3
EVD placement		
No	124	70.9
Yes	51	29.1
Size of aneurysm		
< 5 mm	51	29.1
> 5 mm	124	70.9

significantly influential in pathologies though their role in individual diseases and outcomes are likely to vary substantially and thus should be further investigated in specific cases.[22–24] For example, it has previously been proposed that race-specific ABO antigens may also lead to a disparity in the rates of aneurysms and intraventricular hemorrhages,[25,26] therefore while DCI onset may be associated with the ABO blood group, further investigations and better study methodology are required to answer this with certainty whilst accounting for differences in race and geography. Equally important to account for are treatment paradigms, which for aneurysm securing varied amongst our study, and that of Richards et al[19] who reported endovascular intervention in 89.6% of their cohort. Unda et al[18] cohort underwent

neurosurgical clipping in 33.8% of cases and endovascular coiling in 66.2% of cases. Treatment paradigms for neurovascular surgery differ between centers in the same country, let alone between continents; this is also partly due to socioeconomic reasons. In our setup, all patients undergo neurosurgical clipping due to the lack of affordability for endovascular coils in government sector neurosurgery departments. Therefore, the findings of these studies, including ours, may not be generalizable across demographics.

Richards et al's[19] study, which showed blood group A to be associated with a higher risk of DCI after aSAH, hypothesized that this could be contributed to by the finding that blood group A patients have a higher risk of developing hyperlipidemia, atherosclerosis, and heart failure.[19,27] They postulated

Table 2 Distribution of demographic and clinical variables between ABO type groups

Parameter	ABO type blood group				p-Value
	"O" type		"Non-O" type		
	Count (n = 60)	n (%)	Count (n = 115)	n (%)	
Gender					1.000
Male	29	48.3	57	49.6	
Female	31	51.7	58	50.4	
Age (mean and SD)	51.57 (mean)	12.09 (SD)	54.65 (mean)	10.70 (SD)	0.085
BMI (mean and SD)	28.20 (mean)	2.28 (SD)	29.07 (mean)	2.24 (SD)	0.016*
Smoker					0.707
Current	26	43.3	45	39.1	
Non-smoker (including former)	34	56.7	70	60.9	
Hypertension					0.707
Yes	34	56.7	70	60.9	
No	26	43.3	45	39.1	
Delayed cerebral ischemia (DCI)					0.012*
No	45	75.0	104	90.4	
Yes	15	25.0	11	9.6	
Modified Fisher grade (mFG)					0.727
Grade 0–2	17	28.3	37	32.2	
Grade 3–4	43	71.7	78	67.8	
WFNS grade					0.573
Grade 1–2	39	65.0	81	70.4	
Grade 3–5	21	35.0	34	29.6	
Outcome at discharge (Glasgow Outcome Scale)					0.645
GOS 4–5 (good outcome)	40	66.7	82	71.3	
GOS 1–3 (bad outcome)	20	33.3	33	28.7	
EVD placement					1.000
No	43	71.7	81	70.4	
Yes	17	28.3	34	29.6	
Size of aneurysm					1.000
< 5 mm	17	28.3	34	29.6	
> 5 mm	43	71.7	81	70.4	

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

that the presence of atherosclerotic disease in the cerebral blood vessels, even if subclinical or insignificant may contribute to the vasospasm as these patients would be less likely to tolerate hypoperfusion relative to their O or B blood group counterparts.[19] Richards et al[19] also postulated that the relative degree of vasospasm and hypoperfusion required to induce clinically significant cerebral ischemia might be less if the cerebral vasculature already has pre-existing atherosclerotic plaques causing stenosis.[19] Similarly, Unda et al,[18] who found blood group O patients, have a higher risk of DCI following aSAH, support their results by stating evidence that reduced levels of vWF and factor 8 in plasma of blood group O patients lead to excessive bleeding in the subarachnoid space. However, these authors acknowledged the converse evidence that shows increased levels of factor 8 contribute to peripheral vasospasm[28–30] though Unda et al[18] postulate this evidence may not be translatable to cerebral vasculature after aSAH. Both theories are thought-provoking and provide a solid rationale for studying this topic in further detail. Whether the factor that causes disparity in different ethnic groups in regard to the ABO blood group system and DCI is genetic, environmental or both, works in isolation or conjunction with the type of the blood group in particular ethnicities and/or environments needs to be evaluated in the laboratory. This is vital to address the recent question of the role of the ABO blood group in aSAH. It will add to our knowledge of aSAH pathophysiological sequelae and, at large, the role of the ABO blood group in vascular disorders.

Table 3 Association of demographic and clinical variables with the incidence of DCI

Parameter	Delayed cerebral ischemia (DCI)				p-Value
	No		Yes		
	Count (n = 149)	n (%)	Count (n = 26)	n (%)	
Gender					0.759
Male	72	48.3	14	53.8	
Female	77	51.7	12	46.2	
Age (mean and SD)	53.87 (mean)	11.43 (SD)	52.04 (mean)	10.31 (SD)	0.447
BMI (mean and SD)	28.94 (mean)	2.31 (SD)	27.81 (mean)	1.88 (SD)	0.019*
Smoker					0.375
Current	63	42.3	8	30.8	
Non-smoker (including former)	86	57.7	18	69.2	
Hypertension					1.000
Yes	89	59.7	15	57.7	
No	60	40.3	11	42.3	
Modified Fisher grade (mFG)					0.037*
Grade 0–2	51	34.2	3	11.5	
Grade 3–4	98	65.8	23	88.5	
WFNS grade					0.001**
Grade 1–2	110	73.8	10	38.5	
Grade 3–5	39	26.2	16	61.5	
Outcome at discharge (Glasgow Outcome Scale)					0.772
GOS 4–5 (good outcome)	105	70.5	17	65.4	
GOS 1–3 (bad outcome)	44	29.5	9	34.6	
EVD placement					< 0.001***
No	114	76.5	10	38.5	
Yes	35	23.5	16	61.5	
Size of aneurysm					0.971
< 5 mm	44	29.5	7	26.9	
> 5 mm	105	70.5	19	73.1	

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Individuals with "O" blood type have lower mean levels of vWF followed by A, B, and AB blood types. vWF is a highly glycosylated protein whose properties such as platelet agglutination and susceptibility to proteolytic degradation are affected by removing carbohydrate residues.[31] A, B, and H oligosaccharide structures have also been identified on the N-linked glycan chains of human plasma vWF.[32,33] This gives rise to the plausibility of blood group determinants playing a role in the processing, catabolism, or release of vWF, affecting its plasma concentration.[31] The odds ratio between certain vascular diseases and blood group types are also similar to those predicted by the effect of ABO(H) on vWF levels.[12] The variation in plasma concentrations of the vWF–FVIII complex is clinically significant because low levels increase the risk of deep vein thrombosis, peripheral vascular disease, and myocardial infarction.[34]

Similarly, these low levels may also lead to excessive bleeding in the subarachnoid space. A potential, though

Table 4 Logistic regression with DCI as dependent variable

Predictor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
ABO type blood group		
"Non-O" type	Referent	Referent
"O" type	3.15 (1.34–7.40) p = 0.008	3.27 (1.21–8.82) p = 0.019

statistically insignificant, trend for an increased rebleeding risk has also been observed by Richards et al[19] in patients of aSAH with the O+ blood group.[19] This bleeding may create an environment with excessive amounts of hemoglobin and oxidized hem products that intercept high-affinity free NO rapidly,[35] and synthesize endogenous eNOS inhibitors.[12] The role played by endothelial nitric oxide synthase (eNOS), which regulates NO production, is crucial in maintaining cerebrovascular tone. Low basal NO levels constantly being released contribute to vascular relaxation and thrombosis. Due to eNOS inhibitors, a decreased amount can lead to the inhibition of this relaxation, which may further lead to cerebral vasospasm.[17]

In our study, significant factors linked with DCI with a *p*-value less than 0.05 apart from ABO blood type include BMI, mFG, WFNS grading system, and EVD placement. According to CDC, BMI between 18.5 and less than 25 is considered normal; BMI between 25 and less than 30 is considered overweight; BMI greater than 30 is considered obese. The overweight and obese groups may have an inverse relation with mortality and functional outcome after SAH, partially supporting the obesity paradox. Being overweight lends a protective effect after SAH, whereas obesity is detrimental to death and poor outcome.[36] This may be because an extra amount of nutrients and is helpful until the harms of obesity override these benefits. Some studies, however, directly link high BMI with an increased risk of infarction.[37] In our study, the mean BMI of patients with and without DCI was 27.81 and 28.94, respectively. This value may seem statistically significant but likely holds no clinical significance as both fall in the same overweight category.

The mFG accounts for thick cisternal and ventricular blood. The risk for symptomatic vasospasm increases progressively from grade 0 to 4 because it is directly linked to the worsening of the aneurysm. For each increase in scale level, the odds of symptomatic deterioration increased by almost 28%.[38] The WFNS grading system is the most effective grading system for the clinical condition of SAH, primarily based upon the GCS and the presence of focal neurological deficits[39]; as the scale moves from grade 1 to 5, the severity of SAH increases as the GCS score decreases and the presence of focal neurological deficits increases. This further leads to an increased chance of vasospasm and, ultimately, DCI. The results of our study, where 38.5% of patients with WFNS grades 1 to 2 and 61.5% of patients with WFNS grades 3 to 5 suffered from DCI, support this. EVDs are placed to manage hydrocephalus and intracranial pressure after subarachnoid hemorrhage by draining CSF.[40]

The percentage of patients discharged with a poor functional outcome was higher in the O group (33.3%) versus the non-O group (28.7%). This, however, did not reach statistical significance similar to Unda et al's study. Functional clinical outcomes and other non-significant variables might be influenced by clinical, economic, socio-demographic, and other factors. Therefore, ABO blood type would likely not singlehandedly impact functional recovery after aSAH. However, it is associated with DCI, the most common complication of aSAH and thus may play a role.

Limitations

The single-center retrospective nature of this study limits our findings as it may lead to the inclusion of biases and potential confounders. The absence of data on potential confounders might take away from the opportunity to investigate their associations. Given the conflicting findings of our study, Unda et al[18] and Richards et al[19] study, the association between the ABO blood groups with DCI may be coincidental. Further, a large confidence interval in our study adds to the uncertainty of our results. The scarcity of literature to compare with is also a limitation. Individual studies investigating this topic are limited by the small sample size, especially given that the primary outcome has a low incidence. Multicenter data analysis would be an ideal method to address this limitation. Larger data sets with different modalities to secure the aneurysm would be beneficial to study if method of aneurysm occlusion (microsurgical clipping versus endovascular coiling) is a contributing factor toward the development of DCI. Another limitation in our study was that all aneurysms were of the anterior circulation. This is because there is a single government-funded neurosurgery department in our city where endovascular treatment is provided free of cost, and thus posterior circulation aneurysms are referred to them. Thus, analyzing only anterior circulation aneurysm data adds an important selection bias and again limits generalizability. In addition, data for long-term outcomes after discharge has not been included in this study. However, this study can still serve as a source of pilot data. Given that the associations between ABO blood group and DCI onset following aSAH have been demonstrated by two other studies, there is a strong rationale to investigate this topic further.

Conclusion

This study demonstrates an association between blood group O and a relative increase in the development of DCI following aSAH. Given the limitations of our study and the sparsity of relevant literature, there is a need to investigate the role of the association between the ABO blood group system and DCI development following aSAH.

Conflict of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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