

## ORIGINAL RESEARCH

# Associated Factors of Intracranial Hemorrhage in Patients with Nontraumatic Headache who Underwent Anticoagulation Therapy; A retrospective study

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**Abstract:** **Introduction:** Although anticoagulation is a well-established risk factor for intracranial hemorrhage (ICH) following trauma, its role in determining the need for neuroimaging in patients with nontraumatic headache is less clear. This study evaluated whether anticoagulation alone justifies brain computed tomography (CT) scan imaging in nontraumatic headache. **Methods:** We conducted a retrospective cohort study at a tertiary care center in Riyadh, Saudi Arabia, including adults presenting with nontraumatic headache between January 2020 and 2023. Patients who underwent brain CT scan were assessed for hemorrhage and potential associated factors of ICH were explored. **Results:** Among 909 patients who presented with non-traumatic headache, 162 (17.82%) cases were on anticoagulation therapy, and 20 (2.2%) had ICH on brain CT scan. Anticoagulation use alone was not significantly associated with the risk of ICH following nontraumatic headache ( $p = 0.068$ ). A history of prior ICH or ischemic stroke emerged as a predictor of ICH, in the overall cohort and among anticoagulated patients ( $p < 0.001$  for all comparisons). No statistically significant associations were observed with antiplatelet use, anticoagulant type, combined anticoagulant–antiplatelet therapy, or neurological deficits. **Conclusion:** It seems that, in patients presenting with nontraumatic headache, anticoagulation use alone should not dictate the decision to perform brain CT scan. A history of prior ICH or ischemic stroke is a more reliable predictor of ICH risk and should be prioritized in imaging decisions. These findings support a more targeted imaging strategy to minimize unnecessary scans and improve emergency department resource utilization.

**Keywords:** Headache disorders; Anticoagulants; Intracranial Hemorrhages; Risk Factors, Tomography, X-Ray Computed

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## 1. Introduction

Nontraumatic headache is a common reason for emergency department (ED) visits, accounting for approximately 1%–4% of presentations (1). Headaches are classified as either primary or secondary depending on their underlying cause (1). ED assessment centers on promptly identifying secondary causes, which are responsible for the highest morbidity (2). Brain computed tomography (CT) scan is the most commonly used imaging modality to exclude life-threatening causes of headache (3).

Although neuroimaging is clearly indicated in trauma patients receiving anticoagulation (4), current guidelines for nontraumatic headache do not include anticoagulation use as a standalone indication for imaging (2, 5). Anticoagulation therapy is generally associated with an increased risk

of intracranial hemorrhage (ICH) (2, 4). Consequently, beyond well-recognized factors such as age and trauma, the role of anticoagulation in guiding neuroimaging decisions for headache remains unclear due to limited evidence (4). Woo et al. reported that prior stroke was a risk factor for both lobar and non-lobar ICH (6). Other studies also found that prior ischemic stroke elevated the risk of ICH regardless of anticoagulant or aspirin use (7, 8). Likewise, prior ICH has consistently been identified as a strong predictor of recurrence, even after adjusting for other risk factors (9).

Despite these, ED physicians are more likely to request CT imaging when a patient has a history of anticoagulation use (2). However, adopting a selective imaging strategy is essential to minimize unnecessary radiation exposure, reduce costs, and improve patient throughput (3).

This study aimed to examine the association between anticoagulation use and the presence of ICH on brain CT scan of patients presenting to ED with nontraumatic headache. This would help determine whether anticoagulation use alone warrants obtaining a brain CT scan in patients presenting with nontraumatic headache.

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## 2. Methods

### 2.1. Study design and setting

This was a single-center retrospective cohort study conducted at a tertiary hospital in Riyadh, Saudi Arabia. The emergency department at King Faisal Specialist Hospital & Research Centre manages approximately 75,000 patient visits annually and serves predominantly the oncology and organ transplant population (10). Including adults presenting with nontraumatic headache between January 2020 and 2023, patients who underwent brain CT scan were assessed for ICH and potential associated factors of ICH were analyzed.

The study was approved by the KFSH&RC Ethics Committee (RAC# 2231272). A waiver of informed consent was granted, as the study was observational and involved no impact on patient care.

### 2.2. Participants

Patients aged  $\geq 18$  years who presented to the ED with acute nontraumatic headache and underwent brain CT scan between January 2020 and 2023 were included. The decision to order brain CT scan was at the discretion of the treating emergency physician, guided by internationally recognized red-flag features suggestive of secondary headache (e.g. sudden onset, altered mental status, neurological deficits) (4). Exclusion criteria included patients  $< 18$  years, history of head trauma within the preceding 7 days, ICH following cranial surgery, cases without available brain CT scan reports, chronic headache  $> 4$  weeks, and pregnant women.

### 2.3. Data gathering

An initial list of patients was obtained through the hospital's Healthcare Information Technology Affairs data warehouse using WHO and ICD-10 diagnoses codes of headache and the presence of a brain CT scan order. The records were reviewed and data gathered by three trained data collectors (medical students) using a standardized form capturing demographics, comorbidities, medication history, prior ICH, prior ischemic stroke, neurological deficits, international normalized ratio (INR) on visit, Glasgow coma scale (GCS), and brain CT scan findings (positive or negative) as classified according to reviewing official reports.

All CT scans were interpreted by consultant radiologists and officially reported. Brain CT scan reports were reviewed by data collectors and classified as positive only if an ICH was found, all other findings were classified as negative CT. Anticoagulation use referred to active use of anticoagulants (Warfarin, Apixaban, Rivaroxaban, Heparin, and Enoxaparin) during ED visit and average use of 3 months. Antiplatelet use referred to active use of antiplatelet (Aspirin and Clopidogrel) during ED visit and average use of 6 months. Data regarding anticoagulant and antiplatelet use was obtained from patient records based on histories provided by the patients or their companions.

### 2.4. Statistical analysis

Analyses were performed using R version 4.3.4. Categorical variables were summarized as frequencies and percentages, and continuous variables as means with standard deviations. Comparisons between categorical variables were made using Pearson's chi-squared test or Fisher's exact test (if expected counts  $< 5$ ). The Wilcoxon rank-sum test was applied to continuous variables (e.g., age). P-values  $\leq 0.05$  denoted statistical significance.

## 3. Results

Of 1,170 cases initially identified, 261 were excluded due to duplication or failure to meet inclusion criteria as outlined in Consolidated Standards of Reporting Trials (CONSORT) flowchart figure 1. Table 1 presents the demographic and clinical characteristics of the 909 patients who presented to the ED with nontraumatic headache during the study period. The mean patient age was  $46.50 \pm 16.44$  (range: 18.00-96.00.) years, and females accounted for nearly two-thirds of the cohort (567 (62.38%)). The most common comorbidities were hypertension with 251 (27.61%) cases, malignancy with 238 (26.18%), and diabetes mellitus with 224 (24.64) cases. A history of intracranial hemorrhage was reported in 35 (3.85%) patients, while 68 (7.48%) had a prior ischemic stroke. Neurological examination findings were normal in the majority of patients (767 (84.38%)).

Among 909 patients, 162 (17.82%) were on anticoagulant therapy at the time of ED presentation. Warfarin was the most frequently used agent, reported in nearly half of anticoagulated patients (78 (48.15%)). Other agents, including apixaban, rivaroxaban, enoxaparin, and heparin, were less common. Some patients were prescribed multiple anticoagulants, so percentages do not total 100%. Overall, 125 (13.75%) patients were receiving antiplatelet therapy. Aspirin was the predominant agent, prescribed in 106 (84.80%) of these cases. Similar to anticoagulants, some patients were taking more than one antiplatelet, so totals may exceed 125. The incidence of ICH in the study cohort was 20 (2.20%) cases. A history of prior ICH ( $p = 0.001$ ) and prior ischemic stroke ( $p = 0.001$ ) demonstrated the strongest associations with ICH on brain CT scan. While patients receiving anticoagulant therapy showed a higher likelihood of ICH, the association did not reach statistical significance ( $p = 0.068$ ).

No significant relationship was observed with antiplatelet use ( $p = 0.3$ ), age ( $p = 0.3$ ), or neurological examination findings ( $p > 0.9$ ). Table 2 shows that among anticoagulant users, prior ICH (Odds: 56.4 (95% confidence interval (CI): 21.4 - 157);  $p < 0.001$ ) and prior ischemic stroke (Odds: 17.8 (95% CI: 7.11 - 46.0);  $p < 0.001$ ) remained the strongest predictors of ICH on brain CT scan. Other risk factors did not demonstrate statistically significant associations.

No specific anticoagulant or antiplatelet agent was significantly associated with ICH (table 2). Concurrent use of anticoagulants and antiplatelets was also not significantly as-

sociated with ICH.

## 4. Discussion

This study demonstrates that among anticoagulated patients presenting to the ED with nontraumatic headache, brain CT scan should be prioritized for those with a history of prior intracranial hemorrhage (ICH) or prior ischemic stroke, as these risk factors showed the strongest statistical association with ICH on CT. Similarly, when considering the entire cohort, both anticoagulated and nonanticoagulated patients, prior ICH and prior ischemic stroke remained the most significant predictors of ICH, exceeding the predictive value of anticoagulation use or other clinical factors.

These findings align with previous studies showing that a history of prior ischemic stroke or ICH increases the risk of recurrent ICH, independent of anticoagulation status. Woo et al. reported that prior stroke was a risk factor for both lobar and non-lobar ICH (6). Other studies also found that prior ischemic stroke elevated the risk of ICH regardless of anticoagulant or aspirin use (7, 8). Likewise, prior ICH has consistently been identified as a strong predictor of recurrence, even after adjusting for other risk factors (9). This overlap between ischemic stroke and ICH as risk factors for future hemorrhage has been highlighted in additional studies: one demonstrated that in patients with prior ischemic stroke, a history of ICH significantly increased the risk of recurrent ICH within 30 days (11); another showed that in patients with prior ICH, a previous ischemic stroke independently predicted recurrence (12).

In anticoagulated populations, a systematic review reported moderate-certainty evidence that both previous bleeding and prior stroke are associated with increased ICH risk (13). Much of the available literature focuses on patients with atrial fibrillation, who comprise the majority of those receiving anticoagulation. In this group, prior stroke, cerebrovascular disease, older age, and intensity of anticoagulation have all been linked to elevated ICH risk (14, 15).

To the best of our knowledge, no previous studies have specifically examined risk factors for ICH in anticoagulated patients presenting to the ED with atraumatic headache. Prior research has either focused on risk factors for ICH in anticoagulated patients in general, without limiting the population to those with atraumatic headache, or investigated predictors of significant CT findings in atraumatic headache without restricting outcomes to ICH alone. Only one study directly evaluated the relationship between antiplatelet or anticoagulant use and abnormal intracranial findings on CT in patients with nontraumatic headache, reporting that these medications were associated with an increased risk of abnormal results (2). In contrast, our findings highlight prior ischemic stroke and prior ICH as stronger predictors of ICH than anticoagulation or antiplatelet use. However, direct comparison with that study is limited, as its outcome encompassed a broader range of CT abnormalities rather than ICH alone.

Much of the existing literature on CT findings in atraumatic headache similarly includes all abnormal intracranial pathologies rather than focusing exclusively on ICH. Across these studies, older age and focal neurological deficits have been the most consistently reported predictors of significant CT findings (16, 17). In our study, focal neurological deficits were not significantly associated with ICH. This discrepancy may reflect methodological differences, as we only classified new neurological deficits as positive findings, whereas many patients in our cohort had baseline deficits. Additionally, although patients with ICH in our study tended to be older, consistent with prior reports, age did not reach statistical significance as a risk factor. Notably, one study restricted to geriatric patients (>65 years) reported prior cerebrovascular disease and anticoagulation use as predictors of significant CT findings in atraumatic headache (18).

This study found that, overall, antiplatelet use was not significantly associated with ICH on brain CT, regardless of anticoagulation status. Similar results have been reported in multiple case-control studies that showed no increased ICH risk with antiplatelet therapy (19, 20). However, two meta-analyses did identify a small but statistically significant increase in ICH risk among antiplatelet users (21-23).

Among anticoagulated patients, concomitant antiplatelet use was also not significantly associated with ICH. Consistent with our findings, a meta-analysis reported no significant difference in intracranial bleeding risk between patients receiving combined oral anticoagulation with antiplatelets and those on anticoagulation alone (24). Likewise, a study in ischemic stroke patients found no difference in hemorrhagic stroke risk between these groups (25). In contrast, one study of patients on non-vitamin K antagonist oral anticoagulants (NOACs) reported that concomitant antiplatelet therapy was an independent predictor of ICH (26).

This study also found no significant association between ICH and the type of anticoagulant (NOAC vs. warfarin). Prior research has often shown NOACs to carry a lower ICH risk compared with warfarin (27). The lack of difference in our study may reflect limitations common to observational cohorts, where low event rates reduce the power to detect such associations.

From a clinical standpoint, these results support a more selective approach to CT imaging in patients with atraumatic headache on anticoagulation. Prioritizing individuals with a history of ischemic stroke or ICH, rather than relying solely on anticoagulation status, may improve decision-making, reduce unnecessary imaging, lower costs, and minimize radiation exposure in crowded ED settings.

## 5. Limitations

This study has several limitations. In the anticoagulated subgroup, the small number of ICH cases limited the statistical power to identify associated risk factors. Many patients with postoperative ICH were excluded, further reducing case numbers. Additionally, the decision to obtain a CT was made

by different physicians, potentially leading to missed cases, and all CTs were interpreted by multiple radiologists, introducing inter-observer variability.

Another limitation was the lack of available INR values for many patients, preventing assessment of anticoagulation intensity as a risk factor. Prior studies have shown INR >4.0 to be strongly associated with ICH, though most ICH cases still occur within the therapeutic range of 2.0–3.0.

Future research should include larger, multicenter prospective studies of patients presenting to ED with nontraumatic headache while on anticoagulants or antiplatelets. Importantly, efforts should be made to establish a validated clinical decision rule to guide CT imaging in this population.

## 6. Conclusions

It seems that, in patients presenting with nontraumatic headache, anticoagulation use alone should not dictate the decision to perform brain CT scan. A history of prior ICH or ischemic stroke is a more reliable predictor of ICH risk and should be prioritized in imaging decisions. These findings support a more targeted imaging strategy to minimize unnecessary scans and improve ED resource utilization.

## 7. Declarations

### 7.1. Acknowledgments

The authors would like to thank the Department of Emergency Medicine at King Faisal Specialist Hospital and Research Centre for their support during the study. This research has not been presented at any scientific meeting and has no previously published abstracts.

### 7.2. Authors' contributions

1. Shaikha Almansoor: Writing – original draft (lead); formal analysis (lead); Conceptualization (lead); Methodology (lead); Data curation(supporting); review and editing (lead).
2. Albatoul Alkohlani: Writing – original draft (lead); formal analysis (equal); Methodology (equal); Data curation(supporting); review and editing (lead).
3. Sameeha Abdulwali: Data curation(lead); Writing – original draft (equal); Methodology (equal); review and editing (equal).
4. Sarah Aldahoul: Data curation(lead); Writing – original draft (equal); Methodology (equal); review and editing (equal).
5. Dalia Hamdan: Data curation(lead); Writing – original draft (equal); Methodology (equal); review and editing (equal).
6. Sameer Desai: Software(lead); formal analysis (lead); Conceptualization (equal); Methodology (equal); review and editing (lead); supervision (lead)
7. Danah Alobathani: Software (lead); formal analysis (lead); Conceptualization (equal); Methodology (equal); review and editing (equal); supervision (lead)
8. Muhammad Qureshi: Conceptualization (lead); Method-

ology (equal); review and editing (lead); supervision (lead) All authors read and approved the final version of manuscript.

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### 7.4. Competing interests

The authors declare no financial or non-financial competing interests related to this work. The authors have no affiliations, financial relationships, or personal connections that could be perceived as influencing the study results or interpretation.

### 7.5. Data availability

The datasets generated and analyzed during the current study are not publicly available due to patient confidentiality and institutional restrictions but are available from the corresponding author on reasonable request and with permission from the ethics committee.

### 7.6. Using artificial intelligence chatbots

Artificial intelligence (AI) tools were used solely for language editing and grammar improvement during manuscript preparation. All scientific content, data interpretation, and conclusions were generated and verified by the authors, who take full responsibility for the final manuscript.

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**Table 1:** Comparing the baseline characteristics of studied nontraumatic headache cases between those with and without intracranial hemorrhage (ICH) on brain computed tomography (CT) scan

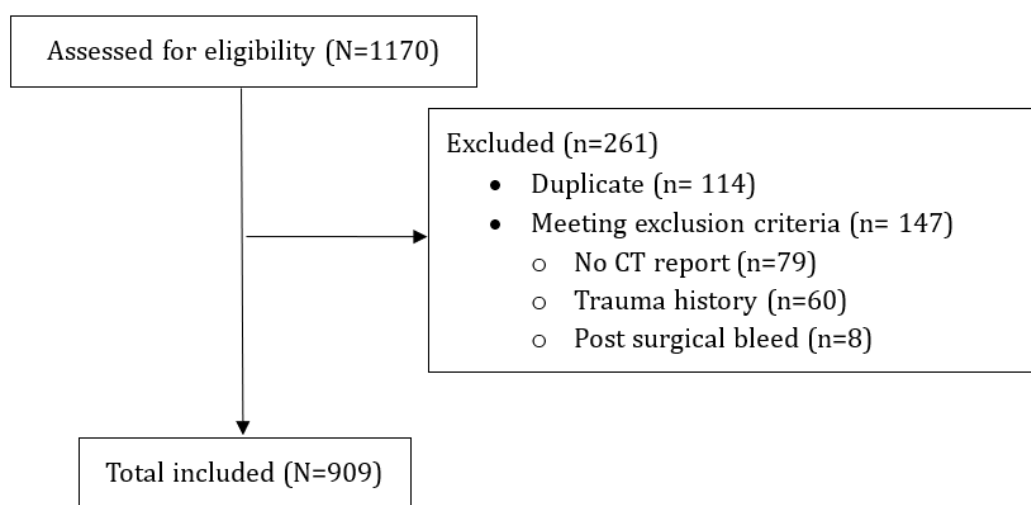
Characteristic	Total (n = 909)	ICH on brain CT scan		P value
		No (n = 889)	Yes (n = 20)	
<b>Age (years)</b>				
Median (IQR)	44 (18–96)	44 (33–59)	50 (37–65)	0.3
<b>Sex</b>				
Female	567 (62.38)	556 (62.54)	11 (55.00)	0.5
Male	342 (37.62)	333 (37.46)	9 (45.00)	
<b>Comorbid disease</b>				
Diabetes	224 (24.64)	220 (24.75)	4 (20.00)	0.8
Hypertension	251 (27.61)	247 (27.78)	4 (20.00)	0.4
Dyslipidaemia	134 (14.74)	131 (14.74)	3 (15.00)	> 0.9
Liver failure	25 (2.75)	25 (2.81)	0 (0.00)	> 0.9
Renal failure	53 (5.83)	51 (5.74)	2 (10.00)	0.3
Malignancy	238 (26.18)	234 (26.32)	4 (20.00)	0.5
<b>Prior ICH</b>				
Yes	35 (3.85)	23 (2.59)	12 (60.00)	< 0.001
<b>Prior ischemic stroke</b>				
Yes	68 (7.48)	57 (6.41)	11 (55.00)	< 0.001
<b>Neurologic findings</b>				
Intact	767 (84.38)	750 (87.82)	17 (89.47)	> 0.9
Positive	106 (11.66)	104 (12.18)	2 (10.53)	
<b>INR on visit</b>				
Median (IQR)	1.00 (1.00–1.13)	1.00 (1.00–1.10)	1.00 (1.00–1.20)	0.9
<b>GCS</b>				
10	1 (0.11)	1 (0.11)	0 (0.00)	> 0.9
13	2 (0.22)	2 (0.23)	0 (0.00)	
14	6 (0.67)	6 (0.68)	0 (0.00)	
15	890 (99.00)	880 (98.98)	20 (100.00)	
<b>Anticoagulant use</b>				
Yes	162 (17.82)	155 (17.44)	7 (35.00)	0.068
<b>Anticoagulant type</b>				
Warfarin	78 (48.15)	74 (47.74)	4 (57.14)	0.7
Rivaroxaban	17 (10.49)	16 (10.32)	1 (14.29)	0.5
Apixaban	23 (14.20)	23 (14.84)	0 (0.00)	0.6
Heparin	23 (14.20)	23 (14.84)	0 (0.00)	0.6
Enoxaparin	22 (13.58)	20 (12.90)	2 (28.57)	0.2
<b>Antiplatelet use</b>				
Yes	125 (13.75)	121 (13.61)	4 (20.00)	0.3
<b>Antiplatelet type</b>				
Aspirin	106 (84.80)	104 (85.95)	2 (50.00)	0.11
Clopidogrel	29 (23.20)	27 (22.31)	2 (50.00)	0.2

Data are presented as median (interquartile range (IQR)) or frequency (%). Wilcoxon rank sum test, Fisher's exact test, and Pearson's Chi-squared test were used for comparisons. INR: international normalized ratio; GCS: Glasgow coma scale.

**Table 2:** Associated factors of intracranial hemorrhage (ICH) on brain computed tomography (CT) scan of nontraumatic headache cases who underwent anticoagulant therapy (n=162)

Factors	ICH on brain CT scan (n = 162)		p-value
	Negative (n = 155)	Positive (n = 7)	
<b>Age (years)</b>			
Median (IQR)	50 (36–63)	50 (46–62)	0.6
<b>Comorbid disease</b>			
Diabetes	41 (26.45)	1 (14.29)	0.7
Hypertension	52 (33.55)	1 (14.29)	0.4
Liver failure	7 (4.52)	0 (0.00)	> 0.9
Renal failure	20 (12.90)	0 (0.00)	0.6
Malignancy	30 (19.35)	0 (0.00)	0.4
<b>Prior ICH</b>			
Yes	2 (1.30)	7 (100.00)	< 0.001
<b>Antiplatelet use</b>			
Yes	33 (21.29)	1 (14.29)	> 0.9
<b>Prior ischemic stroke</b>			
Yes	23 (14.84)	7 (100.00)	< 0.001
<b>Neurologic status</b>			
Intact	133 (88.67)	5 (83.33)	0.5
Positive	17 (11.33)	1 (16.67)	
<b>Anticoagulant types</b>			
Warfarin	74 (47.74)	4 (57.14)	0.7
Rivaroxaban	16 (10.32)	1 (14.29)	0.5
Apixaban	23 (14.84)	0 (0.00)	0.6
Heparin	23 (14.84)	0 (0.00)	0.6
Enoxaparin	20 (12.90)	2 (28.57)	0.2
<b>Antiplatelet types</b>			
Aspirin	104 (85.95)	2 (50.00)	0.11
Clopidogrel	27 (22.31)	2 (50.00)	0.2

Data are presented as median (interquartile range (IQR)) or frequency (%). Wilcoxon rank sum test, Fisher's exact test, and Pearson's Chi-squared test were used for comparisons.

**Figure 1:** Consolidated Standards of Reporting Trials (CONSORT) flowchart of patients' inclusion. CT: computed tomography.