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Original Article

ORIGINAL ARTICLE

Stroke in hemodialysis patients and its association with CHA_2DS_2-VASC and HAS-BLED scores: a retrospective study

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ABSTRACT

Background. In the general population, the CHA_2DS_2-VASC and the HAS-BLED scores are helpful to predict cerebrovascular events and hemorrhage in patients with atrial fibrillation (AF). However, their predictive value remains controversial in the dialysis population. This study aims to explore the association between these scores and cerebral cardiovascular events in hemodialysis (HD) patients.

Methods. This is a retrospective study including all HD patients treated between January 2010 and December 2019 in two Lebanese dialysis facilities. Exclusion criteria are patients younger than 18 years old and patients with a dialysis vintage less than 6 months.

Results. A total of 256 patients were included (66.8% men; mean age 69.3 ± 13.9 years). The CHA_2DS_2-VASc score was significantly higher in patients with stroke ($P = .043$). Interestingly, this difference was significant in patients without AF ($P = .017$). Using receiver operating curve analysis, CHA_2DS_2-VASc score had an area under the curve (AUC) of 0.628 [95% confidence interval (CI): 0.539–0.718) and the best cut-off value for this score was 4. The HAS-BLED score was also significantly higher in patients with a hemorrhagic event ($P < .001$). AUC for HAS-BLED score was 0.756 (95% CI: 0.686–0.825) and the best cut-off value was also 4.

Conclusions. In HD patients, CHA_2DS_2-VASc score can be associated with stroke and HAS-BLED score can be associated with hemorrhagic events even in patients without AF. Patients with a CHA_2DS_2-VASc score ≥4 are at the highest risk for stroke and adverse cardiovascular outcomes, and those with a HAS-BLED score ≥4 are at the highest risk for bleeding.

Keywords: CHA_2DS_2-VASc, chronic hemodialysis, HAS-BLED, atrial fibrillation, stroke

INTRODUCTION

Chronic kidney disease (CKD) patients are known to be at an increased risk for developing stroke, which is almost 3.7 times higher than that of the general population [1]. In hemodialysis (HD) patients, this risk is even higher, estimated to be 5–10 times more than the population with normal kidney function [2]. Neurological complications and the mortality related to stroke are also increased in this specific population. [3, 4]. In addition to the higher risk of thromboembolic events, HD patients are also prone to bleeding [5]. Therefore, the use of anticoagulation in their management is still

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controversial. Randomized clinical studies evaluating the efficacy of antithrombotic therapy in chronic kidney disease stage 5 patients (CKD-5) patients are lacking since these patients are excluded from these trials, despite their increased cardiovascular risk [6].

The CHA_2DS_2-VASc score estimates the annual thromboembolic risk in patients with nonvalvular atrial fibrillation (AF) [4, 7]. Several studies reported an area under the curve (AUC) of 0.65–0.69 [8–10], whereas one study showed an AUC > 0.7 [11], reflecting an acceptable predictive value of the CHA_2DS_2-VASc score for stroke [11]. In parallel the HAS-BLED score demonstrated its superiority over other scores, such as the $HEMORR_2AGES$ and the ATRIA scores, in predicting bleeding events with an AUC between 0.6 and 0.72 [12–15]. Therefore, the HAS-BLED score is a helpful tool to assess the bleeding risk in patients with AF at risk for stroke. In recent years, CHA_2DS_2-VASc was shown to be useful as well regardless of the presence of AF [16]. However, its application remains controversial in HD patients [17].

The aim of this study is to unveil the risk factors for ischemic stroke in HD patients, to assess the correlation between the CHA_2DS_2-VASc score and stroke in HD patients with or without AF, and to study the relation between the HAS-BLED score and any type of bleeding in this population.

MATERIALS AND METHODS

Study population

We performed a retrospective observational study that included all the CKD-5D patients treated with chronic HD between January 2010 and December 2019 in two Lebanese dialysis facilities: one urban, Hotel Dieu de France University hospital-Beirut; and one rural, Saint Georges Hospital, Ajaltoun. Patients younger than 18 years old and patients with a dialysis vintage less than 6 months were excluded.

Study variables

Demographic and clinical variables were retrieved from each dialysis facility computerized database for calculation of the CHA_2DS_2-VASc and the HAS-BLED score.

The outcome of stroke was defined by the occurrence of any ischemic stroke event or transient ischemic attack (TIA) occurring after the initiation of dialysis. The stroke diagnosis was searched for and retrieved from patients' medical records and confirmed by reviewing their previous cerebral imaging. The outcome of bleeding was defined by any gastro-intestinal, cerebral or other organ bleeding occurring after HD initiation. The bleeding diagnosis was also made by the revision of all patients' medical records: bleedings were either reported by patients during their HD follow-up or were a cause of admission to the emergency department.

Data collected for each patient included in the study are: age, sex, end-stage kidney disease etiology, date of initiation of HD, tobacco or alcohol consumption, systolic blood pressure level, parathormone level; and the presence of: diabetes mellitus, hypertension, dyslipidemia, AF, heart failure, liver disease, labile INR, vascular disease, stroke before dialysis initiation, stroke/myocardial infarction/peripheral ischemia after dialysis initiation, bleeding before or after dialysis initiation, medications (anticoagulant drugs, antiplatelet drugs, statins, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers).

Definition of scores

For the CHA_2DS_2-VASc score, patients were given 1 point for each of the following: congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65–74 years, and sex (female) category; and 2 points for age ≥75 years and prior stroke or TIA.

The CHA_2DS_2-VASc score was evaluated:

- Just before the stroke for patients who suffered from a stroke.
- At time of death for patients who died without any history of stroke
- On 1 July 2020, for those who were still alive and did not suffer from any stroke.

For the HAS-BLED score, patients were given 1 point for each of the following: hypertension defined by a systolic blood pressure >160 mmHg, abnormal kidney function defined by the presence of chronic dialysis, renal transplantation or serum creatinine ≥200 μmol/L, liver cirrhosis, prior stroke, prior bleeding, age >65 years, antiplatelet use and drug or alcohol abuse history.

The HAS-BLED score was evaluated:

- Just before the last bleeding episode for patients who suffered from bleeding.
- At the time of death for patients who died without having a bleeding episode.
- On 1 July 2020, for those who were still alive and did not suffer from a bleeding episode.

Statistical analysis

Continuous data are reported as mean and standard deviation (SD) if variables are normally distributed and as median and interquartile range (IQR) if the variables are skewed. Categorical data are reported as numbers or percentages.

Patients were classified into three groups according to their CHA_2DS_2-VASc score: 0–3 (low), 4–5 (intermediate) and 6–9 (high), and these groups were compared.

CHA_2DS_2-VASc was calculated for all the patients while HAS-BLED was missing for roughly 20% of the patients because of missing systolic blood pressure levels.

The t independent test was used to compare means and Mann–Whitney U test to compare medians (if data were skewed). The risk factors for stroke were analyzed using the binary logistic regression analysis. A univariate analysis was used to assess the relationship between the outcomes or dependent variables and each risk factor then all covariates with a univariate P-value <.2 were included in the multiple logistic regression analysis.

P-value is considered significant when <.05.

Ethical considerations

To ensure that ethical and legal principles were respected, the study was submitted and approved by the Saint Joseph University of Beirut ethical committee (reference number TFEM 2020/76) and was conducted in accordance with the Declaration of Helsinki.

RESULTS

A total of 256 patients were included: 141 patients treated in the dialysis center at Hotel Dieu de France in Beirut and 115 patients treated in the dialysis center at St Georges Hospital in Ajaltoun. The average age was 69.3 ± 13.9 years. The M/F sex ratio was 2/1 and 51.2% were diabetics, 96.9% were hypertensive, 71.5% had dyslipidemia, 54.3% were smokers, 30.5% had AF and

Table 1: General characteristics and treatments of patients in two groups.

	Stroke after dialysis initiation, N = 22	No stroke after dialysis initiation, N = 234	P-value
Age			
Mean ± SD	73.24 ± 9.46	68.83 ± 14.20	0.164[a]
Median [IQR]	76 [66, 80.5]	71.5 [62, 79]	0.249[b]
Sex, M/F, *n* (%)	15/7 (68.2/31.8)	156/78 (66.7/33.3)	0.999[c]
Smoking, *n* (%)	16 (72.7)	123 (52.6)	0.097[c]
Diabetes, *n* (%)	9 (40.9)	122 (52.1)	0.415[c]
Hypertension, *n* (%)	22 (100)	226 (96.6)	0.389[c]
Dyslipidemia, *n* (%)	16 (72.7)	167 (71.4)	0.981[c]
Statin, *n* (%)	15 (68.2)	120 (51.3)	0.402[c]
Aspirin, *n* (%)	12 (54.5)	87 (37.2)	0.077[c]
Acenocoumadin, *n* (%)	4 (18.2)	37 (15.8)	0.543[d]
Clopidogrel, *n* (%)	10 (45.5)	64 (27.4)	0.132[c]
NOAC, *n* (%)	3 (1.3)	0	0.999[d]
PTH (normal values: 6.3–36.8)			
Mean ± SD	177.93 ± 163.13	200.28 ± 207.33	0.767[b]
Median [IQR]	106 [73, 220]	131.45 [70.35, 263]	
Myocardial infarction, *n* (%)	10 (45.5)	43 (18.4)	0.003[c]
Peripheral artery disease, *n* (%)	10 (45.5)	61 (26.1)	0.054[c]
Coronary artery disease, *n* (%)	17 (77.3)	99 (42.3)	0.002[c]
Peripheral ischemia, *n* (%)	6 (27.3)	23 (9.8)	0.014[c]
Atrial fibrillation, *n* (%)	10 (45.5)	68 (29.1)	0.110[c]

[a]t independent test.
[b]Mann–Whitney U test.
[c]Chi-Square test.
[d]Fisher's Exact test.
M, male; F, female; NOAC, novel oral anticoagulant; PTH, parathyroid hormone.

18% suffered from heart failure. The causes of end-stage kidney disease were diabetes (46.5%), nephrosclerosis (16.5%), glomerulonephritis (12.9%), tubulo-interstitial disease (6.2%), polycystic kidney disease (6.6%) and other causes (12.1%).

The median follow-up was 2.71 years (IQR 1.45–4.99). Of the 256 patients: 22 (8.6%) experienced stroke after initiation of dialysis, 53 (20.75%) suffered from a myocardial infarction, 29 (11.3%) from acute peripheral ischemia, 84 (32.81%) from at least one bleeding episode, 39 (15.23%) from digestive bleeding and 12 (4.69%) from a cerebral bleed (hematoma or hemorrhagic stroke).

Risk factors for ischemic stroke in HD patients

When comparing patients who suffered from ischemic stroke with those who did not, a significant difference was found between the two groups for the following three factors: coronary artery disease, myocardial infarction and acute peripheral ischemia (Table 1). There was a higher risk of ischemic stroke in patients with a history of coronary artery disease [odds ratio (OR) = 4.63; 95% confidence interval (CI): 1.65, 12.99], and in those who suffered from myocardial infarction (OR = 3. 7; 95% CI: 1.50, 9.12) and acute peripheral ischemia (OR = 3.44; 95% CI: 1.22, 9.65). CHA_2DS_2-VASc ≥ 4 was also associated with ischemic stroke (OR = 4.56; 95% CI: 1.31, 15.85) (Table 2).

CHA_2DS_2-VASc score

In our population the CHA_2DS_2-VASc score was associated with ischemic stroke (*P*-value = .043). When stratifying by AF, CHA_2DS_2-VASc score was associated with stroke in the subgroup of patients without AF (Table 3). However, it was not associated with stroke in the subgroup with AF. Using receiver operating curve (ROC) analysis (Fig. 1), CHA_2DS_2-VASc score had an AUC = 0.628 (95% CI: 0.539–0.718) as predictor of stroke.

Further analysis revealed that CHA_2DS_2-VASc score was also associated with myocardial infarction (*P* < .001) and peripheral ischemia (*P* < .001).

The patients who had an intermediate (4–5) or a high (6–9) CHA_2DS_2-VASc score were at a higher risk of suffering from: stroke, myocardial infarction and peripheral ischemia (Table 4).

Table 2: Univariate logistic regression analysis for assessment of risk factors for stroke.

Variable	OR	95% CI	P-value
Aspirin	2.00	0.83–4.82	.123
Acenocoumadin	1.25	0.39–3.91	.706
Clopidogrel	1.99	0.80–4.95	.138
Statin	0.99	0.85–1.14	.890
CAD	4.63	1.65–12.99	.004
Peripheral ischemia	3.44	1.22–9.65	.022
Myocardial infarction	3.7	1.50–9.12	.004
Atrial fibrillation	2.03	0.84–4.93	.116
CHA_2DS_2-VASc ≥ 4	4.56	1.31–15.85	.017
CHA_2DS_2-VASc > 5	1.24	0.49–3.07	.649
Uncontrolled hypertension	1.71	0.57–5.16	.340
Age	1.03	0.992–1.074	.118
Diabetes	0.64	0.26–1.56	.326

CAD, coronary artery disease.

Table 3: CHA_2DS_2-VASc score median comparison between different groups.

Total sample	Patients with stroke, N = 22	Patients with no stroke, N = 234	P-value[a]
CHA_2DS_2-VASc, median [IQR]	4 [4, 5]	4 [2, 5]	.043[a]
Subgroup of patients with AF			
	Patients with stroke, N = 10	Patients with no stroke, N = 68	P-value[a]
CHA_2DS_2-VASc, median [IQR]	4 [3.75, 5]	4 [4, 6]	.679
Subgroup of patients without AF			
	Patients with stroke, N = 11	Patients with no stroke, N = 166	P-value[a]
CHA_2DS_2-VASc, median [IQR]	4 [4, 5]	3.5 [2, 5]	.017

[a]Mann–Whitney U test.

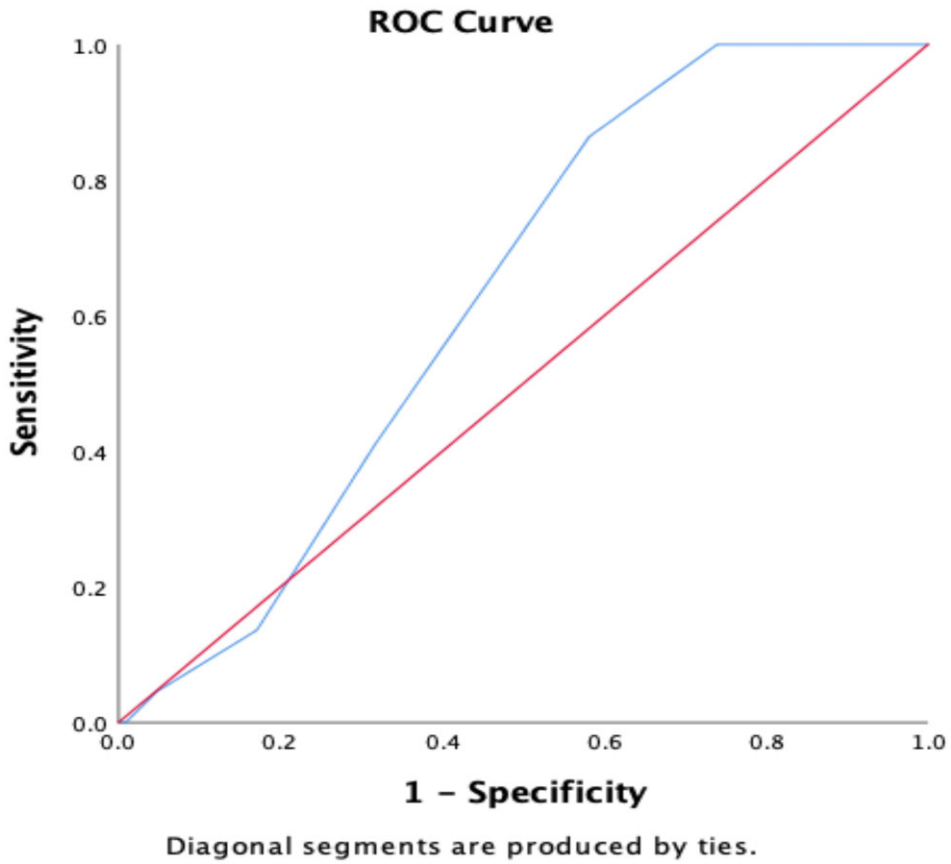

Figure 1: ROC curve for the CHA_2DS_2-VASC score for prediction of stroke.

Table 4: Distribution of stroke and cardiovascular events among three categories of CHA_2DS_2-VASc score.

	CHA_2DS_2-VASc score (≤3), N = 101	CHA_2DS_2-VASc score (4–5), N = 112	CHA_2DS_2-VASc score (≥6), N = 43	P-value
Stroke, *n* (%)	3 (3)	16 (14.3)	3 (7)	.012[a]
Myocardial infarction, *n* (%)	6 (5.9)	33 (29.5)	14 (32.6)	<.001[a]
Peripheral ischemia, *n* (%)	5 (5)	13 (11.6)	11 (25.6)	.002

[a]Chi-square test.

HAS-BLED score

HAS-BLED score was also associated with the risk of bleeding of any type ($P < .001$), digestive bleeding ($P < .001$) and cerebral bleeding ($P = .029$) after the initiation of dialysis (Table 5). In ROC analysis (Fig. 2), HAS-BLED score had an AUC = 0.756 (95% CI: 0.686–0.825).

Sensitivity, specificity, and positive and negative predictive values of scores

The characteristics of each value of the CHA_2DS_2-VASc and HAS-BLED with their sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at predicting the risk

Table 5: HAS-BLED score as a predictor of bleeding, GI bleeding and cerebral bleeding.

HAS-BLED score and bleeding			
	Patients with bleeding	Patients without bleeding	P-value[a]
HAS-BLED, median [IQR]	4 [3, 5]	3 [2, 3]	<.001
HAS-BLED score and GI bleeding			
	Patients with GI bleeding	Patients without GI bleeding	P-value[a]
HAS-BLED, median [IQR]	4 [3, 5]	3 [2, 4]	<.001
HAS-BLED score and cerebral bleeding			
	Patients with cerebral bleeding	Patients without cerebral bleeding	P-value[a]
HAS-BLED, median [IQR]	4 [3, 5]	3 [2, 4]	.029

[a]Mann–Whitney U test.
GI, gastrointestinal.

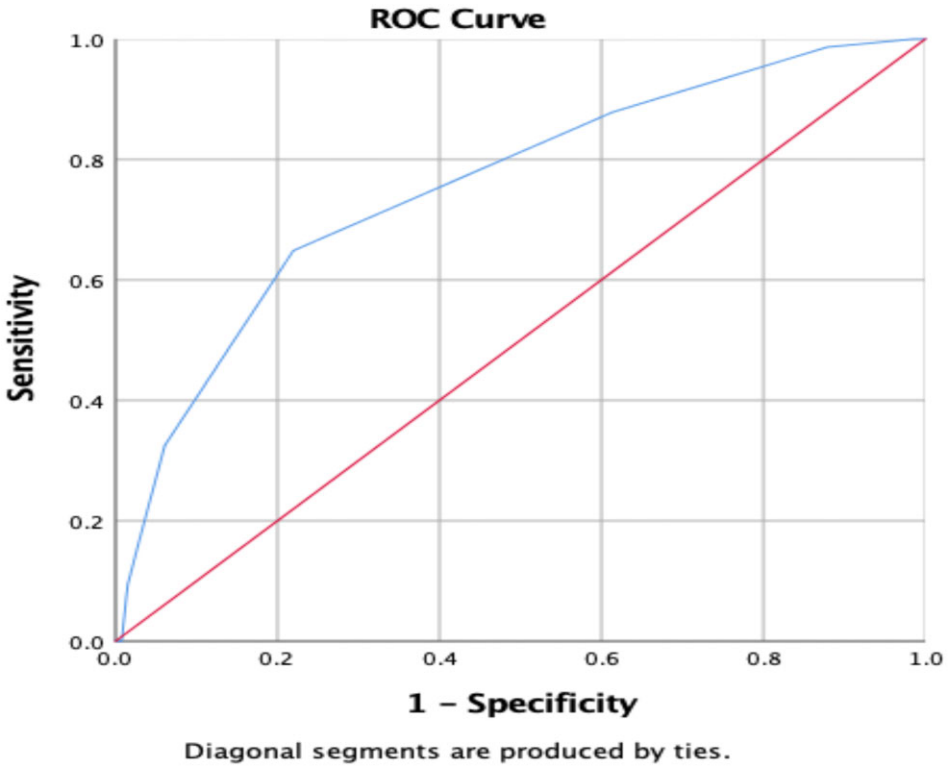

Figure 2: ROC curve for the HAS-BLED score for prediction of stroke.

for Stroke and the risk for bleeding respectively are shown in Table 6.

DISCUSSION

CHA_2DS_2-VASc score

According to our study, the CHA_2DS_2-VASc score was shown to be predictive of stroke in HD patients. The ROC AUC of the CHA_2DS_2-VASc score in the current sample was 0.628, a value above 0.5, which makes the test an acceptable predictor of stroke. This level of AUC for the CHA_2DS_2-Vasc score concurs well with other studies of the general population where it varied between 0.65 and 0.72, specifically in patients with AF [8–11]. In 2014, Chao *et al.* reported also an AUC of 0.68 in a sample of HD patients with AF [18]. The current study included patients with and without AF. CHA_2DS_2-VASc score was not linked to ischemic stroke in the patients with AF presumably due to lack of statistical power or genuinely reflecting no predictive value of CHA_2DS_2-VASc for stroke in HD patients with AF. Several studies found a minimal risk of ischemic stroke due to AF in patients already at high thromboembolic risk [12], corroborating the current findings not showing AF as a risk factor for ischemic stroke, unlike coronary artery disease, myocardial infarction and acute peripheral ischemia.

Our study also showed a progressive increase in episodes of myocardial infarction and peripheral ischemia as the CHA_2DS_2-VASc score increases. This was not the case for stroke, whose episodes reach the highest values for scores 4–5. We can speculate that patients with a score ≥6 are mostly patients who previously experienced stroke and were therefore treated. Another possibility is that the patients who have a score that high died of cardiac events before the occurrence of stroke.

Table 6: CHA_2DS_2-VASc score and HAS-BLED score characteristics.

CHA_2DS_2-VASc score	Sensitivity	Specificity	PPV	NPV	HAS-BLED score	Sensitivity	Specificity	PPV	NPV
1	100%	0.85%	8.66%	100%	1	100%	1.51%	36.27%	100%
2	100%	11.54%	9.61%	100%	2	98.65%	12.12%	38.62%	94.12%
3	100%	26.07%	11.28%	100%	3	87.84%	38.64%	49.24%	85%
4	86.36%	41.9%	12.25%	97%	4	64.86%	78.03%	62.34%	79.84%
5	40.91%	68.38%	10.84%	92.49%	5	32.43%	93.94%	75%	71.26%
6	13.64%	82.91%	6.98%	91.08%	6	9.46%	98.48%	77.78%	65.99%
7	4.55%	95.30%	8.33%	91.39%	7	0%	99.24%	0%	63.90%
8	0%	99.14%	0%	91.34%	8	0%	100%		64.08%
9	0%	100%	0%	91.4%	9	0%	100%		64.08%

Interestingly, the best cut-off value for the CHA_2DS_2-VASc score yielding maximal sensitivity and specificity (Youden index) in the HD population appears to be 4, corroborating the observation by Pravda *et al.* that HD patients with AF and CHA_2DS_2-VASc $\geq$ 4 are at higher mortality and cardiovascular risk within the first year of HD initiation [19].

For AF, the 2020 European guidelines recommend a CHA_2DS_2-VASc cutoff of 1 for men and 2 for women [20].

In a recent NICE review [21], the cutoff of 2 in patients with AF has a sensitivity of 92.3% and a specificity of 22.3%, while the cutoff of 3 has a sensitivity of 80.9% and a specificity of 43.1% for predicting stroke. This is quite close to the sensitivity and specificity of the cutoff of 4 in our study.

However, neither in our study nor in this NICE review was there a specific calculation of sensitivity and specificity for each score separately for men and women. Such an analysis might be interesting in showing if the threshold should be different between men and women as suggested by the European recommendations of 2020.

HAS-BLED score

In patients with AF, the HAS-BLED score has an AUC ranging between 0.6 and 0.72 according to most studies [12–15]. Ocak *et al.* found a HAS-BLED score AUC of 0.58 in the HD population, lower than in the AF patients [22].

The HAS-BLED AUC of 0.756 found in the current study is higher than usually reported in the literature of HD patients. One possible explanation could be that in the current study the score was calculated at the time of the last bleeding episode and not at the initiation of dialysis.

The Youden point for the ROC analysis for the HAS-BLED score has a 64.86% sensitivity and a 78.03%, specificity corresponding to a cutoff of 4.

Strengths and limitations

Although the study was conducted in two dialysis units, the authors believe its findings are generalizable to the whole Lebanese dialysis population for several reasons. First, the number of patients included in the sample was sufficient to be representative of the 4000 HD patients in Lebanon. Second the geographical distribution of the two HD centers in two different governorates ensured a good regional representativity. Third, the two units are among the largest in each governorate.

The study's major limitation is its retrospective design, exposing it to several biases, mainly in the form of information bias, with probable inconsistency in documenting minor bleeding episodes. Another caveat was missing systolic blood pressure data in a fraction of the patients, affecting the calculation of the HAS-BLED score.

CONCLUSION

To the best of our knowledge, this is the first study to find an association between CHA_2DS_2-VASc and the occurrence of stroke in non-AF HD patients, with a sensitivity and a specificity comparable to those of the general population. The CHA_2DS_2-VASc score cutoff of 4 was associated with an increased risk of ischemic stroke, myocardial infarction and peripheral ischemia.

HAS-BLED score was associated with the occurrence of bleeding of any type, gastrointestinal and/or cerebral bleeding, and the cutoff of 4 was found to ensure maximal sensitivity and specificity.

Further prospective studies are needed to validate these scores and improve the management of HD patients at high risk of thromboembolic events.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

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