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Performance of the CHA_2DS_2-VASc score in predicting new onset atrial fibrillation during hospitalization for community-acquired pneumonia

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ABSTRACT

Background: Cardiovascular events are common during hospitalization for community-acquired pneumonia (CAP), with new onset atrial fibrillation (NOAF) being the second most relevant complication. In this study, we aimed to investigate the role of CHA_2DS_2-VASc score in predicting NOAF during hospitalization for CAP.

Methods: Patients admitted for CAP were prospectively assessed using CHA_2DS_2-VASc. The end-point of the study was the occurrence of any objectively documented episode of NOAF during hospitalization in patients that were in sinus rhythm at hospital admission.

Results: Of 468 patients enrolled (median age 76 years), 48 (10.3%) experienced NOAF during hospitalization. They were older, had more comorbidities, more severe pneumonia, and higher CHA_2DS_2-VASc than those who remained in sinus rhythm (4.4 ± 1.6 vs 3.4 ± 1.9, respectively; $p < .0001$). There was a direct relationship between CHA_2DS_2-VASc score and risk of NOAF. At ROC curve analysis, a CHA_2DS_2-VASc score > 3 was the most accurate cut-off for prediction of NOAF (AUC 0.653; 95% CI 0.577–0.729; $p = .001$). In two different multivariable models, each CHA_2DS_2-VASc point increase and a score > 3 both were independently associated with NOAF (HR 1.3; 95% CI 1.09–1.55; $p = .003$ and 2.3; 95% CI 1.19–4.44; $p = .007$, respectively).

Conclusions: CHA_2DS_2-VASc score is an accurate and independent predictor of NOAF in patients with CAP, and a score > 3 features a population at high risk of developing the arrhythmia during hospitalization. This simple and effective tool should be incorporated in the evaluation of patients hospitalized for CAP, with implications ranging from arrhythmic prevention to anticoagulation management.

1. Introduction

Community-acquired pneumonia (CAP) is a common cause of hospitalization and death in developed countries [1–3], occurring preferentially in frail and elderly subjects. A frequent association between CAP and in-hospital cardiovascular (CV) complications, such as heart failure, acute coronary syndromes (ACS), atrial fibrillation (AF), and stroke has been recently observed [4–7]. Results from the SIXTUS study group [6], a prospective multicenter experience, reported CV complications in roughly one-third of patients hospitalized for CAP. Notably, CV complications independently increased by a factor of five the risk of 30-day mortality, after adjustment for age, PSI score, and preexisting comorbid conditions. Furthermore, the occurrence of CV complications during hospitalization for CAP is associated with increased need for intensive care unit admission and prolonged hospital stay.

AF is the second most common CV complication, after de novo or worsening heart failure, in patients hospitalized for CAP and, in general, it is the most common arrhythmia encountered in hospitalized patients. The occurrence of AF in the course of CAP has clinical implications, since it can determine acute cardiorespiratory decompensation and substantially increases cardioembolic risk both in the short period and long-term [8,9]. To date however, no strategy has

Abbreviations: AF, atrial fibrillation; CAP, community-acquired pneumonia; CHA_2DS_2-VASc, Congestive heart failure/left ventricular dysfunction, Hypertension, Age (≥ 75 years 2 points), Diabetes, Stroke/transient ischemic attack (2 points), Vascular disease, Sex category; CURB-65, Confusion, Urea, Respiratory rate, Blood pressure, age > 65 years; CV, cardiovascular; NOAF, new onset atrial fibrillation

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Table 1
Demographic and clinical characteristics, laboratory findings and in-hospital course of the general population with CAP and in the two subgroups according to the occurrence of new onset atrial fibrillation (NOAF) during hospital stay.

NOAF[a] during hospitalization				
	Overall	Yes	No	*p* value
Number of patients	468 (100%)	48 (10.3%)	420 (89.7%)	
Age (years)	75.5 ± 14.4	82.2 ± 9.4	74.7 ± 14.7	0.001
Female	243 (52%)	22 (46%)	221 (53%)	0.446
Coexisting diseases				
Arterial hypertension	265 (56.6%)	35 (72.9%)	230 (54.8%)	0.020
COPD[b]	139 (29.7%)	15 (31.3%)	124 (29.5%)	0.868
Dementia	127 (27.1%)	16 (33.3%)	111 (26.4%)	0.308
Diabetes mellitus	115 (24.6%)	19 (39.6%)	96 (22.9%)	0.020
Other cardiopathies	110 (23.5%)	16 (33.3%)	94 (22.4%)	0.105
Chronic heart failure	103 (22.0%)	14 (29.2%)	89 (21.2%)	0.203
Coronary heart disease	79 (16.9%)	13 (27.1%)	66 (15.7%)	0.065
Chronic kidney disease	72 (15.4%)	11 (22.9%)	61 (14.5%)	0.139
Cancer	65 (13.9%)	6 (12.5%)	59 (14.1%)	1.000
Previous stroke	64 (13.7%)	10 (20.8%)	54 (12.9%)	0.180
Active smoker	62 (13.2%)	4 (9.3%)	58 (14.3%)	0.488
Peripheral artery disease	54 (11.5%)	8 (16.7%)	46 (11.0%)	0.236
Autoimmune disease	38 (8.1%)	4 (8.3%)	34 (8.1%)	1.000
Chronic liver disease	24 (5.1%)	4 (8.3%)	20 (4.8%)	0.293
Number of comorbidities	3.3 ± 2.4	4.3 ± 2.6	3.1 ± 2.4	0.001
Clinical parameters, laboratory and radiographic findings on admission				
Systolic blood pressure (mm Hg)	128.8 ± 28.0	134.8 ± 24.0	128.1 ± 28.3	0.113
Diastolic blood pressure (mm Hg)	69.9 ± 12.1	71.7 ± 11.6	69.6 ± 12.2	0.252
Heart rate (bpm)	87.5 ± 17.1	90.1 ± 18.4	87.2 ± 16.9	0.254
Body temperature (°C)	36.6 ± 5.7	37.3 ± 1.4	36.6 ± 5.9	0.626
C-reactive protein (mg/L)	105.0 ± 88.7	103.1 ± 80.0	105.4 ± 91.1	0.932
Total cholesterol (mg/dL)	142.1 ± 39.0	142.1 ± 38.6	142.1 ± 39.1	1.000
PCT[c] (admission) (pg/mL)	3.2 ± 12.5	2.4 ± 5.5	3.3 ± 13.1	0.651
PCT[c] (day 1) (pg/mL)	2.4 ± 10.6	3.1 ± 7.3	2.3 ± 10.9	0.646
PCT[c] (day 4) (pg/mL)	2.6 ± 6.0	1.6 ± 1.9	2.7 ± 6.4	0.448
PCT[c] (day 6) (pg/mL)	1.3 ± 3.4	0.7 ± 0.5	1.4 ± 3.7	0.514
Leukocyte count (million cells/L)	13.5 ± 20.1	13.1 ± 9.3	13.5 ± 21.0	0.884
Hemoglobin (mg/dL)	12.0 ± 2.2	11.3 ± 2.3	12.0 ± 2.2	0.021
Creatinine (mg/dL)	1.2 ± 1.2	1.1 ± 0.6	1.2 ± 1.2	0.843
Blood glucose (mg/mL)	1.4 ± 0.6	1.4 ± 0.6	1.4 ± 0.6	0.722
Sodium (mEq/L)	138.0 ± 6.7	137.5 ± 7.5	138.0 ± 6.7	0.635
Troponin I (1st sample) (μg/L)	0.2 ± 0.7	0.2 ± 0.7	0.2 ± 0.7	0.917
Troponin I (2nd sample) (μg/L)	0.2 ± 1.1	0.2 ± 1.1	0.2 ± 1.1	0.921
Troponin I (3rd sample) (μg/L)	0.9 ± 2.2	1.0 ± 2.2	0.9 ± 2.2	0.880
NT-proBNP[d] (pg/mL)	6824.8 ± 17,414.6	8497.1 ± 10,141.5	6585.6 ± 18,221.7	0.562
Cardiovascular medications				
Clopidogrel	42 (9.0%)	6 (12.8%)	36 (8.6%)	0.416
Ticlopidine	14 (3.0%)	3 (6.4%)	11 (2.6%)	0.159
Aspirin	173 (37.0%)	25 (53.2%)	148 (35.4%)	0.025
Oral anticoagulants	12 (2.6%)	1 (2.1%)	11 (2.6%)	1.000
Heparin	272 (58.1%)	32 (68.1%)	240 (57.4%)	0.211
Statin	102 (21.8%)	11 (23.4%)	91 (21.8%)	0.853
Pneumonia severity and scores				
Multilobar pneumonia	242 (51.7%)	31 (64.6%)	211 (50.2%)	0.068
Pleural effusion	197 (42.1%)	24 (50.0%)	173 (41.2%)	0.281
CURB-65[e]	1.9 ± 1.0	2.3 ± 0.9	1.9 ± 1.0	0.005
CHA_2DS_2-VASc[f]	3.5 ± 1.9	4.4 ± 1.6	3.4 ± 1.9	< 0.0001
CHA_2DS_2-VASc[f] > 3	243 (51.9%)	34 (70.8%)	209 (49.8%)	0.006
Course of hospitalization and outcome				
Hospital stay (days)	9.5 ± 5.1	9.7 ± 5.1	9.5 ± 6.2	0.822
In-hospital mortality	57 (12.2%)	9 (18.8%)	48 (11.4%)	0.16

[a] NOAF: new onset atrial fibrillation.
[b] COPD: chronic obstructive pulmonary disease.
[c] PCT: procalcitonin.
[d] NT-proBNP: N-terminal pro-brain-type natriuretic peptide.
[e] CURB-65: Confusion, Urea, Respiratory rate, Blood pressure, age > 65 years.
[f] CHA_2DS_2-VASc: Congestive heart failure/left ventricular dysfunction, Hypertension, Age (≥ 75 years 2 points), Diabetes, Stroke/transient ischemic attack (2 points), Vascular disease, Sex category.

been proposed to identify patients at increased of AF during the in-hospital course of CAP. This is plausibly the first significant step towards prevention of the arrhythmia and its complications.

A simple clinical risk score, such as the CHA_2DS_2-VASc (Congestive heart failure/left ventricular dysfunction, Hypertension, Age [> 75 years 2 points], Diabetes, Stroke/transient ischemic attack [2 points], Vascular disease, Sex category), which is the sum of the single items featuring the score, is currently recommended by guidelines to

Table 2
Type of antibiotic and duration of treatment in the 468 hospitalized CAP patients with and without new onset atrial fibrillation (NOAF).

	NOAF[a] during hospitalization			
In-hospital treatments	Overall	Yes	No	*p* value
Ceftriaxone	253 (54.1%)	26 (54.2%)	227 (54.0%)	1.000
Levofloxacin	180 (38.5%)	20 (41.7%)	160 (38.1%)	0.611
Azithromicyn	175 (37.4%)	18 (37.5%)	157 (37.5%)	1.000
Piperacillin/tazobactam	121 (25.9%)	14 (29.2%)	107 (25.5%)	0.603
Glycopeptides	76 (16.2%)	13 (27.7%)	63 (15.0%)	0.036
Meropenem	43 (9.2%)	3 (6.3%)	40 (9.5%)	0.773
Imipenem	32 (6.8%)	4 (8.3%)	28 (6.7%)	0.557
Clarithromicyn	30 (6.4%)	2 (4.2%)	28 (6.7%)	0.756
Amoxicillin/clavulanate	29 (6.2%)	1 (2.1%)	28 (6.7%)	0.342
Imidazole derivatives	22 (4.7%)	2 (4.2%)	20 (4.8%)	1.000
Ceftazidime	10 (2.1%)	1 (2.1%)	9 (2.1%)	1.000
Ciprofloxacin	7 (1.5%)	1 (2.1%)	6 (1.4%)	0.534
Ertapenem	5 (1.1%)	0 (0.0%)	5 (1.2%)	1.000
Duration of antibiotic therapy (days)	8.8 ± 5.1	8.9 ± 4.9	8.8 ± 5.2	0.818

[a] NOAF: new onset atrial fibrillation.

estimate the risk of ischemic stroke, thromboembolism, and death in patients with AF [10]. Since, CHA_2DS_2-VASc score clusters multiple CV risk factors of broad clinical significance, its use has been proposed and tested in contexts different from the one for which it was developed. In recent years, CHA_2DS_2-VASc score has been shown to predict major CV events including AF in heterogeneous populations [11-15]. Based on this rationale, we performed a prospective study to evaluate the performance of CHA_2DS_2-VASc in predicting new onset atrial fibrillation (NOAF) in patients hospitalized for CAP.

2. Methods

2.1. Study design and setting

This was a prospective study carried out in two Internal Medicine Units (a total of 82 beds) of the University and General Hospital of Careggi, Florence, Italy, enrolling patients consecutively hospitalized for CAP from November 1st 2013 to July 30th 2016.

Patients were included in the study if they met the following criteria on admission: age ≥ 18 years, sinus rhythm confirmed by ECG on admission, no previous documented episodes of AF, objective evidence of pneumonia defined by the presence of newly discovered abnormal infiltrates on chest radiograph or CT scan and at least two of the following clinical features consistent with pneumonia: fever ≥37.8 °C, chest symptoms (dyspnea, productive cough), abnormal chest signs on physical examination (crepitation, bronchial breathing, pleural effusion). Patients were excluded from the study if they met criteria for hospital-acquired pneumonia (HAP), if they were immunocompromised or refused or were unable to give their consent. The study protocol was submitted and approved by our Local Ethics Committee (SepsiMed Study protocol number 0018329) and was performed in compliance with the principles of the Declaration of Helsinki.

2.2. Data collection and study endpoint

Demographic and clinical characteristics, Confusion, Urea nitrogen, Respiratory rate, Blood pressure, and age > 65 years (CURB-65) score, CHA_2DS_2-VASc score, and main laboratory values were collected at the time of hospitalization.

The end-point of the study was the occurrence of any episode of NOAF within the period of hospitalization, which referred to a newly and objectively recognized episode of AF during the hospitalization in persons that were in sinus rhythm at hospital admission as documented by medical records, ECGs, rhythm strips, and Holter monitors according to the definition used in the SIXTUS study [16].

2.3. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), while categorical data was expressed as proportions and percentages. Student's *t*-test and one-way ANOVA models were used for the comparison of continuous normally distributed variables and Mann-Whitney *U* test for continuous not normally distributed variables. The chi square test or Fisher's exact test were used for the comparison of categorical variables. Hazard ratio (HR) of variables and 95% confidence intervals (CIs) were calculated using univariate and multivariate logistic regression analysis. Multivariate analysis was performed using a stepwise forward regression model, with an entry probability for each variable set at 0.05. The variables tested in the multivariate model were: age, sex, chronic kidney disease, dementia, cancer, chronic liver disease, COPD, severity of pneumonia as indicated by clinical variables and CURB-65 score. Diabetes and other relevant CV comorbidities included in CHA_2DS_2-VASc were not tested separately for the analysis, since they were components of the score itself. Curves describing the proportional hazards over time were constructed according to the Cox model. A receiver-operating-characteristic (ROC) curve analysis was used to obtain the most accurate CHA_2DS_2-VASc score cut-off for the identification of NOAF during the hospital stay. All *p*-values were two-tailed and considered significant when < 0.05 (95% CI). All analyses were performed using the Statistical Package for Social Sciences 21.0 (SPSS Inc., Chicago, Ill, USA).

3. Results

During the study period a total of 645 patients admitted with pneumonia were screened. Of these, 468 (72,6%) were eligible for the study, as described in Table 1. Of note, most patients were elderly including 71% > 70 years; genders were equally represented. The overall burden of comorbidities, mainly CV diseases, chronic obstructive pulmonary disease (COPD), and dementia was high with 52% of the population having three or more comorbidities. Cephalosporins, fluoroquinolones and macrolides were the most frequently used antibiotics alone or in combination (Table 2). In 22% of patients antibiotics were started at home prior to hospitalization and in 28.8% the initial, empiric antibiotic therapy was modified during in-hospital course. Overall mortality and in-hospital stay were 12.2% and 9.5 days, respectively.

During hospital stay, 48 patients (10.3%) experienced NOAF. Of these, 35% had AF within the first day and 54% within 2 days, respectively; 90% of NOAF episodes occurred within the first week from admission. Compared to those in stable sinus rhythm, patients with NOAF were older, had a greater number of comorbidities, had more severe pneumonia according to CURB-65 (Table 1). Overall mortality and in-hospital stay were similar in the two groups. There were no differences in antibiotic classes employed in patients who experienced NOAF with respect to those in sinus rhythm. However, patients who received treatment with glycopeptides more frequently had NOAF during hospitalization (Table 2).

The CHA_2DS_2-VASc score was markedly increased in NOAF patients compared to those in sinus rhythm (4.4 ± 1.6 vs 3.4 ± 1.9; $p < .0001$), and there was a clear direct relationship between CHA_2DS_2-VASc score and risk of NOAF (Fig. 1). At ROC curve analysis the most accurate cut-off for prediction of NOAF was > 3 (AUC 0.653; 95% CI 0.577–0.729; $p = .001$; NPV 93.8%; PPV 13.9%; sensitivity 50.2%; specificity 70.8%) and the hazard ratio associated with a score > 3 was 2.3. As shown in Fig. 2, a Cox regression proportional hazard estimate, a CHA_2DS_2-VASc score > 3 clearly identified a population at high- versus low-risk of NOAF during hospitalization. Of note, CURB-65 also proved capable of predicting NOAF, and a score > 2 was associated with an AUC of 0.624 (95% CI 0.547–0.702; $p = .005$; NPV 91.6%; PPV 14.9%; sensitivity 72.8%; specificity

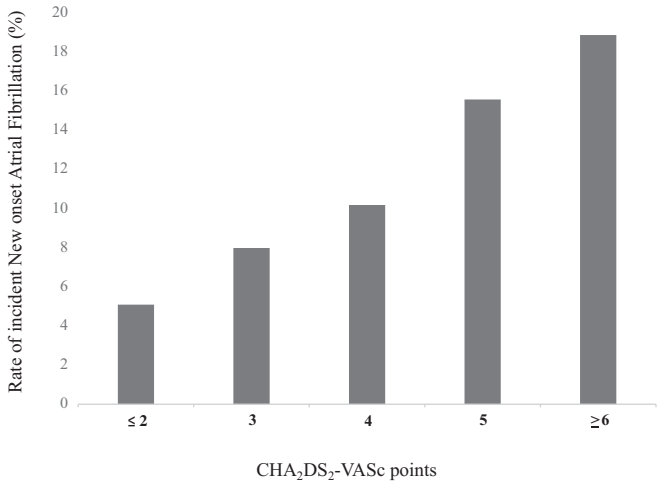

Fig. 1. Rate of new onset atrial fibrillation (NOAF) according to CHA_2DS_2-VASc score in community-acquired pneumonia patients.

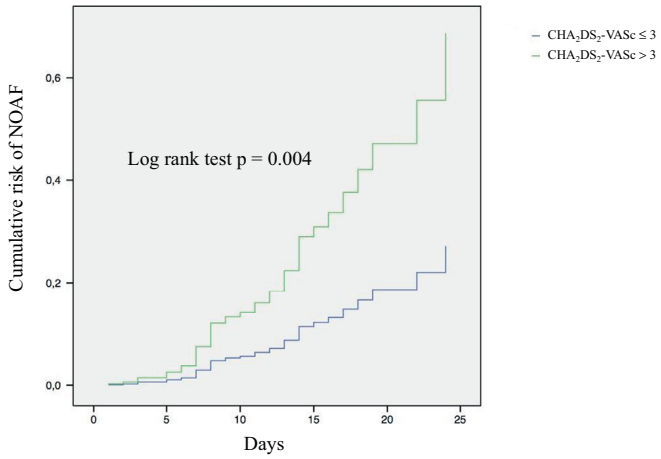

Fig. 2. Cox proportional hazards regression model for the cumulative risk of new onset atrial fibrillation (NOAF) in community-acquired pneumonia patients based on CHA_2DS_2-VASc at time of admission.

41.6%). However, at multivariate logistic regression analysis, only CHA_2DS_2-VASc (whether considering single unit increase or a threshold of 3) retained independent significance in predicting NOAF (Table 3).

4. Discussion

NOAF was a common CV complication in patients hospitalized for CAP, occurring early during admission [6] and affecting 10% of our population during the acute course of the disease. The prevalence of NOAF in our study was similar to that reported in patients hospitalized for CAP in the studies by Corrales-Medina [4] and Violi [6]. In both these studies, AF was documented as the second most common CV complication after heart failure with a prevalence of 10% and 9%, respectively. In the present study, we could demonstrate that the CHA_2DS_2-VASc score powerfully predicts the occurrence of NOAF in patients with hospitalized for CAP. We observed a sharp, progressive increase in risk of NOAF with increasing values of CHA_2DS_2-VASc score (Fig. 1). Risk was particularly high in patients with CHA_2DS_2-VASc score > 3, which more than doubled the independent likelihood of NOAF during hospitalization.

CHA_2DS_2-VASc is a tool designed, validated, and recommended to estimate the risk of ischemic stroke, thromboembolism, and death in patients with non valvular AF [10]. The single items constituting the score, however, are also known to predisposed to AF in the general population [17–19]. Therefore, a potential in predicting AF in patients hospitalized for CAP could be expected. However, the power and accuracy of such prediction had not been previously assessed and evidence on the role of CHA_2DS_2-VASc as a predictor of CV events and outcome in patients without AF remains limited. In a study by Melgaard et al. assessing the CHA_2DS_2-VASc score in predicting ischemic stroke, thromboembolism, and death in a cohort of patients with incident heart failure, the score was able to predict such events irrespective of the presence of AF [11].

Assessing CHA_2DS_2-VASc score in patients hospitalized for CAP may provide important information for several reasons. CHA_2DS_2-VASc score can help to identify patients at higher risk of AF, allowing the implementation of specific measures such as ECG monitoring and detection of pre-fibrillatory states warranting early treatment with antiarrhythmic agents and other measures such as preservation of acid-base and electrolyte homeostasis, thus preventing the acute effects of AF on the cardiac and respiratory balance. Patients with a score > 3 may benefit from direct cardiac rhythm monitoring as well as cardiac telemetry, mainly within the first 3 days since admission when the risk of NOAF is highest. Furthermore, CHA_2DS_2-VASc is key in selecting those

Table 3
Univariate and multivariate predictors of new onset atrial fibrillation (NOAF) in hospitalized patients with CAP.

	Univariate logistic regression analysis			Multivariate logistic regression analysis		
	HR[a]	95% CI[b]	*p* value	HR[a]	95% CI[b]	*p* value
Chronic kidney disease		0.85–3.61	0.139			
Cancer		0.35–2.14	1.000			
Dementia		0.73–2.63	0.308			
Chronic liver disease		0.59–5.56	0.293			
COPD[c]		0.57–2.07	0.868			
Multilobar pneumonia		0.97–3.36	0.068			
Pleural effusion		0.78–2.60	0.281			
CURB-65[d] (each point)	1.51	1.13–2.02	0.005	1.41	1.03–1.92	0.031
CURB-65[d] > 2	1.92	1.04–3.54	0.037	1.73	0.93–3.22	0.083
CHA_2DS_2VASc[e] (each point)	1.34	1.13–1.58	0.001	1.30	1.09–1.55	0.003
CHA_2DS_2-VASc[e] > 3	2.45	1.28–4.70	0.007	2.30	1.19–4.44	0.007

[a] HR: hazard ratio.
[b] CI: confidence interval.
[c] COPD: chronic osbtructive polmunary disease.
[d] CURB-65: Confusion, Urea, Respiratory rate, Blood pressure, age > 65 years.
[e] CHA_2DS_2-VASc: Congestive heart failure/left ventricular dysfunction, Hypertension, Age (≥ 75 years 2 points), Diabetes, Stroke/transient ischemic attack (2 points), Vascular disease, Sex category.

patients requiring early anticoagulation [10,20]. Finally, identifying patients with CAP at higher risk of NOAF, such as those with CHA_2DS_2-VASc > 3, suggests caution in the use of antibiotics with higher arrhythmogenic potential, such as fluorchinolones [21,22]. Even though we could not identify difference in outcome during hospitalization between patients with and without NOAF, we expect that timely treatment or prevention of arrhythmia in CAP patients may ultimately result in a prognostic benefit given the established adverse consequences of the arrhythmia. This important aspect requires dedicated studies.

We acknowledge that there are limitations in our study. Even though the prevalence of incident AF and patient characteristics associated with CAP are similar to other reports [4,6] the monocentric nature of the study can limit the generalizability of the findings to other settings and realities. In addition, since not all patients included in the study were monitored, the prevalence of NOAF was documented by ECGs, rhythm strips, and Holter monitors, leaving the possibility that silent AF may have been undetected in some instances. Nonetheless, patients were examined daily, generally often more than once, and the occurrence of AF being neglected in a significant subset of patients appears unlikely.

5. Conclusions

CHA_2DS_2-VASc is an accurate and independent predictor of AF in patients hospitalized with CAP. A score > 3 identifies a population of patients at high risk of developing the arrhythmia during hospitalization. This simple and effective tool should be incorporated in the evaluation of patients hospitalized for CAP, with implications ranging from arrhythmic prevention to anticoagulation management.

Conflict of interest disclosure

None.

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FP, VV, and BB conceived the original scope of the study, they also had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. BB, LM, GD, EA, CC contributed equally to data collection. FP, VV, BB, MF, CN and IO contributed substantially to data analysis and interpretation, and the writing of the manuscript.

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