Received: 2 May 2024 | Accepted: 13 July 2024

DOI: 10.1111/eci.14293

ORIGINAL ARTICLE

WILEY

Usefulness of the C_2HEST score to predict new onset atrial fibrillation. A systematic review and meta-analysis on >11 million subjects

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Abstract

Background: The incidence of new-onset atrial fibrillation (NOAF) is increasing in the last decades. NOAF is associated with worse long-term prognosis. The C_2HEST score has been recently proposed to stratify the risk of NOAF. Pooled data on the performance of the C_2HEST score are lacking.

Methods: Systematic review and meta-analysis of observational studies reporting data on NOAF according to the C_2HEST score. We searched PubMed, Web of Science and Google scholar databases without time restrictions until June 2023 according to PRISMA guidelines. Meta-analysis of the area under the curve (AUC) with 95% confidence interval (95% CI) and a sensitivity analysis according to setting of care and countries were performed.

Results: Of 360 studies, 17 were included in the analysis accounting for 11,067,496 subjects/patients with 307,869 NOAF cases. Mean age ranged from 41.3 to 71.2 years. The prevalence of women ranged from 10.6 to 54.75%. The pooled analysis gave an AUC of .70 (95% CI .66–.74). A subgroup analysis on studies from general population/primary care yielded an AUC of 0.69 (95% CI 0.64–0.75). In the subgroup of patients with cardiovascular disease, the AUC was .71 (.69–.79). The C_2HEST score performed similarly in Asian (AUC .72, 95% CI .68–.77), and in Western patients (AUC .68, 95% CI .62–.75). The best performance was observed in studies with a mean age <50 years (n = 3,144,704 with 25,538 NOAF, AUC .78, 95% CI .76–.79).

Conclusion: The C_2HEST score may be used to predict NOAF in primary and secondary prevention patients, and in patients across different countries. Early detection of NOAF may aid prompt initiation of management and follow-up, potentially leading to a reduction of AF-related complications.

KEYWORDS
atrial fibrillation, prevention, risk stratification; C_2HEST score

1 | INTRODUCTION

The incidence of new onset atrial fibrillation (NOAF) is increasing over time. In a large cohort study including 500,684 patients free of AF at baseline, standardized AF incidence rates increased from 4.74 to 6.82 cases per 1000 person-years from 2006 to 2018.[1] NOAF may be the result of exposure to multiple modifiable and non-modifiable risk factors,[2,3] or may occur following acute conditions, such as acute infections[4] or sepsis,[5] and after cardiac[6,7] and non-cardiac surgery.[8] All these conditions are associated with increased systemic inflammation and oxidative stress that have been linked to an increased susceptibility to develop AF.[9,10]

Detection of NOAF is of clinical importance, as NOAF has been associated with worse clinical outcomes in different cardiovascular and non-cardiovascular settings. Indeed, in patients undergoing transcatheter aortic valve replacement, NOAF is associated with increased risk of mortality, bleeding, stroke and heart failure (HF) hospitalizations.[11] In patients admitted to the intensive care unit, NOAF is associated with an increased risk of 90-day and 1-year mortality.[12] Similarly, NOAF occurring during sepsis is associated with increased risk of in-hospital and post-discharge mortality and stroke.[13] Additionally, NOAF following coronary artery bypass grafting associates with stroke and mortality risk.[14]

For this reason, some risk scores/schemes have been proposed over the years to predict NOAF both in the general population and in patients at high cardiovascular risk. However, some of these risk scores require many variables to be calculated (11 variables for the FIND-AF scheme[15] and CHARGE-AF[16]) or include instrumental and physical variables, like in the Framingham Heart Study.[17]

In 2019, a new score, namely the C_2HEST score, calculated as coronary artery disease or chronic obstructive pulmonary disease (1 point each), hypertension (1 point), elderly (age ≥75 years, 2 points), systolic heart failure (2 points), thyroid disease (1 point) was developed and validated on a large cohort of >800,000 people.[18] This score incorporated simple clinical variables making it easy to use in daily clinical practice.

This score has been recently suggested as a potentially useful tool in patients with cryptogenic stroke, to identify those in whom AF is likely to be the cause of the ischemic stroke,[19] suggesting the need for a longer monitoring and screening for this arrhythmia in patients classified as high risk.[20]

Since then, an increasing amount of evidence has been accumulating on the C_2HEST score, with studies testing it to predict NOAF in the general population and in cohorts of patients at high cardiovascular risk, such coronary heart disease or patients undergoing surgery. In the 2023 ACC/AHA/ACCP/HRS Guidelines for the Diagnosis and Management of Atrial Fibrillation, the C2HEST score has been nominated as one of the major risk model for assessing individual risk of developing NOAF.[21]

The aim of this systematic review/metanalysis is to provide a pooled estimation of the predictive value of the C_2HEST score based on current available evidence.

2 | METHODS

2.1 | Selection of study for inclusion

We performed a systematic review and meta-analysis according to PRISMA guidelines.[22] Two physicians (D.P. and D.M.) independently screened the titles and abstracts of manuscripts identified through the database searches to identify studies potentially eligible for further assessment. A third physician (T.B.) reviewed eligible studies for appropriateness and completeness. The study selection was performed in multiple phases. In the first phase, potentially relevant studies were obtained by combined searches of electronic databases using the "C_2HEST" keyword. Then, studies not in English language, not involving humans or not addressing study question were excluded. In the second phase, studies were reviewed and selected according to the inclusion and exclusion criteria. The phases of study selection were summarized by PRISMA flowchart diagram. All disagreements during the study selection were solved by collegial discussion.

2.2 | Risk of bias assessment

To assess the quality and relevance of studies included, two authors (D.M. and T.B.) independently assessed the risk of bias (RoB) using the Cochrane RoBINS tool for observational studies, which evaluates the following domains: bias due to confounding, to selection of participants, in classification of interventions, to deviations from intended interventions, due to missing data, in measurement of outcomes and in selection of the reported result.[19] ROBINS figures were created with the ROBINS online tool.[20] All disagreements during assessment of RoB were solved by collegial discussion. Publication bias was assessed by funnel plots.

2.3 | Types of studies for inclusion

We included only original research journal articles in English language with full text available. We included observational (both prospective and retrospective) cohort studies, and RCTs in which C_2HEST score was tested to predict NOAF and in which area under the ROC curve (AUC) was reported. We excluded cross-sectional and case–control studies, case reports, editorials/comments, letters, review and metanalysis and experimental studies.

2.4 | Participants/population

We included only studies that evaluated the predictive role of C_2HEST score for NOAF reporting AUC values.

2.5 | Data extraction

We performed a systematic review of the literature searching MEDLINE via PubMed, Web Of Science and Google Scholar databases using the following keyword "C_2HEST" AND "atrial fibrillation" OR "new-onset atrial fibrillation" OR "NOAF." The research strategy was performed according to PRISMA guidelines with no time restrictions until 10 June 2023.

For each study, the following information was retrieved: author/study name, year of publication, study design, setting-country, number of patients, proportion of patients with NOAF, age, proportion of women, hypertension, diabetes, HF, coronary heart disease (CHD), Stroke/transient ischemic attack (TIA), Hyperthyroidism, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD).

2.6 | Data analysis

Random-effects meta-analyses were performed for the area under the ROC Curve (AUC). Results were expressed by forest plots with pooled AUC and its associated 95% CI. We performed subgroups analysis according to the clinical setting (primary care/general population vs. cardiovascular disease) and country of origin (Asian vs. Western population). Publication bias was assessed by means of funnel plots. Funnel plot asymmetry was then formally assessed by means of rank correlation tests. Random effects meta-regression analyses for age, proportion of women, average C_2HEST score at baseline, proportion in the study with hypertension, diabetes, HF, CHD, stroke or TIA, hyperthyroidism, COPD, and CKD were also performed and summarized by means of bubble plots.

We also performed the following subgroup analysis: (1) prospective/RCT studies only; (2) studies with low/no RoB; (3) studies with a mean age <50 years; (4) after the exclusion of the only study including cardiac surgery.

All *p*-values were two-sided, and $p < .05$ were considered statistically significant. All analyses were conducted in R version 4.1.2.

2.7 | Ethical review, patient and public involvement

Given the study type (review and meta-analysis article), an ethical approval was not required. Patients were not involved in the design and the development of this study.

2.8 | Study registration

This study protocol was registered on PROSPERO (registration number CRD42023436837).

3 | RESULTS

3.1 | Study characteristics

PRISMA flowchart diagram is reported in Figure S1. Strategy search retrieved 360 articles. Of these, 17 studies[23–39] were included in the analysis accounting for 11,067,496 subjects with 307,869 NOAF cases. Characteristics of studies are reported in Table 1. Mean age ranged from 41.3 to 71.2 years. The proportion of women ranged from 10.6 to 54.75. The prevalence of risk factors was highly variable and was 1.4%–9.1% for arterial hypertension, 3.53%–51.1% for diabetes, .59%–29.52% for HF, 3.91%–76.7% for coronary heart disease, 1.05%–22.2% for stroke/TIA, .42%–12.45% for hyperthyroidism, 1.18%–32.65% for COPD and 0.13%–100% for chronic kidney disease. The pooled analysis including all studies gave and AUC of 0.70 (95% CI 0.66–0.74) with high heterogeneity ($I^2 > 99\%$) (Figure 1).

TABLE 1 Characteristics of studies included in the metanalysis.

Author/Study name	Year	Study design	Setting—Country	Patients	NOAF	Age	% of women	HTN%	Diabetes %	HF %	CHD %	Stroke/TIA %	Hyper-thyroid %	COPD %	CKD %
Li YG[18]	2019	R	Post-stroke patients—France	240,459	14,095	71.2	47.18	63.5	22.88	16.44	18.5	–	1.68	16.21	18.34
Hulme OL[23]	2019	R	General population—USA	412,085	14,334	61	58	28	9.4	3.1	9.3	3.8	1.5	9.7	3.4
Hu WS[24]	2020	R	LHID—end stage renal disease—Taiwan	4601	209	62.6	50.2	90.7	51.1	22.4	45.3	19.4	1.59	19	100
Lip GYH—65[25]	2019	R	Danish general population	1,047,330	28,252	–	51.3	22.1	5	2.9	7.4	2.7	1.4	3.2	1
Lip GYH—70[25]	2019	R	Danish general population	839,284	31,998	–	53	29.8	6	4.3	9.6	3.8	1.5	4.6	1.3
Lip GYH—75[25]	2019	R	Danish general population	612,621	34,262	–	55.5	31.2	6.4	6.1	11.6	5	1.7	6	1.6
Guo Y[26]	2020	P	General population—Huawey Heart Study China	209,274	374	–	10.63	1.4	3.62	1.01	2.91	–	1.4	32.65	–
Hu WS[27]	2020	R	General population Asia	692,691	12,051	41.3	49.4	14.4	–	0.59	6.25	1.05	0.46	3.66	0.13
Khurshid S[28]	2021	R	General population—Explorys Dataset—USA	4,508,180	153,151	62.5	56.3	52.7	21.7	3.7	12.1	5	1.2	–	6.7
Liang W[29]	2021	pRCT	TOPCAT—HfpEF—multinational[a]	2202	130	67.01	54.75	91.87	34.17	29.52	28.77	6.62	12.45	10.49	–
Li YG[30]	2021	R	General population—China	23,523	520	52.6	53.86	23.37	13.25	1.39	9.48	2.39	0.42	1.18	2.24
Han J[31]	2022	R	Ablation for AF—China	261	83	58.4	36	45.2	21.5	27.1	19.5	8.8	1.9	4.6	3.1
Hu WS[32]	2022	R	Rheumatological disease—Taiwan	370,874	6101	43.5	50.4	18.5	3.63	1.07	12.6	4.59	1.43	12.6	0.29
Rasmussen LF[33]	2022	R	Cardiac surgery—Denmark	14,279	4298	66.8	24.1	88.3	20.8		76.7	7.8	2.3	11.6	0.82

TABLE 1 (Continued)

Author/Study name	Year	Study design	Setting—Country	Patients	NOAF	Age	% of women	HTN%	Diabetes %	HF %	CHD %	Stroke/TIA %	Hyper-thyroid %	COPD %	CKD %
Hsieh CY[34]	2022	R	Post-stroke patients—Taiwan	5412	316	68	38.5	78.7	44.5	2.5	9.6	22.2	0.6	7.9	–
Zhang J[35]	2023	P	Non-cardiac surgery—China	2474	213	67	37.9	48.4	22.6	12.7	11.3	9	0.7	4.4	1.7
Nadarajah R[36]	2023	R	Primary care FIND-AF—UK	2,081,139	7386	49.9	50.69	12	3.53	0.73	3.76	1.84	0.8	1.22	1.42
Levent F[37]	2023	R	Ablation for AF—Turkey	252	51	60.12	54.75	40.07	36.88	7.95	19.41	5.98	3.97	7.16	
Bicciré FG[38]	2023	P	PCI—Italy	555	45	65.6	22.9	67.2	29.5	6.5	23	5.6	0.5	7.7	12.7

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; COPD, Chronic obstructive pulmonary disease; HF, heart failure; HTN, hypertension; NOAF, new onset atrial fibrillation.

[a]USA, Canada, Brazil, and Argentina and Russia/Georgia.

3.2 | Primary versus secondary prevention studies

Results in the subgroup of general population/primary care ($n=10{,}426{,}127$ with 282,328 NOAF) were consistent with the overall analysis yielding an AUC of 0.69 (95% CI .64–.75) with high heterogeneity ($I^2>99\%$) (Figure 2A). In the subgroup of patients with cardiovascular disease ($n=263{,}420$ with 19,018 NOAF) (Figure 2B), the AUC was quite similar with an AUC of 0.71 (95% CI .69–.79) with high heterogeneity ($I^2>99\%$).

3.3 | Analysis by region

We also performed a subgroup analysis by region of origin, comparing studies from Asia versus those from Western Countries. For this analysis, the study by Liang et al.[29] was excluded as it included a mixed population from USA and Russia/Georgia. We found that the C_2HEST score performed similarly in studies with Asian patients ($n=1{,}309{,}110$ with 19,867 NOAF) with an AUC .72 (95% CI .68–.77) ($I^2>99\%$) (Figure 3A), and in those with Western ones ($n=9{,}756{,}184$ with 287,872 NOAF) with an AUC .68 (95% CI .62–.75) ($I^2>99\%$) (Figure 3B).

3.4 | Other subgroup analysis

Prospective/RCT studies only

We performed a subgroup analysis after the exclusion of retrospective studies including four studies, three prospectives[26,35,38] and 1 post-hoc RCT analysis,[29] C_2HEST score performed similarly than primary analysis (AUC .72, 95% CI .70–.74) (I^2 47.7%).

Studies with low/no risk of bias

In addition, analysis including only studies without any concerns in the RoB assessment, showed that the C_2HEST score performed similarly than the overall analysis (AUC .71, 95% CI .67–.76) (I^2 98.9%).

Studies with a mean age <50 years

When we included only studies with patients with a mean age <50 years at enrolment[32,36] ($n=3{,}144{,}704$ with 25,538 NOAF), the performance of the score was AUC .78, 95% CI .76–.79 (Figure S2).

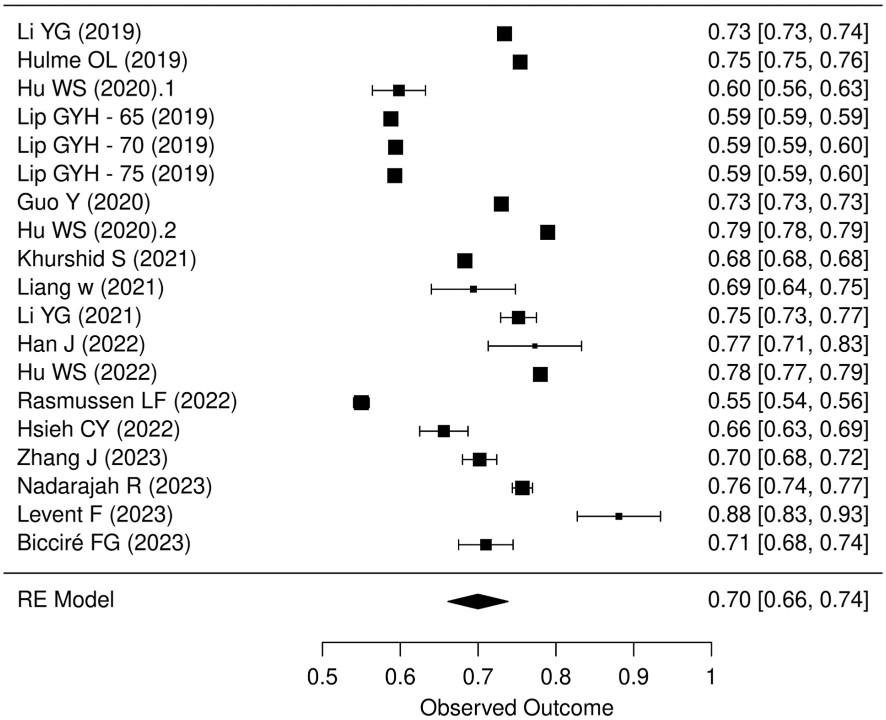

FIGURE 1 Forest plot for the pooled area under the ROC curve (AUC) values of the C_2HEST score in the overall population.

After the exclusion of the only study including cardiac surgery

We repeated the analysis by removing the study by Rasmussen et al.[33] that included patients with structural heart disease. We observed that the AUC for the score was .71 (95% CI .67–.75) (Figure S3).

3.5 | Risk of bias assessment

The RoB of observational cohorts included in meta-analysis is presented in Figure 4. All studies were considered at low RoB due confounding factors. At least one study had moderate RoB for each of these domains: selection of participants, to missing data and in selection of the reported results domains. Two studies had a moderate RoB for classification of intervention domains. No studies had several risks of bias in ROBINS domains. Overall, the RoB assessment showed a low to moderate RoB.

In summary, the most represented RoB was for classification of intervention domains with a moderate risk (D3), then a moderate RoB was observed also for selection of participants (D2), to missing data (D5) and in selection of the reported results (D7).

Funnel plots for publication bias are displayed in the Figure S4. The overall publication bias risk is moderate-high. In the subgroup analysis, according to Asian or Western country and according to general population or patients with cardiovascular disease the publication bias risk is moderate-high. Similar results were obtained in the subgroups analyses when retrospective studies or studies with any concerns in the RoB were removed.

3.6 | Meta-regression analysis

We performed some meta-regression analysis for some factors potentially affecting the performance of the C_2HEST score, such as age, proportion of women, baseline risk of NOAF (C_2HEST score at baseline), hypertension, diabetes, HF, coronary heart disease, stroke/TIA, hyperthyroidism, COPD, chronic kidney disease (bubble plots are reported in the Figure S5A–K).

We found that the C_2HEST score performed better in young patients ($p=.024$), in those with low C_2HEST score at baseline ($p=.017$) and with low prevalence of coronary disease ($p=.043$). No effect of the other variables was observed.

Coefficients of meta-regressions are reported in the Table S1.

4 | DISCUSSION

This is the first meta-analysis on a sample of >11 million patients with >300,000 incident NOAF showing that the C_2HEST score has an adequate predictive value (AUC .70) to be used in clinical practice for the prediction of NOAF. The best performance was observed in studies with a mean age at enrollment <50 years (AUC .78). In particular, our

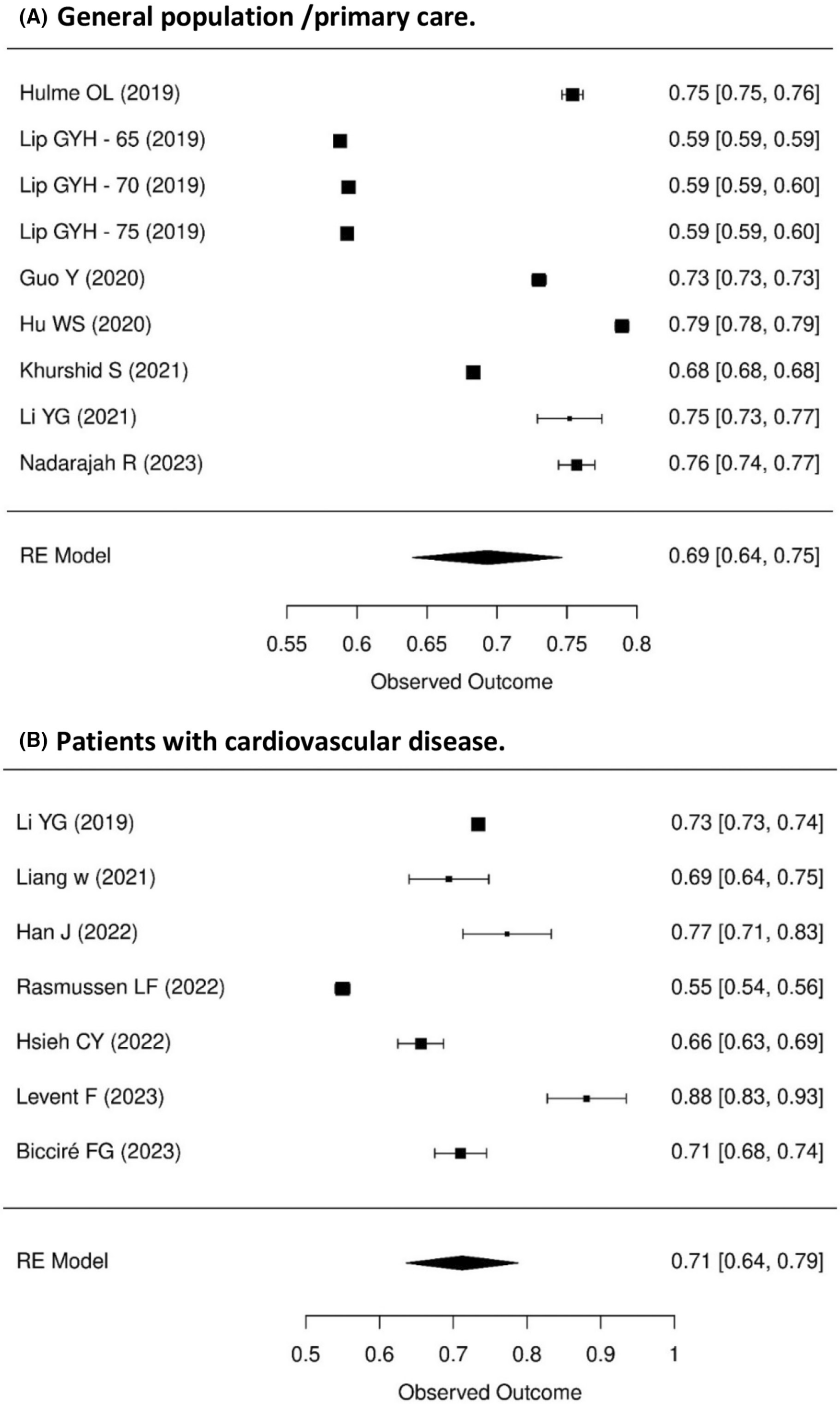

FIGURE 2 Pooled area under the ROC curve (AUC) of the C_2HEST score according to different settings. In Panel A, we evaluated studies performed in the general population/primary care patients. In Panel B, it is reported the analysis restricted to patients with cardiovascular disorders. Panel A. General population /primary care. Panel B. Patients with cardiovascular disease.

results showed that the C_2HEST score may be used both in the general population (AUC 0.69) and in secondary prevention patients (AUC .71). Also, the C_2HEST score performed similarly in Asian (AUC .72), and in Western (AUC .68) patients.

The use of the C_2HEST score in the general population may result in the early recognition of patients at high risk of NOAF allowing a prompt diagnosis and management of these patients. Indeed, once classified as high risk according to the C_2HEST score, a patient may undergo a closer follow-up to detect NOAF. There are now wearable devices that may allow a longer non-invasive monitoring of patients that have been shown to be more efficient than routine monitoring to detect NOAF.[39] Continuous monitoring with mobile health technology also resulted in lower clinical outcomes in patients diagnosed with AF, supporting the role of a continuous non-invasive monitoring also after the diagnosis of AF.[40]

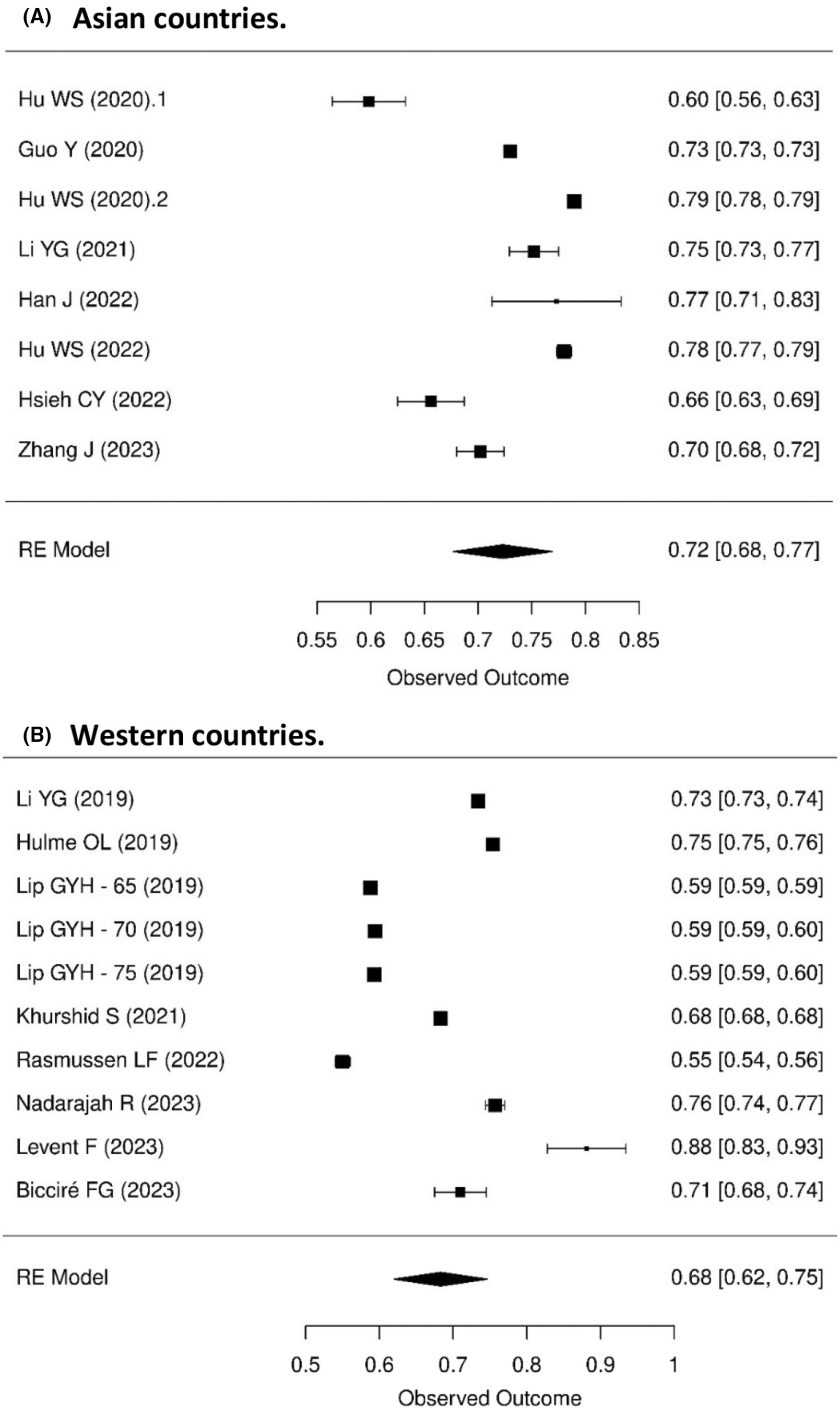

FIGURE 3 Pooled area under the ROC curve (AUC) of the C_2HEST score according to different countries. In Panel A, we evaluated studies performed in Asian countries. In Panel B, it is reported the analysis including studies from Western countries. Panel A. Asian countries. Panel B. Western countries.

Also, in patients with or at risk of cardiovascular disease, the usefulness of the C_2HEST score may be related to different aspect. Indeed, in patients with cryptogenic stroke, a high C_2HEST score along with imaging characteristics of the stroke, claim for a more intensive and continuous monitoring of high risk patients who may therefore be candidates for oral anticoagulation after AF detection. The C_2HEST score may be used in combination with clinical information such as the presence of AF-related symptoms. Indeed, a combination of symptomatic palpitations and C_2HEST score improved AF detection (c-indexes .72 vs. 0.76).[26]

Furthermore, preoperative risk evaluation for NOAF using the C_2HEST score, especially in surgery predisposing to AF such as cardiac[33] and lung interventions, may flag up patients who need a closer post-operative monitoring or who may benefit from preoperative administration of drugs known to reduce NOAF, such as statins, and

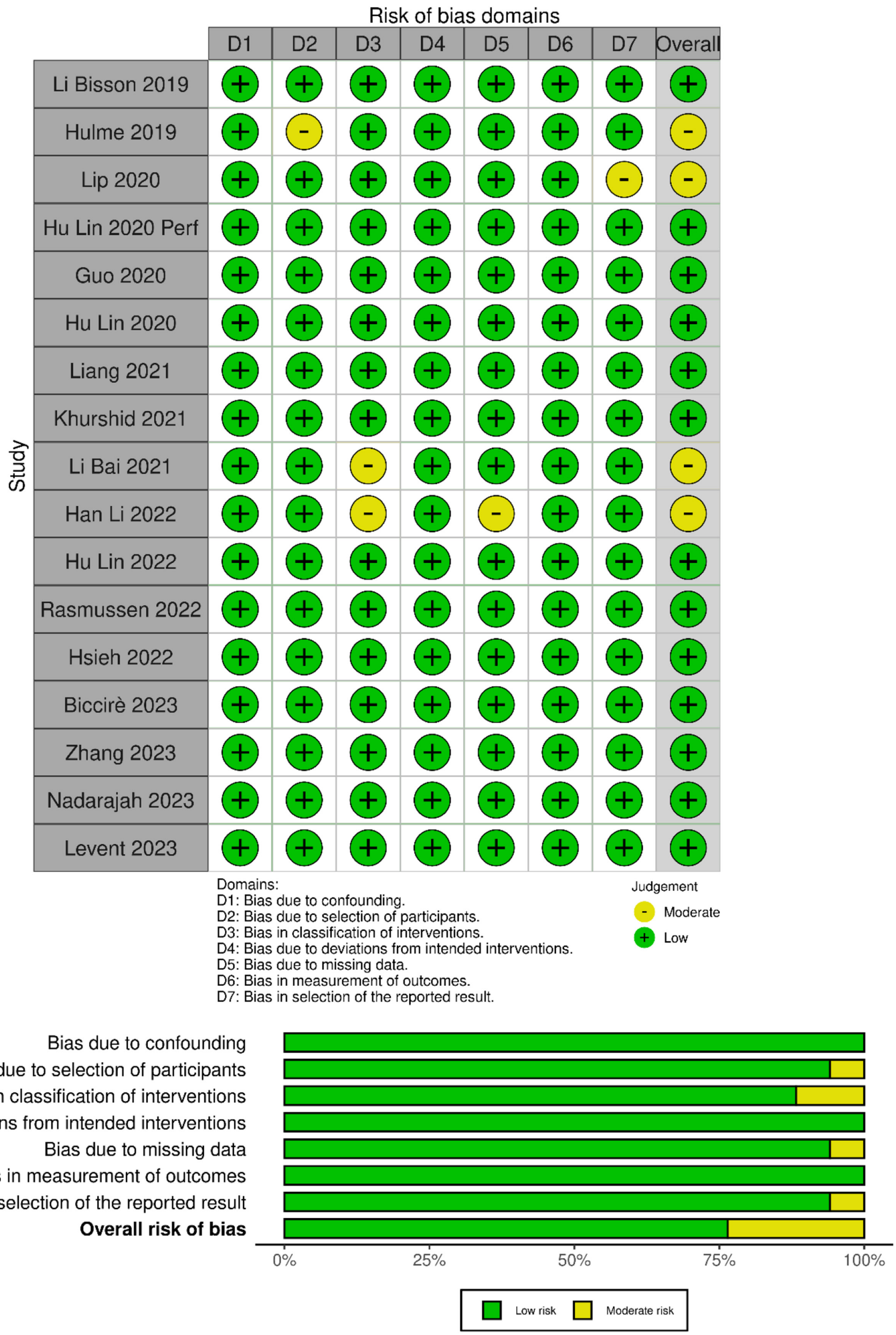

FIGURE 4 Risk of bias assessment.

in particular atorvastatin as shown by the ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) trial.[41]

Another novelty of the present study relies on the separate analysis of studies including subjects/patients from Eastern and Western countries. This subgroup analysis provides important information for at least two reasons. First, the risk of AF changes across countries and is generally lower in Asian countries, where there is an estimated annual incidence of AF for both men and women of 33.8 and 19.8 per 100,000 person-years, respectively, while the highest rates were reported in North America (264.5 and 196.3 per 100,000 person-years for men and women, respectively).[42] Furthermore, the C_2HEST score was been initially developed and validated on a large cohort of patients from China and Korea, respectively.[43] As such, the prevalence of some risk factors for NOAF may greatly differ across countries; for instance, the prevalence of hyperthyroidism is lower in Asian countries than in Western ones.[44] In the present study, we found a similar predictive performance of the C_2HEST score in studies including patients either from Asia or Western countries, indicating its suitability in both populations.

Preliminary data also showed that the C_2HEST score may be useful to detect subclinical AF, namely atrial high rates episodes (AHREs). Indeed, in the West Birmingham Atrial Fibrillation Project that included 500 patients with cardiac implantable electronic devices without AF at baseline, the C_2HEST score predicted sustained AHREs lasting >24 h with an AUC (0.73; 95% CI, .64–.81) performing better than CHA_2DS_2-VASc, $CHADS_2$, HATCH scores.[45] However, more data on AHREs prediction are needed.

The overall AUC of the C_2HEST score of .70 is similar if not even better than that observed with other clinical risk scores used in AF patients. As an example, a recent meta-analysis on the CHA_2DS_2 VASc score, that is currently guideline-recommended to stratify thromboembolic risk and to decide the eligibility of patients to start anticoagulation, showed an overall AUC of .65.[46] A similar value of 0.65 was recently reported also for the HAS-BLED score.[47] In addition to this, we have observed some important differences among studies regarding the predictive value of the C_2HEST score. These differences, along with the high heterogeneity, may be attributable to the different study characteristics.

At this regard, it is important to note that the lowest AUC value was observed in the study by Rasmussen et al.[33] that included patients undergoing cardiac surgery. However, as for the original derivation study of the C_2HEST score, it is intended to predict NOAF in patients without cardiac structural disease. Indeed, patients with cardiac disease are by definition at high-risk of developing NOAF; this is also demonstrated by the disproportionally high rate of NOAF (30%) observed in the study by Rasmussen et al.[33] compared to others (8.6% in non-cardiac surgery[35]). Therefore, the use of the C_2HEST score in this patient population may have limited usefulness.

Another important difference relies on the mean age of patients included in the analysis. The best performance of the C_2HEST score was observed in the studies including patients with a mean age <50 years at enrollment. In these studies, the AUC of the C_2HEST score was .78, indicating a good predictive value. Tis information is even more important in light of the recent evidence showing that earlier is the diagnosis of AF, higher is the risk of myocardial disease and premature death.[48]

Despite the overall value resulting from the meta-analysis shows an adequate predictive value of the C_2HEST score, a recent study sought to improve the predictivity of the C_2HEST score by refining the age stratum in the so-called modified mC_2HEST.[30] Indeed, the mC_2HEST score showed better predictive performance (AUC of .809) compared with the original C_2HEST (AUC of .752).[30] This new version of the score needs further validation.

What are the clinical implications? Early detection of NOAF may aid prompt initiation of management and follow-up, especially given the increasing focus on integrated care pathways for diagnosis, characterization and management of AF patients in a holistic manner.[49,50] Adherence with such an approach is associated with improved clinical outcomes[51,52] and is also recommended in guidelines.[19,53]

4.1 | Limitations

Limits of the current analysis of available evidence certainly include that many of the studies have retrospective design despite some of them having a very large sample of patients. In addition, some studies used ICD codes to calculate the score, and as for all clinical scores, this may result in some approximation of some variables (such as COPD). Finally, we have no data yet on many specific high-risk subgroups of patients such as those with obesity, cancer and sepsis/pneumonia, all clinical conditions leading to NOAF. Another limitation is represented by the high statistical heterogeneity, given the high numerosity of single studies. However, the large sample of patients and the low RoB of included studies are certainly strengths of this analysis.

5 | CONCLUSION

The easy C_2HEST score may be used to predict NOAF in primary and secondary prevention patients, and in patients across different countries. Early detection of NOAF may aid prompt initiation of management and follow-up, potentially leading to a reduction of AF-related complications.

AUTHOR CONTRIBUTIONS

Daniele Pastori: Conceptualization, writing—original draft. Danilo Menichelli: Conceptualization, Methodology, writing—original draft. Yan-Guang Li: Supervision, writing—review and editing. Tommaso Brogi: Methodology, data curation. Flavio Giuseppe Biccirè: Data curation, writing—original draft. Pasquale Pignatelli: Supervision, writing—review and editing. Alessio Farcomeni: Formal analysis, Methodology. Gregory Y. H. Lip: Supervision, writing—review and editing.

ACKNOWLEDGEMENTS

None.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

None.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pastori D, Menichelli D, Li Y-G, et al. Usefulness of the C_2HEST score to predict new onset atrial fibrillation. A systematic review and meta-analysis on >11 million subjects. *Eur J Clin Invest*. 2024;00:e14293. doi:10.1111/eci.14293