Supplementary Material

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Table S1. PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Paragraph 1,2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Paragraph 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Paragraph 3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Paragraph 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary table 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Paragraph 4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Paragraph 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Paragraph 3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Paragraph 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Paragraph 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Paragraph 7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Paragraph 7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Paragraph 7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Paragraph 7
	13d	Describe any methods used to synthesize results and provide a	Paragraph 7-

Section and Topic	Item #	Checklist item	Location where item is reported
		rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Paragraph 9,10
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Paragraph 10
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Paragraph 10
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	None
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Paragraph 1, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Paragraph 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1, Paragraph 2-14
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Paragraph 15-16
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supplementary Figures 1,2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supplementary Figures 1,2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figures 2, Paragraph 17
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Paragraph 18, 20
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Paragraph 19
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Figures 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	None
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Paragraph 1
	23b	Discuss any limitations of the evidence included in the review.	Paragraph 7
	23c	Discuss any limitations of the review processes used.	Paragraph 7
	23d	Discuss implications of the results for practice, policy, and future research.	Paragraph 8
OTHER INFORMATION			

Section and Topic	Item #	Checklist item	Location where item is reported
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods Paragraph 1
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods Paragraph 1
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Methods Paragraph 1
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Declarations
Competing interests	26	Declare any competing interests of review authors.	Declarations
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Declarations

Table S2. Search strategy

Database	Search query	Record results
Pubmed	((((((((((("Machine Learning"[Mesh]) OR ("Supervised Machine Learning"[Mesh])) OR ("Artificial Intelligence"[Mesh])) OR ("random forest"[Title/Abstract])) OR ("nearest neighbor"[Title/Abstract])) OR ("support vector"[Title/Abstract])) OR ("logistic regression"[Title/Abstract])) OR (LASSO[Title/Abstract])) OR (algorithm[Title/Abstract])) OR (machin*[Title/Abstract])) AND ("Atrial Fibrillation"[Mesh])) AND ("Stroke"[Mesh])	952
Embase	('cerebrovascular accident'/exp OR 'cerebrovascular accident') AND ('atrial fibrillation'/exp OR 'atrial fibrillation') AND ('machine learning'/exp OR 'machine learning' OR 'artificial intelligence'/exp OR 'artificial intelligence' OR 'supervised machine learning'/exp OR 'support vector' OR 'nearest neighbor' OR 'algorithm') AND [article]/lim AND [english]/lim	833
Web of Science	(((((((TS=(machine learning)) OR TS=(artificial intelligence)) OR TS=("random forest")) OR TS=("nearest neighbor")) OR TS=("support vector")) OR TS=(LASSO))OR TS=(algorithm)) AND ((((TS=("cerebrovascular accident")) OR TS=(CVA)) OR TS=(stroke))) AND TS=("atrial fibrillation")) Refined By:Document Types: Article, Languages: English	892
Total		2,677

Table S3. Summary of calibration and clinical utility reporting in the included studies

First author, year	Calibration method	Calibration conclusion	Absolute risk output; compared to observed	Decision curve	NRI / IDI reported	Reclassification tables	Other clinical utility metrics	Implementation or impact study	General rating
Letham et al., 2015 [1]	N/A	N/A	Yes (Bayesian Rule List 1-year stroke risk); No	None	No	No	None	No	**Absent**
Li et al., 2016 a [2]	N/A	N/A	No; No	None	No	No	None	No	**Absent**
Li et al., 2016 b [3]	N/A	N/A	No; No	None	No	No	None	No	**Absent**
Leonarduzzi et al., 2018 [4]	N/A	N/A	No; No	None	No	No	None	No	**Absent**
Han et al., 2019 [5]	Calibration plot with 20 bins of predicted probability vs observed event percentage in test set	Ensemble model underconfident with maximum predicted probability around 40–50% but showing increasing observed event percentage across bins whereas other methods including CHA2DS2-VASc showed little relationship and clustering at low or high predicted probabilities	Yes (predicted probability of near-term stroke from ML models and CHA2DS2-VASc LR); Yes (observed event percentages compared across predicted probability bins in calibration plot)	None	No	No	None	No	**Partial**
Goto et al., 2020 [6]	N/A	N/A	No; No	None	No	No	Kaplan–Meier curves by ML risk group (no formal decision or impact analysis)	No	**Absent**
Loring et al., 2020 [7]	Calibration plots of predicted vs observed 1-year event rates for stepwise LR, RF and GB models in each registry and in cross-registry validation	Stepwise model showed close agreement between predicted and observed risk for stroke, whereas RF and GB generally underestimated event rates and ML calibration was affected by outcome up-sampling	Yes (models output 1-year probabilities of stroke); Yes (observed vs predicted event rates in calibration plots for both derivation and cross-registry validation)	None	Yes (NRI for RF and GB vs stepwise in cross-registry models)	No	None	No	**Good**
Watanabe et al., 2021[8]	Calibration plots of predicted versus observed 2-year event rates across quintiles for RF and LR and categorical calibration of clinical risk scores	RF and LR overestimated thromboembolism risk in the high-risk group and LR underestimated low risk while CHADS2 and CHA2DS2-VASc generally underestimated risk in high-risk categories	Yes (RF and LR estimated 2-year probabilities of thromboembolism); Yes (in calibration plots and categorical risk score groups)	None	Yes (continuous NRI RF versus LR and categorical NRI RF versus CHADS2 CHA2DS2-VASc)	No	None	No	**Good**
Jung et al., 2022 [9]	N/A	N/A	Yes (deep NN output approximate probability of ischemic stroke occurrence on a 0–1 scale); No	None	No	No	None	No	**Absent**
Lu et al., 2022 [10]	Brier score for each outcome and each model including multilabel GBM, SVM, Multilayer NN, and LR risk scores	ML models reported to have better calibration than clinical risk scores with similar calibration across different multilabel ML models	Yes (models output 1 year predicted probabilities for ischemic stroke); No	None	Yes (NRI for ischemic stroke comparing best performing multilabel GBM with CHA2DS2-VASc)	No	Threshold-based rule-out description (no formal decision analysis)	No	**Good**
Nishi et al., 2022 [11]	N/A	N/A	Yes (ML model outputs predicted probabilities of cerebral infarction and defines low, moderate and high-risk groups, CHADS2 and CHA2DS2-VASc used as clinical risk scores); No	None	No	No	Kaplan–Meier curves and hazard ratios by risk group plus counts of anticoagulation recommendations (rudimentary clinical impact analysis)	No	**Partial**

Li et al., 2023 [12]	N/A	N/A	Yes (Deep NN output approximate probability 0–1 of ischemic stroke with fixed threshold 0.5); No	None	No	No	None	No	**Absent**
Bernardini et al., 2024 [13]	N/A	N/A	No; No	None	No	No	None	No	**Absent**
Chen et al., 2024 [14]	N/A	N/A	Yes (models output one year stroke probability via ML classifiers and web-based tool); No	None	No	No	Threshold-based classification with online tool (no formal decision or impact analysis)	No	**Absent**
Gao et al., 2024 [15]	N/A	N/A	Yes (LightGBM based models output 2-year stroke risk probabilities); No	None	No	No	None	No	**Absent**
Papadopoulou et al., 2024 [16]	N/A	N/A	No; No	None	No	No	None	No	**Absent**
Lu et al., 2024 [17]	N/A	N/A	Yes (model outputs risk probabilities); No	Yes (decision-curve analysis of net benefit for ML-GBDT vs clinical scores and treat-all/treat-none across thresholds)	Yes (NRI reported for stroke comparing ML-GBDT with clinical risk scores)		Kaplan–Meier curves by risk quartile (formal clinical utility analysis)	No	**Partial**

GB: Gradient Boosting; **GBDT:** Gradient Boosting Decision Tree; **IDI:** Integrated Discrimination Improvement; **LR:** Logistic Regression; **ML:** Machine Learning; **N/A:** Not Applicable / Not Available; **NN:** Neural Network; **NRI:** Net Reclassification Improvement; **RF:** Random Forest; **SVM:** Support Vector Machine; **TIA:** Transient Ischemic Attack.

Table S4. Summary of study-level handling of anticoagulation therapy

First author, year	Relevant eligibility criteria	OAC type (s)	Baseline status reported	Incident OAC during follow-up (reporting/ handling)	Exposure intensity / duration modelled	Adherence / persistence considered	Handling of time-varying OAC (quality rating)	Role of OAC in prediction model	OAC-related findings
Letham et al., 2015 [1]	N/R	N/R	No	N/R, N/R	N/R	N/R	No	N/R	None
Li et al., 2016 a [2]	Excluded: OAC	N/A	Yes	N/R, N/R	N/A	N/A	N/A	N/A	None
Li et al., 2016 b [3]	Excluded: OAC	N/A	Yes	N/R, N/R	N/A	N/A	N/A	N/A	None
Leonarduzzi et al., 2018 [4]	Mixed	N/S (antithrombotic in general)	Yes	N/R, N/R	No	No	No	Subgroup analysis for OAC use	Scattering transform features of RR dynamics predicted ischemic stroke better in patients not receiving antithrombotic treatment with AUCs around 0.8 to 0.85 whereas performance in treated patients was modest and driven mainly by CHA2DS2-VASc and entropy features. **the type of antithrombotic agent is not reported.
Han et al., 2019 [5]	Excluded: OAC	N/A	Yes	Yes, No	N/A	N/A	No	N/A	None
Goto et al., 2020 [6]	Included: OAC (VKA)	VKA only	Yes	N/A	Duration-intensity modeled via TTR	No	Partly	TTR as predictor	Serial PT-INR pattern over the first 30 days of VKA therapy predicted stroke or systemic embolism up to 1 year with c-statistics around 0.70 for stroke and outperformed TTR as a marker of warfarin control
Loring et al., 2020 [7]	Mixed	VKA / DOAC	Yes	N/R, N/R	N/R	No	No	Subgroup analysis for OAC use	Subgroup analysis by anticoagulation status showed similar discrimination and calibration to the overall models
Watanabe et al., 2021[8]	Mixed	VKA only	Yes	N/R, N/R	Duration-intensity modeled via TTR	No	Partly	OAC use as predictor	Most patients (86.5%) were on warfarin and the model included labile INR (time in therapeutic range <60%) as predictor. **the authors note that near-universal warfarin use and absence of DOACs may limit generalizability and confound stroke risk prediction.
Jung et al., 2022 [9]	N/R	N/R	No	N/R, N/R	N/R	N/R	No	N/R	None
Lu et al., 2022 [10]	Mixed	VKA / DOAC	Yes	N/R, N/R	No	No	No	OAC use as predictor, Subgroup analysis for OAC use	OAC therapy at discharge (warfarin or DOAC) was included as a predictor. **a sensitivity analysis restricted to patients not on OAC showed maintaining similar performance (AUC) for stroke.
Nishi et al., 2022 [11]	Excluded: OAC	N/A	Yes	N/R, N/R	N/A	N/A	No	N/A	None
Li et al., 2023 [12]	N/R	N/R	No	N/R, N/R	N/R	N/R	No	N/R	None

Bernardini et al., 2024 [13]	Included: OAC	VKA / DOAC / reduced dose DOAC	Yes	N/A	N/R	No	No	Subgroup analysis for OAC type	AUCs are reported separately for overall DOAC and VKA groups with no meaningful difference
Chen et al., 2024 [14]	Mixed	VKA / DOAC	Yes	N/R, N/R	N/R	No	No	None	None
Gao et al., 2024 [15]	N/R	N/R	No	N/R, N/R	N/R	N/R	No	N/R	None
Papadopoulou et al., 2024 [16]	N/R	N/R	No	N/R, N/R	N/R	N/R	No	N/R	None
Lu et al., 2024 [17]	Mixed	VKA / DOAC	Yes	Yes, No	No	No	No	OAC use as predictor, Subgroup analysis for OAC use	anticoagulant therapy (and OAC type) ranked among the most important predictors: VKA was the most influential OAC type with dabigatran next; the ML model outperformed CHA2DS2-VASc in general population, yet the differences were no longer statistically significant (likely underpowered, especially in the non-OAC group)

AF: atrial fibrillation; **OAC**: oral anticoagulant; **VKA**: vitamin K antagonist; **DOAC**: direct oral anticoagulant; **N/R:** not reported; **N/A**: not applicable; **N/S**: not specified; **TTR**: time in therapeutic range; **INR**: international normalized ratio; **PT-INR**: prothrombin time–international normalized ratio; **RR**: R–R (beat-to-beat) interval; **AUC**: area under the receiver operating characteristic curve.

Main Analysis

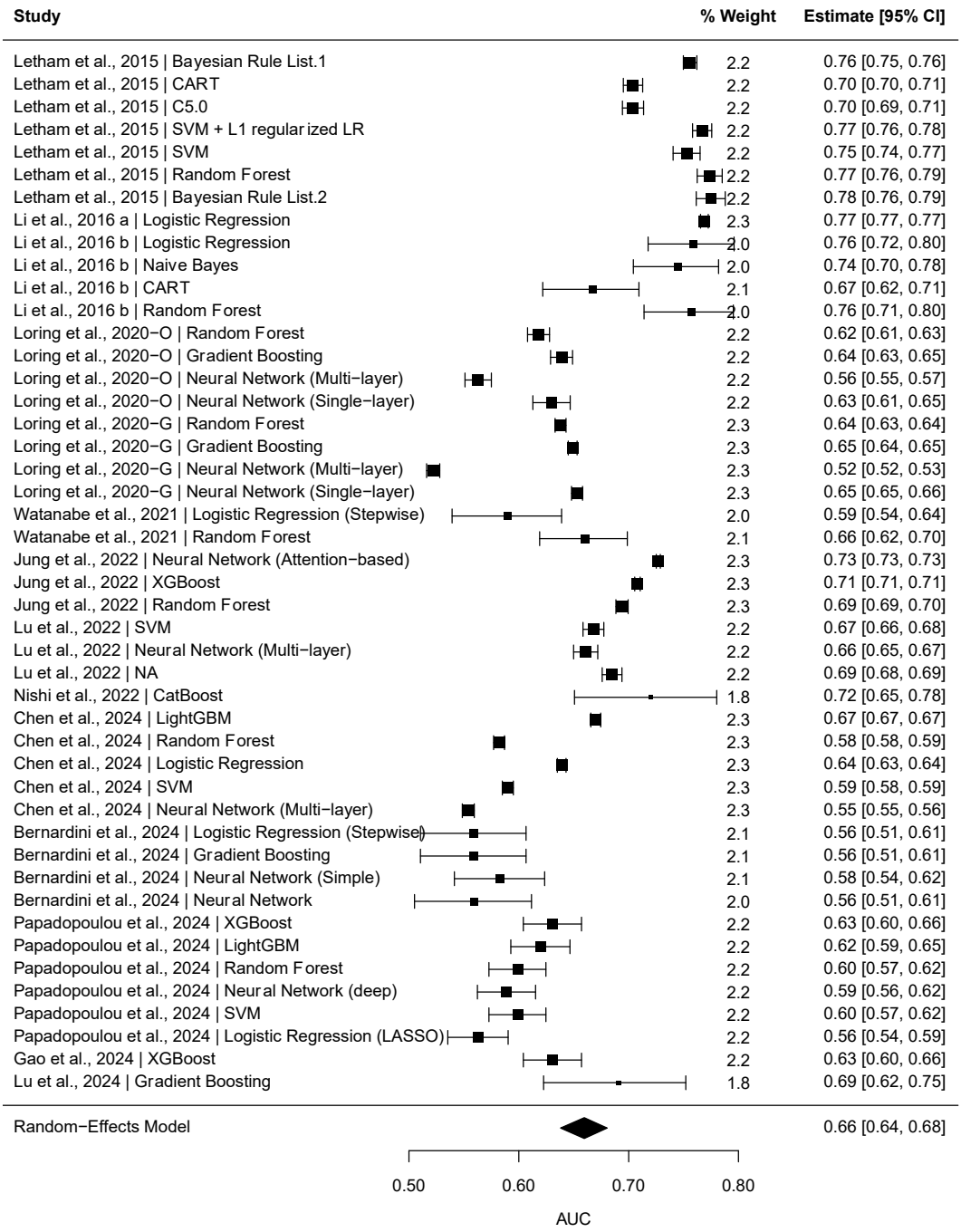

Figure S1. Forest plot showing AUROCs of individual ML models and the pooled estimate with 95% CI.

Heterogeneity: $I^2 = 99.8\%$, $\tau^2 = 0.1031$, Q (45) = 16298.06, $p < 0.0001$;
AUROC = area under the receiver operating characteristic curve; CI = confidence interval; ML = machine learning.

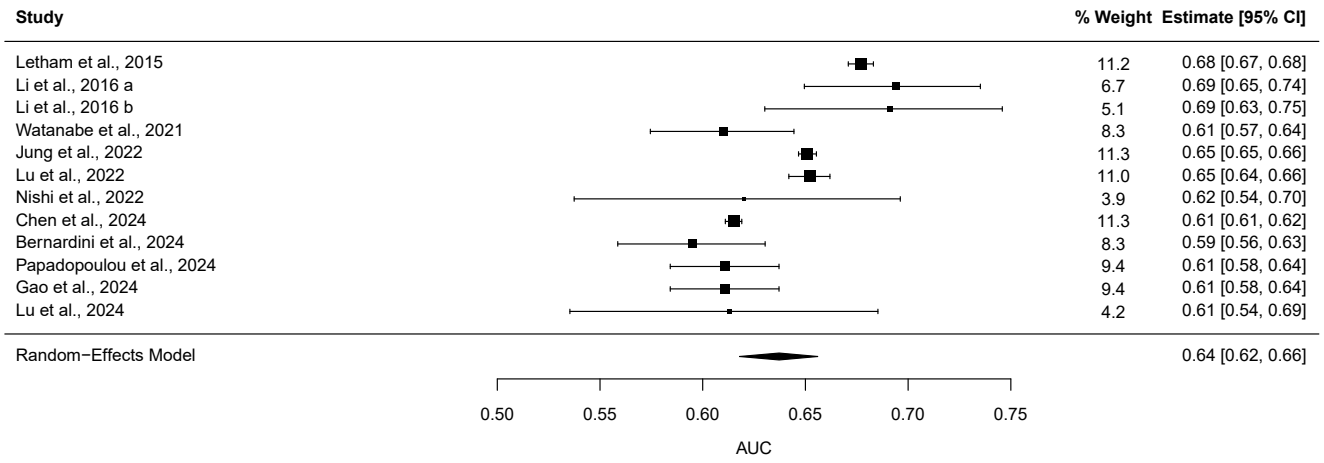

Figure S2. Forest plot showing AUROCs of individual CHA_2DS_2-VASc models and the pooled estimate with 95% CI.

Heterogeneity: $I^2 = 96.9\%$, $\tau^2 = 0.0156$, Q (11) = 343.34, $p < 0.0001$;
AUROC = area under the receiver operating characteristic curve; CI = confidence interval.

Subgroup Analysis

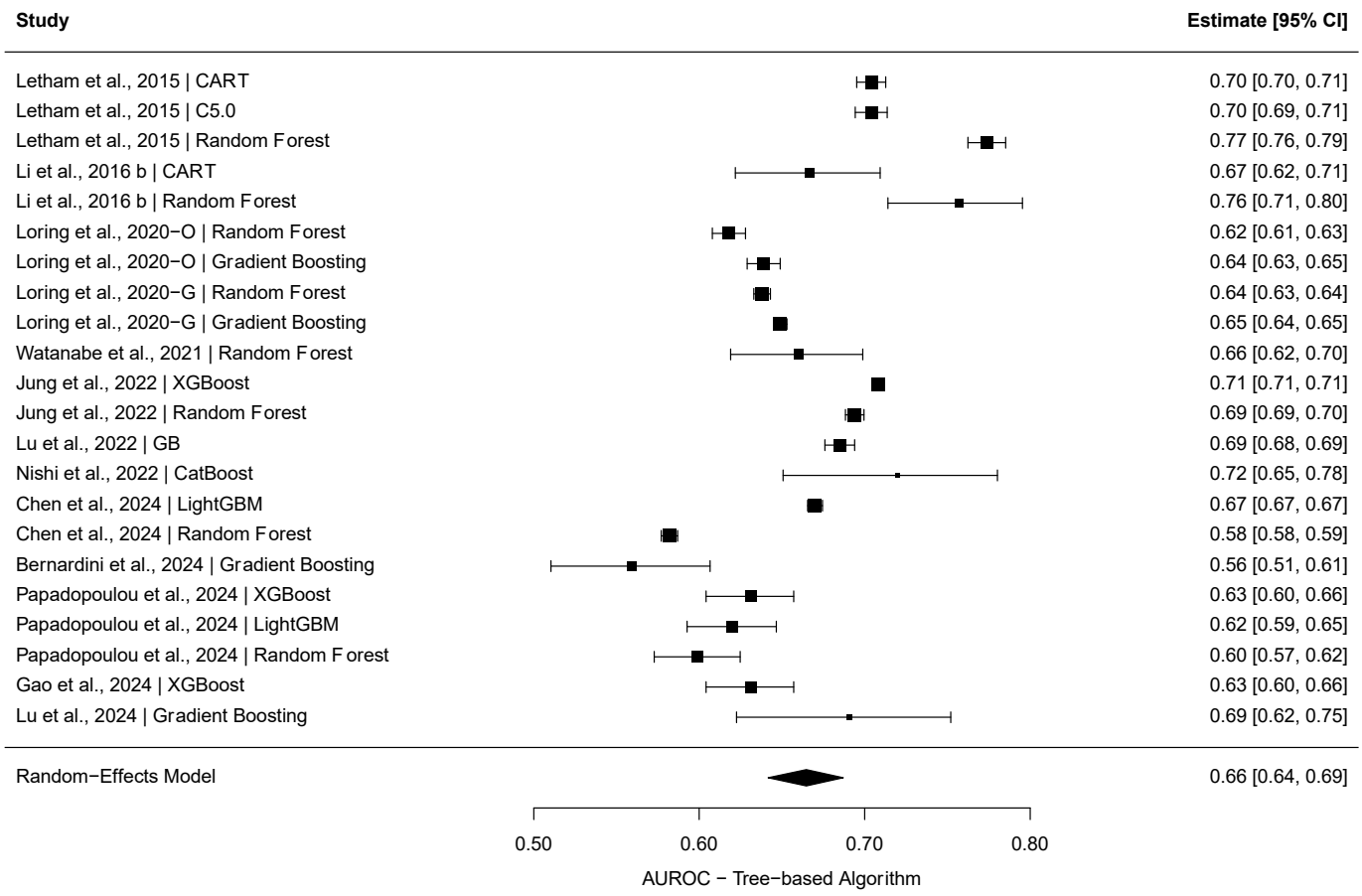

Figure S3. Forest plot showing AUROCs of individual tree-based models and the pooled estimate with 95% CI.

Heterogeneity: $I^2 = 99.5\%$, $\tau^2 = 0.0552$, Q (21) = 3084.31, $p < 0.0001$;
AUROC = area under the receiver operating characteristic curve; CI = confidence interval.

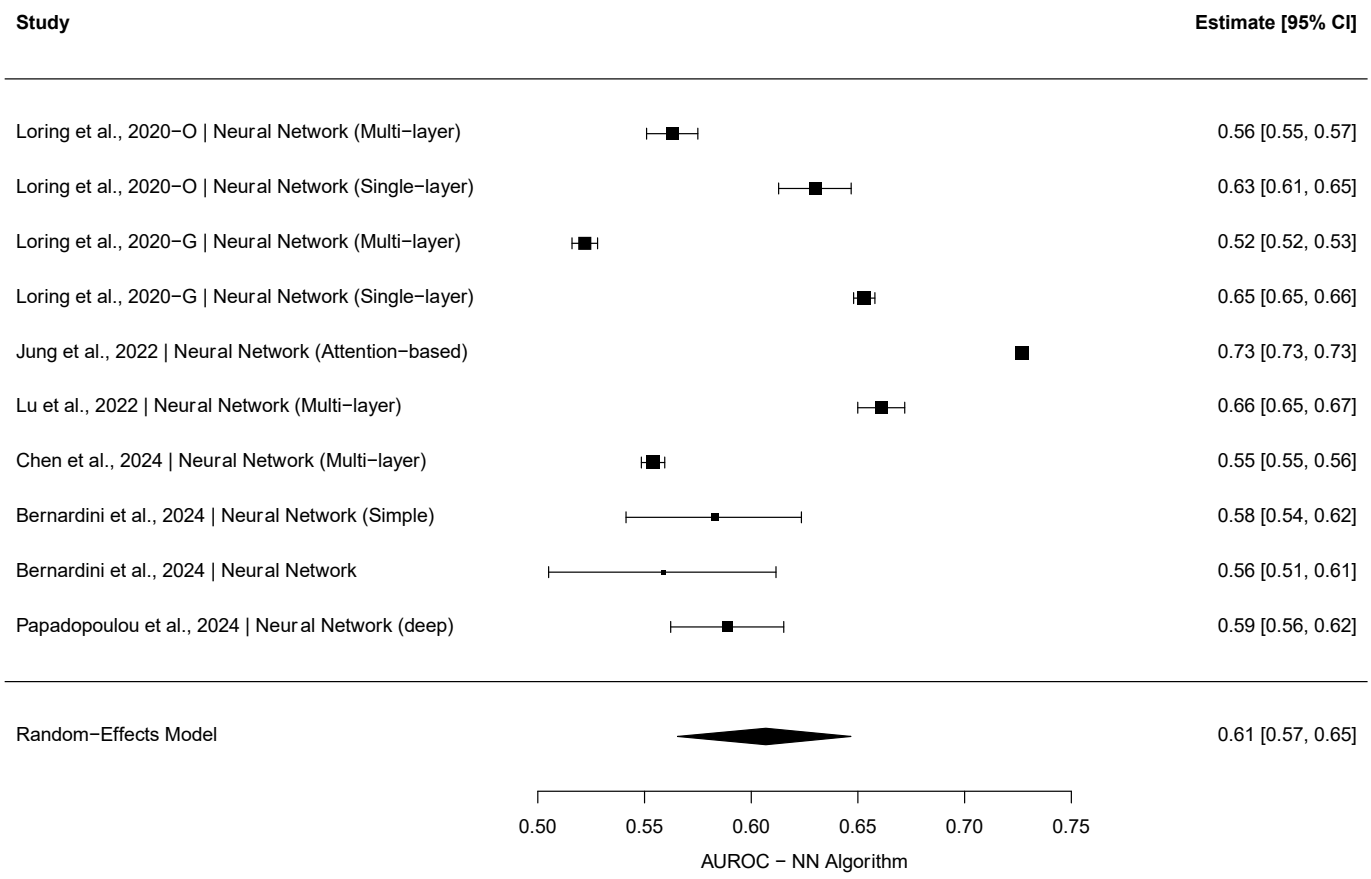

Figure S4. Forest plot showing AUROCs of individual NN models and the pooled estimate with 95% CI.

Heterogeneity: $I^2 = 99.7\%$, $\tau^2 = 0.0734$, Q (9) = 8057.72, $p < 0.0001$;
AUROC = area under the receiver operating characteristic curve; CI = confidence interval; NN = neural network.

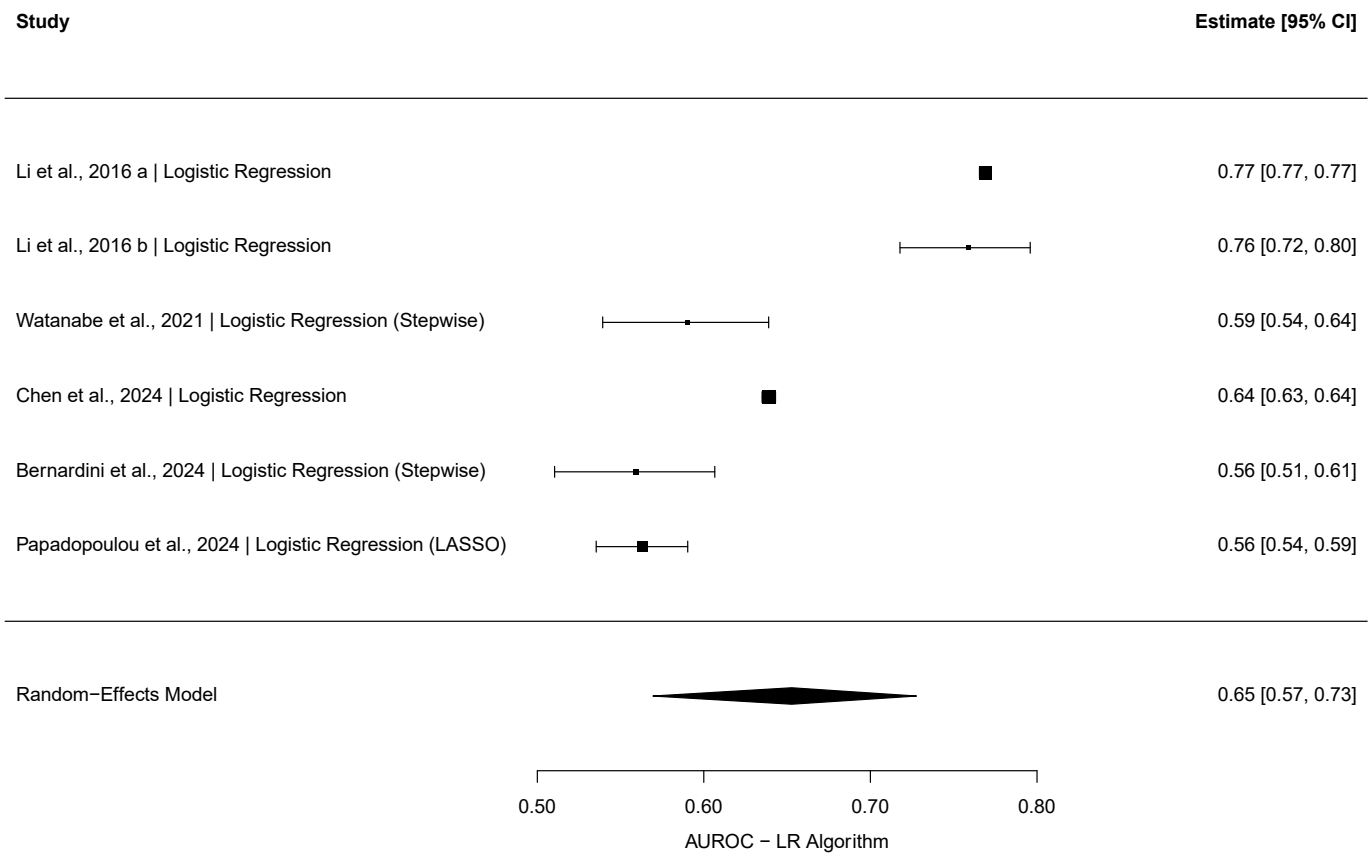

Figure S5. Forest plot showing AUROCs of individual LR models and the pooled estimate with 95% CI.

Heterogeneity: $I^2 = 99.8\%$, $\tau^2 = 0.1871$, Q (5) = 2391.42, $p < 0.0001$;
AUROC = area under the receiver operating characteristic curve; CI = confidence interval; LR = logistic regression.

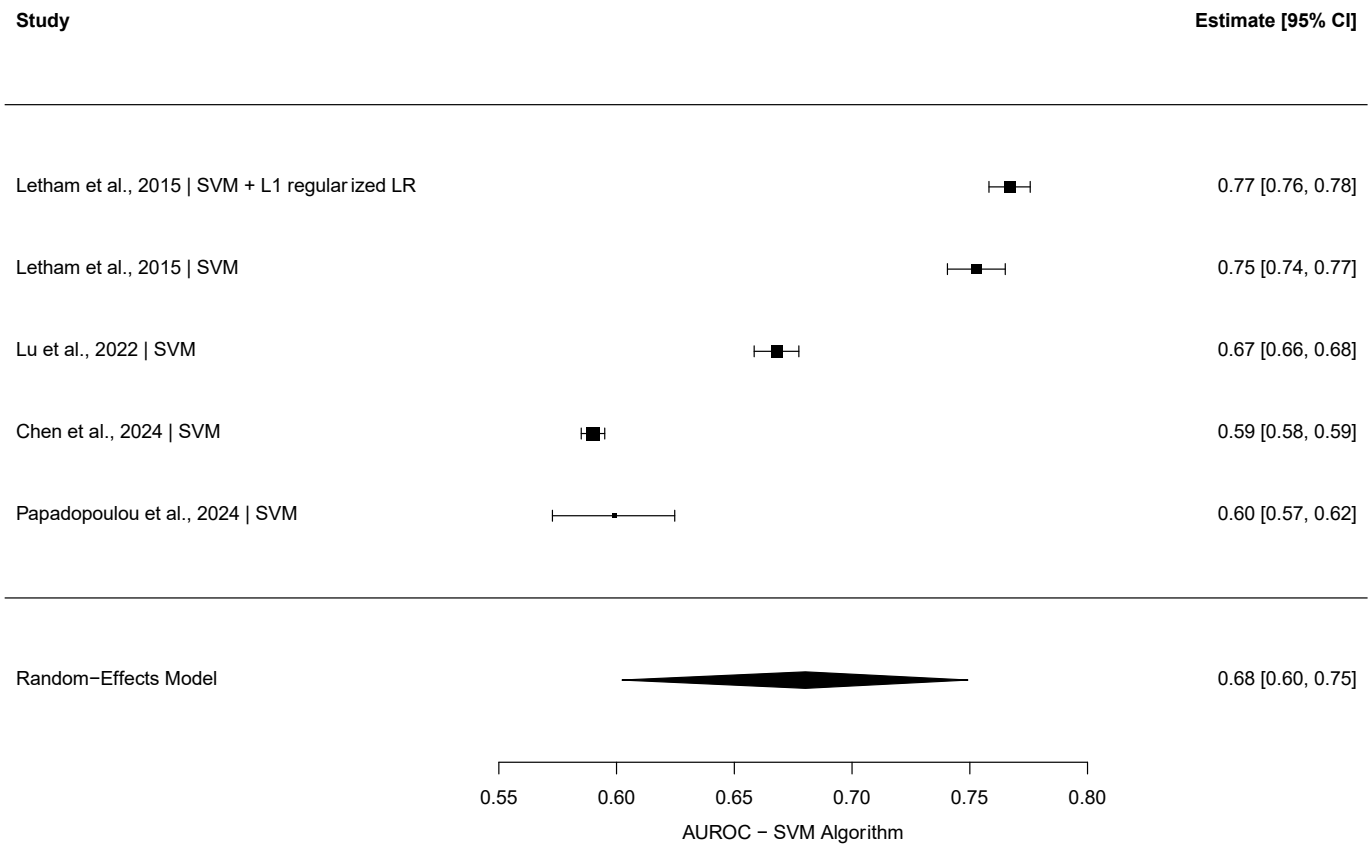

Figure S6. Forest plot showing AUROCs of individual SVM models and the pooled estimate with 95% CI.

Heterogeneity: $I^2 = 99.6\%$, $\tau^2 = 0.1491$, Q (4) = 1302.52, $p < 0.0001$;
AUROC = area under the receiver operating characteristic curve; CI = confidence interval; SVM = support vector machine.

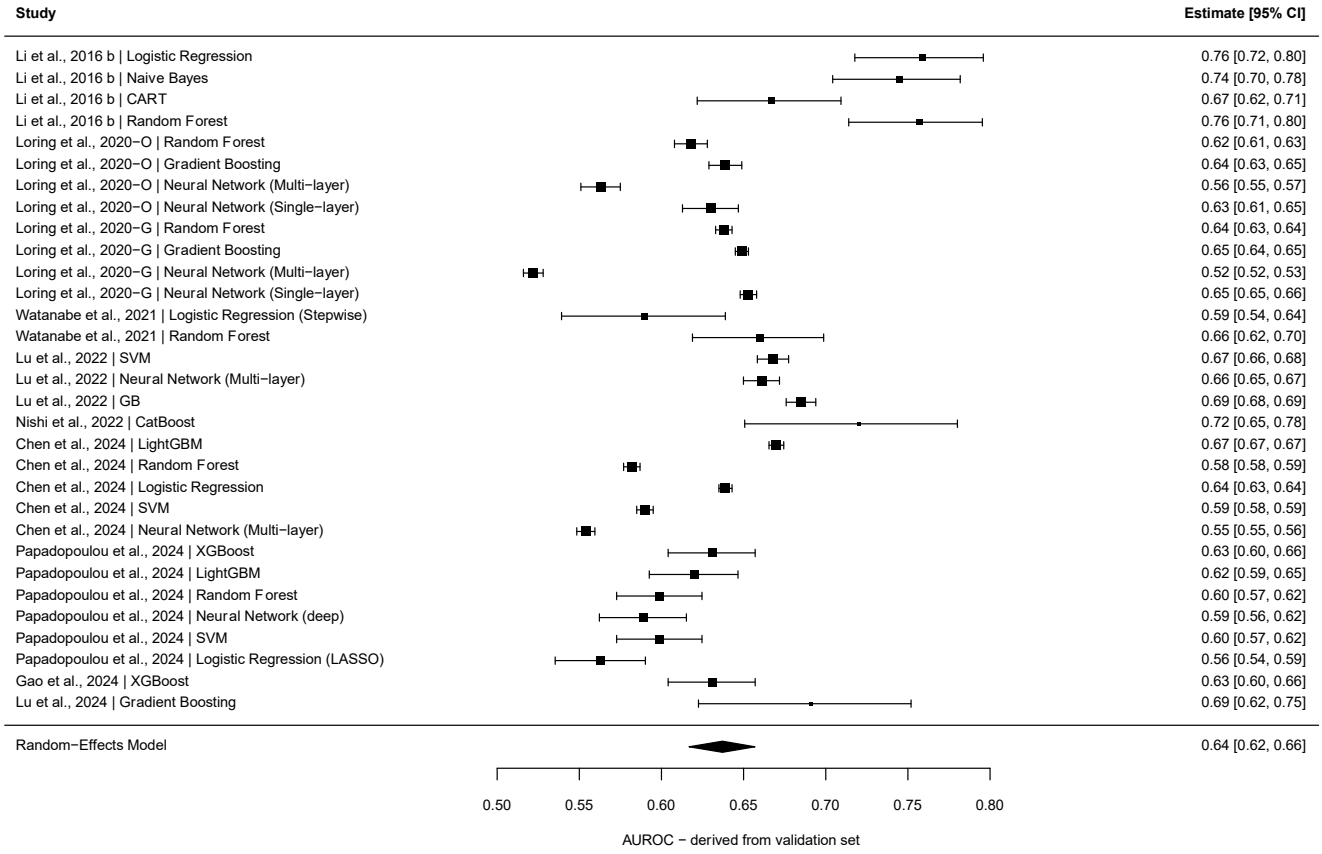

Figure S7. Forest plot showing AUROCs of ML models derived from the validation set with pooled estimate and 95% CI.

Heterogeneity: $I^2 = 99.4\%$, $\tau^2 = 0.0570$, Q (30) = 3530.08, $p < 0.0001$;
AUROC = area under the receiver operating characteristic curve; CI = confidence interval; ML = machine learning.

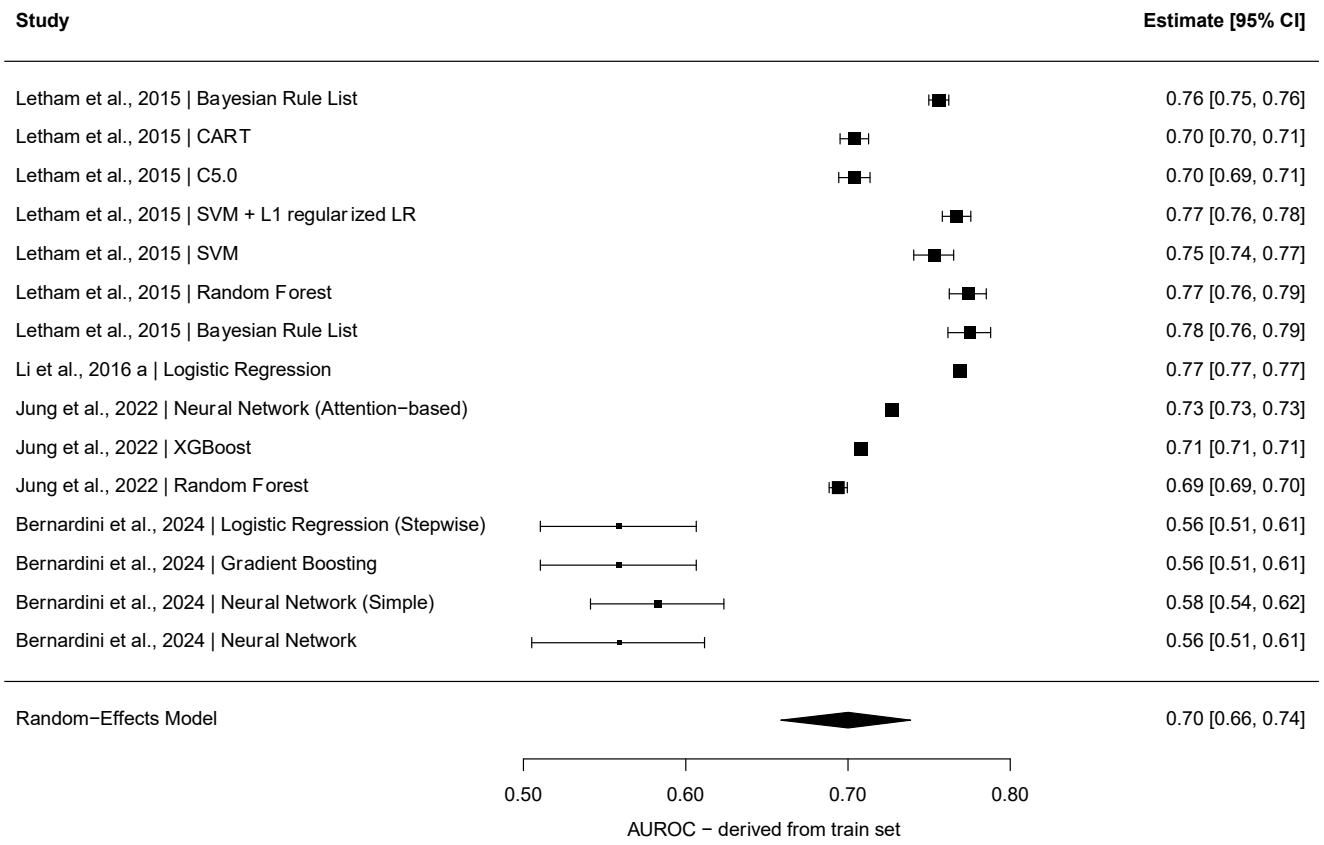

Figure S8. Forest plot showing AUROCs of ML models derived from the training set with pooled estimate and 95% CI.

Heterogeneity: $I^2 = 99.9\%$, $\tau^2 = 0.1391$, Q (14) = 1398.05, $p < 0.0001$;
AUROC = area under the receiver operating characteristic curve; CI = confidence interval. ML = machine learning.

Sensitivity Analyses

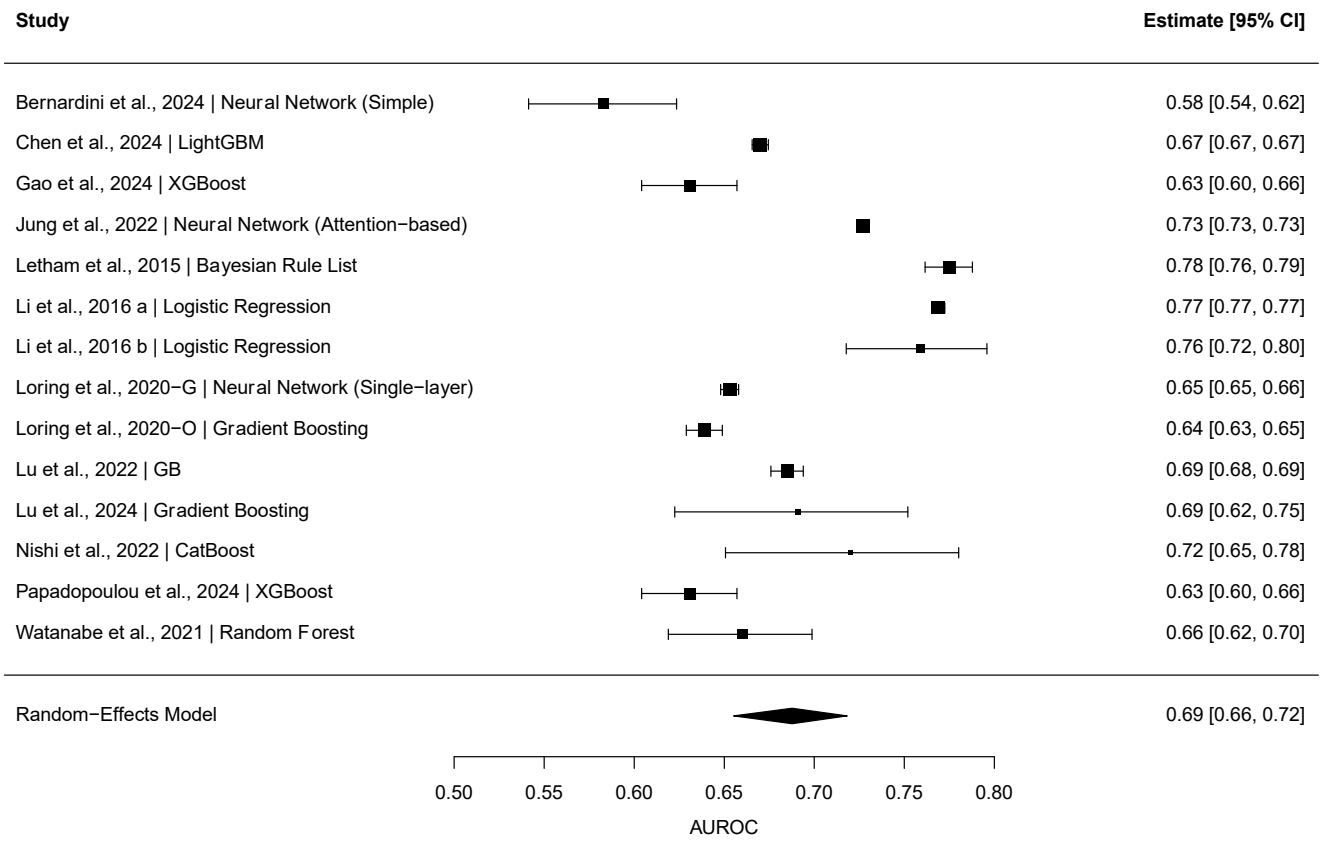

Figure S9. Forest plot of AUROCs for the best-performing model from each study and the pooled estimate with 95% CI

Heterogeneity: $I^2 = 99.6\%$, $\tau^2 = 0.0732$, Q (13) = 2519.86, $p < 0.0001$;
AUROC = area under the receiver operating characteristic curve; CI = confidence interval.

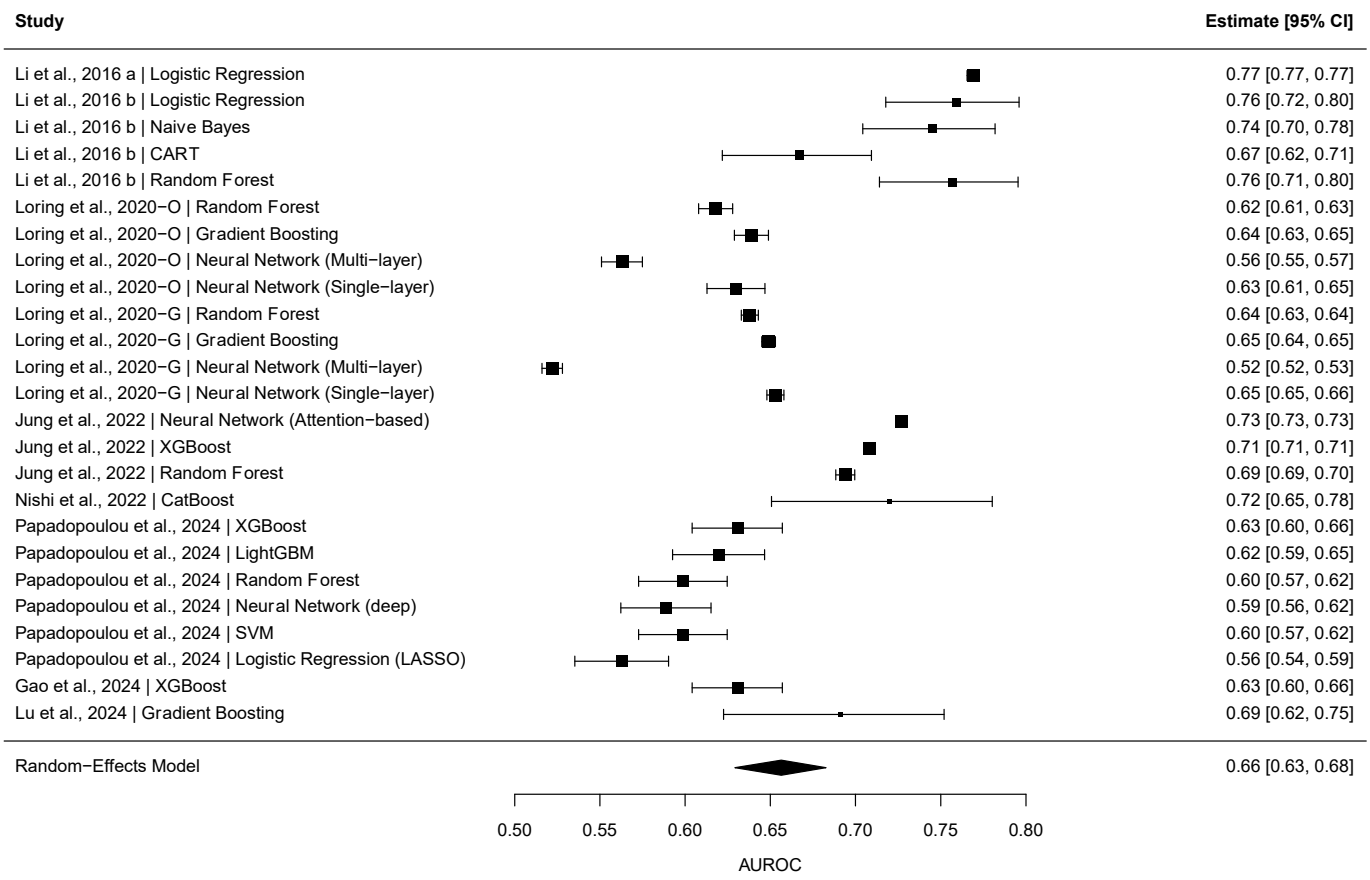

Figure S10. Forest plot showing AUROCs of individual ML models and the pooled estimate with 95% CI, restricting to studies with low risk of bias.

Heterogeneity: $I^2 = 99.7\%$, $\tau^2 = 0.0871$, Q (24) = 8877.48, $p < 0.0001$;
AUROC = area under the receiver operating characteristic curve; CI = confidence interval; ML = machine learning.

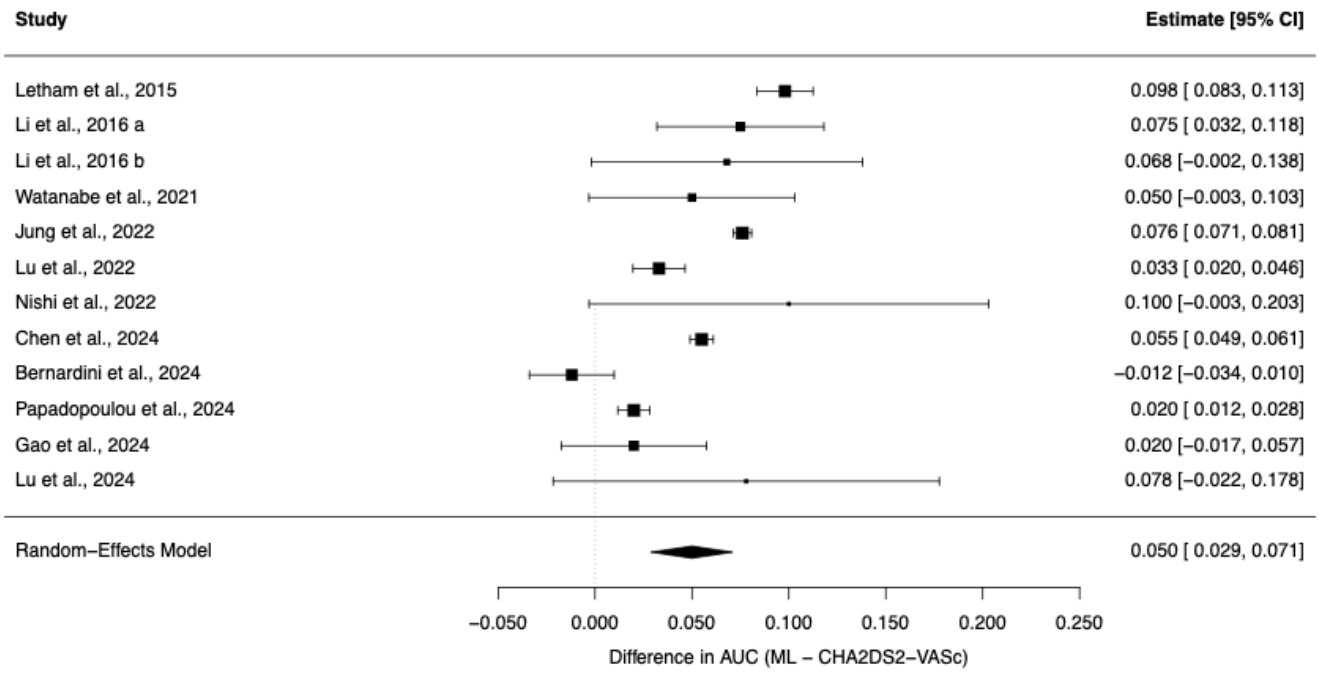

Figure S11. Forest plot of within-study differences in AUROC (ΔAUROC) between the best-performing machine learning model and the CHA_2DS_2-VASc score, along with the pooled estimates and 95% CI.

Positive values indicate better discrimination by the machine learning model compared with CHA_2DS_2-VASc.
Heterogeneity: $I^2 = 96.19\%$, $\tau^2 = 0.001$, Q (11) = 224.9232, $p < .0001$;
AUROC = area under the receiver operating characteristic curve; CI = confidence interval; ML = machine learning.

Assessment of Small-Study Effects

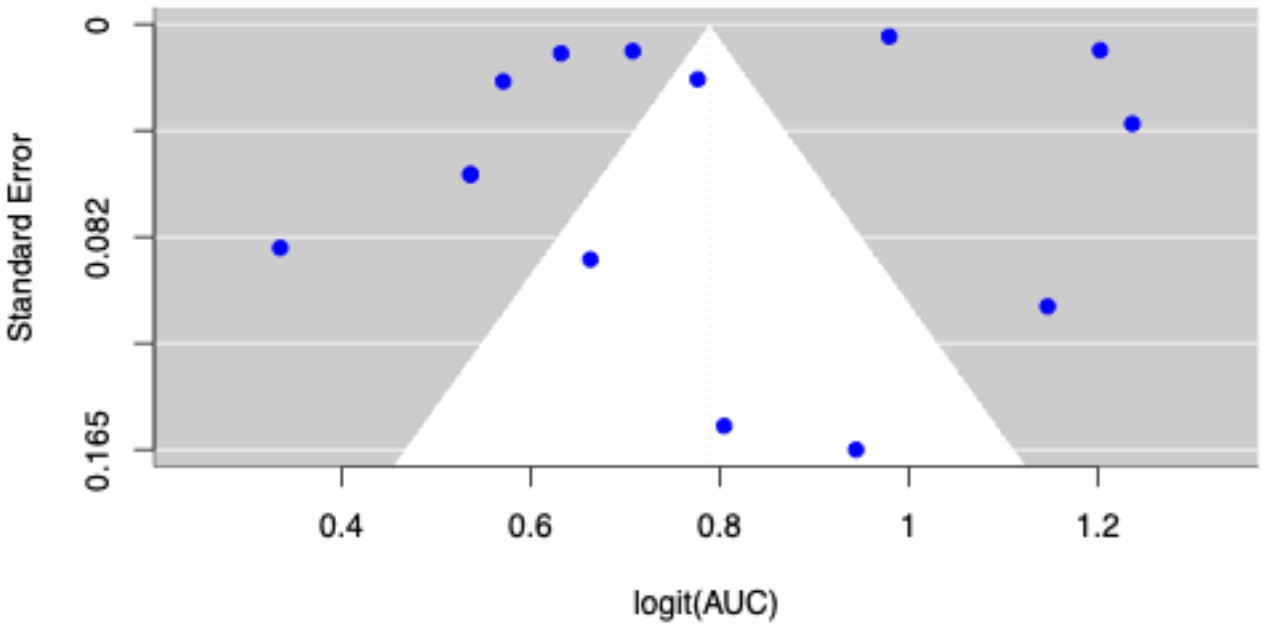

Figure S12. Funnel plot assessing potential small-study effects for the AUROC of the best-performing ML model from each included study.

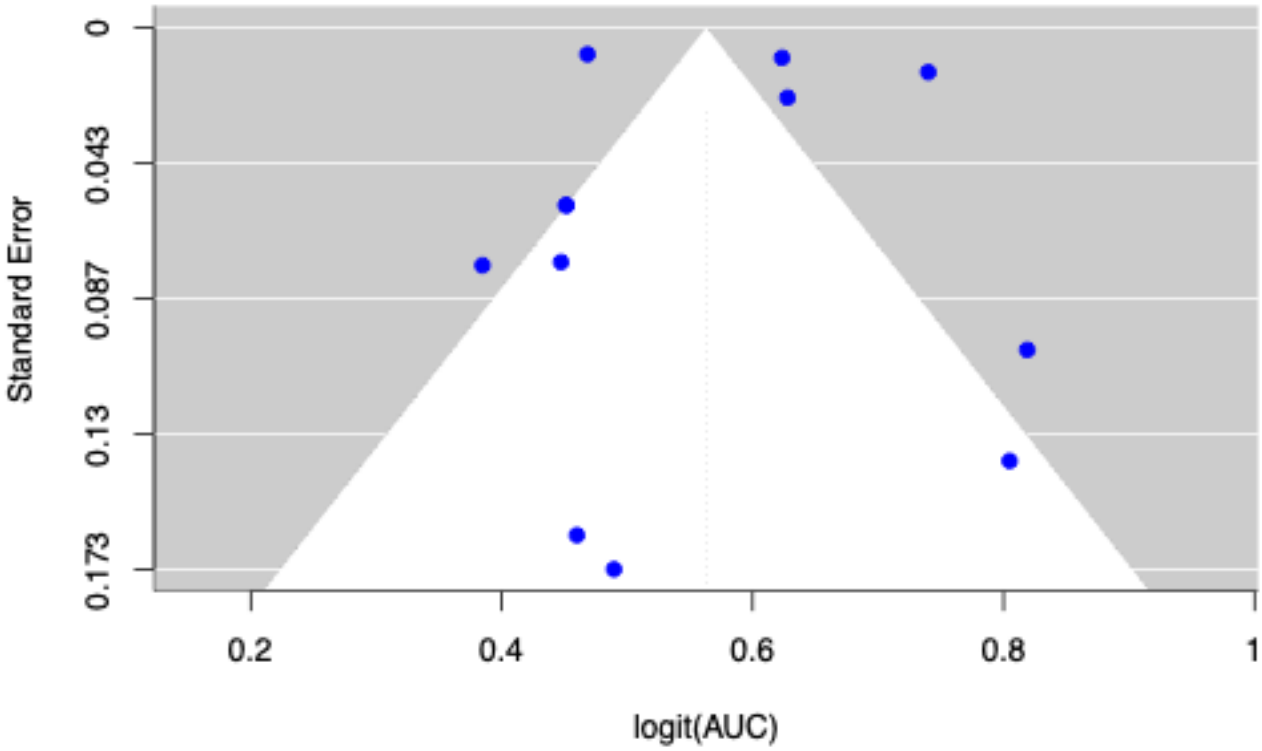

Figure S13. Funnel plot assessing potential small-study effects for the AUROC of the CHA_2DS_2-VASc score from each included study.

References

1. Letham B, Rudin C, McCormick T, et al. INTERPRETABLE CLASSIFIERS USING RULES AND BAYESIAN ANALYSIS: BUILDING A BETTER STROKE PREDICTION MODEL. *ANNALS OF APPLIED STATISTICS*. 2015–9 2015;9(3):1350–1371. doi:doi:10.1214/15-AOAS848
2. Li X, Liu H, Du X, Hu G, Xie G, Zhang P. Using Frequent Item Set Mining and Feature Selection Methods to Identify Interacted Risk Factors - The Atrial Fibrillation Case Study. *Stud Health Technol Inform*. 2016 2016;228:562–566. doi:doi:
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