

Early Predictive Accuracy of Machine Learning for Hemorrhagic Transformation in Acute Ischemic Stroke: A Systematic Review and Meta-Analysis

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Abstract

Background: Hemorrhagic transformation (HT) is commonly detected in acute ischemic stroke (AIS), and often leads to poor outcomes. Currently, there is no ideal tool for early prediction of HT risk. Recently, machine learning has gained traction in stroke management, prompting the exploration of predictive models for HT. However, systematic evidence on these models is lacking. Therefore, we assessed the predictive capability of machine learning models for HT risk in AIS, aiming to inform the development of HT prediction tools.

Objective: Hemorrhagic transformation (HT) is commonly detected in acute ischemic stroke (AIS), and often leads to poor outcomes. Currently, there is no ideal tool for early prediction of HT risk. Recently, machine learning has gained traction in stroke management, prompting the exploration of predictive models for HT. However, systematic evidence on these models is lacking. Therefore, we assessed the predictive capability of machine learning models for HT risk in AIS, aiming to inform the development of HT prediction tools.

Methods: We conducted a thorough search of medical databases, such as Web of Science, Embase, Cochrane, and PubMed up until October 2023. The risk of bias was determined through Prediction Model Risk of Bias Assessment Tool (PROBAST). Subgroup analysis was performed based on treatment backgrounds, diagnostic criteria, and types of HT.

Results: Sixty eligible articles were included, containing 69 models and 68678 AIS patients with 6977 HT cases. There were 72 validation sets with a total c-index of 0.822 (95%CI: 0.800-0.844), sensitivity of 0.82 (95%CI: 0.79-0.85), and specificity of 0.77 (95%CI: 0.71-0.82). Subgroup analysis indicated that the combined model achieved superior prediction accuracy. Moreover, we also analyzed the predictive performance of six mature models.

Conclusions: Currently, although several prediction methods for HT have been developed, their predictive values are not satisfactory. Fortunately, our findings suggest that machine learning methods, particularly those combining clinical features and radiomics, hold promise for improving the predictive accuracy. Our meta-analysis may provide evidence-based guidance for subsequent development of more efficient clinical predictive models for HT. Clinical Trial: Trial Registration: Not applicable

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Original Manuscript

Early Predictive Accuracy of Machine Learning for Hemorrhagic Transformation in Acute Ischemic Stroke: A Systematic Review and Meta-Analysis

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Abstract

Background: Hemorrhagic transformation (HT) is commonly detected in acute ischemic stroke (AIS), and often leads to poor outcomes. Currently, there is no ideal tool for early prediction of HT risk. Recently, machine learning has gained traction in stroke management,

prompting the exploration of predictive models for HT. However, systematic evidence on these models is lacking.

Objective: In this study, we assessed the predictive capability of machine learning models for HT risk in AIS, aiming to inform the development of HT prediction tools.

Methods: We conducted a thorough search of medical databases, such as Web of Science, Embase, Cochrane, and PubMed up until March 2025. The risk of bias was determined through Prediction Model Risk of Bias Assessment Tool (PROBAST). Subgroup analysis was performed based on treatment backgrounds, diagnostic criteria, and types of HT.

Results: 83 eligible articles were included, containing 106 models and 88197 AIS patients with 9323 HT cases. There were 104 validation sets with a total c-index of 0.832 (95%CI: 0.814-0.849), sensitivity of 0.82 (95%CI: 0.79-0.84), and specificity of 0.78 (95%CI: 0.74-0.81). Subgroup analysis indicated that the combined model achieved superior prediction accuracy. Moreover, we also analyzed the predictive performance of six mature models.

Conclusions: Currently, although several prediction methods for HT have been developed, their predictive values are not satisfactory. Fortunately, our findings suggest that machine learning methods, particularly those combining clinical features and radiomics, hold promise for improving the predictive accuracy. Our meta-analysis may provide evidence-based guidance for subsequent development of more efficient clinical predictive models for HT.

Trial Registration: PROSPERO CRD42024498997;

<https://www.crd.york.ac.uk/PROSPERO/view/CRD42024498997>

Key words: Machine learning, Hemorrhagic transformation, Acute ischemic stroke, Predictive model

Introduction

Acute ischemic stroke (AIS) is a significant global health challenge with high disability and

mortality rates worldwide[1]. It affects roughly 10.1 out of every million people globally, and the case-fatality rate appears to be rising in recent years[2]. Fortunately, many patients are now benefiting from increasingly effective treatment methods. Positive and effective treatments, such as intravenous thrombolysis and mechanical thrombectomy, can improve functional outcomes, especially for cases within the limited time window[3]. However, some patients have poor outcomes in clinical practice, such as hemorrhagic transformation (HT), which increases the risk of mortality and disability in AIS patients[4].

Several studies have demonstrated that matrix metalloproteinase-9 (MMP-9) can independently predict HT in AIS[5, 6]. Moreover, IL-33 was found to predict HT in AIS with an area under the curve (AUC) of 0.739[7]. Additionally, serum S100B was reported to reflect the risk of HT in AIS after thrombolytic therapy[8]. However, the predictive performance of these markers remains contentious due to limitations such as small sample sizes, non-multicenter study designs, and potential oversight of combined factors. Consequently, effective early prediction tools for HT are still lacking in clinical practice[9]. Therefore, it is essential to identify the HT risk early and guide the corresponding preventive measures.

Machine learning has been widely used in medicine in recent years. Multiple meta-analyses have shown that the models based on machine learning play an important role in the prognosis evaluation and treatment efficacy prediction of nervous system diseases, and machine learning has better prediction performance than clinical features[10-13]. In this setting, a series of models have developed for early prediction of HT in stroke patients based on machine learning. However, due to diversified methods of machine learning and various variables[14], there is a lack of systematic evidence on the predictive performance of these models, which is challenging for the subsequent development of simpler clinical prediction tools. Consequently, this systematic review and meta-analysis intended to explore the predictive performance of various prediction tools, including machine learning models, for HT in AIS patients across

different scenarios, in order to provide evidence-based guidance for promoting the development of artificial intelligence in this field and further developing simple and clinically practical prediction tools based on machine learning methods.

Methods

Registration of the study

The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Moreover, we have prospectively registered this study on PROSPERO (CRD42024498997).

Eligibility criteria

Inclusion criteria: (1) The subjects we included were patients with AIS; (2) The types of the included publications were case-cohort studies, nested case-control studies, cohort studies, or case-control studies; (3) A complete HT prediction model must be constructed; (4) Articles should be written in English.

Exclusion criteria: (1) Types of research: meta-analyses, reviews, guidelines, publicly published conference abstracts without peer review, and expert opinions. (2) Studies that conducted only differential factor analysis without developing a complete machine learning model. (3) Studies lacking outcome indicators for predictive accuracy of machine learning models, such as AUC, c-statistic, c-index, among others. (4) Publications with less than 20 cases.

Data retrieval and screening

A systematic and comprehensive literature search was performed on the PubMed, Cochrane, Embase, and Web of Science databases from inception up to March 2025 using a combination of MeSH terms, with no limitation on year of publication or region. The general key terms used included brain infarct, stroke, machine learning, and intracranial hemorrhage. Detailed search strategies are shown in **Table S1**.

Data extraction and analysis

The EndNote 20 was employed to filter the data and select eligible studies. Full-text versions of studies that met the inclusion criteria for this systematic review were then downloaded for further reading. Prior to data extraction, a structured spreadsheet was prepared, including fields such as title, first author, publication year, country, study type, patient source, treatment backgrounds, type of HT, and diagnostic criteria for HT, follow-up duration, number of HTs, number of subjects, HT number of trainings, patient number of trainings, generation of validation set, methods to avoid overfitting, HT number of validation, patient number of validations, handling of missing values, variable selection, types of models, variables for modeling. Subgroup analyses were performed according to different modeling variables (clinical features, radiomics, and radiomics + clinical features). Within modeling variables, subgroup analyses were also performed according to treatment background, diagnostic criteria, and type of HT.

Two investigators (BW, BJ) screened the identified studies and extracted data independently, and a third investigator (DL) was involved to cross-check the retrieved data.

Risk of bias in studies

The risk of bias in the studies was reviewed utilizing the Prediction Model Risk of Bias Assessment Tool (PROBAST)[15], which comprises specific questions divided into four domains: participants, predictor variables, outcome measures, and statistical methods. Each domain includes a set number of questions (2, 3, 6, and 9 respectively), with responses categorized as "yes/probably yes," "no/probably no," or "no information." A domain was considered high risk if it included at least one "no/probably no" response. Conversely, a domain was deemed low risk if all responses were "yes/probably yes." The overall risk of bias was characterized as low if all domains were rated low risk, and high if at least one domain was rated high risk. The risk of bias was determined using PROBAST by two investigators (BW, BJ).

The results were cross verified by a third investigator (DL) in case of discrepancies. In addition, in case where the above approach fails to resolve disagreements, the advice of blind review from another investigator (RZ) in our study, a professor with 20 years of experience in clinical practice and research will be ultimately adopted.

Outcomes

The main outcome of our systematic review was the c-index, which indicates the overall accuracy of machine learning models. However, due to the potentially low incidence of HT in AIS patients, some models may be developed using imbalanced data. Assessing machine learning accuracy solely based on the c-index presents challenges. Therefore, sensitivity and specificity were also considered our primary outcomes to provide a more comprehensive evaluation.

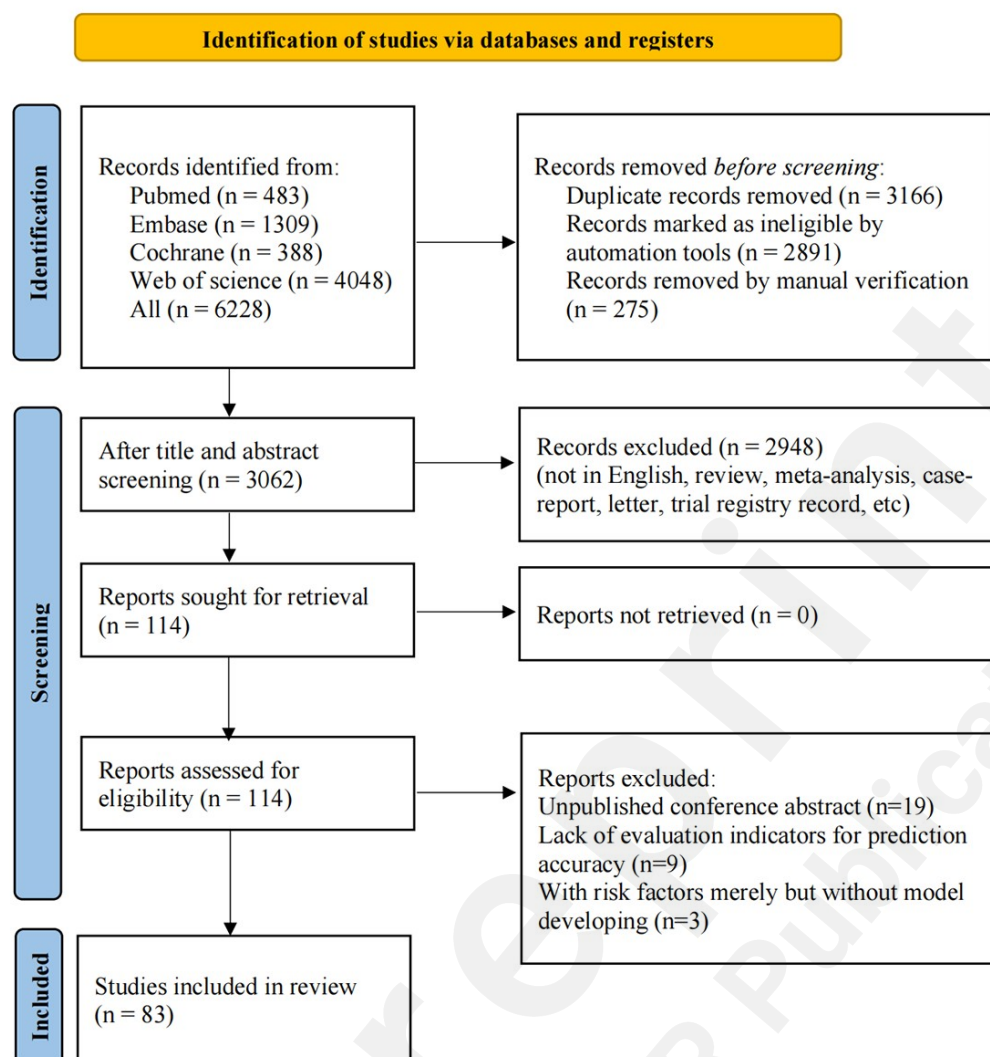
Analysis methods

A meta-analysis of c-index was conducted to evaluate the accuracy of machine-learning models. In some original studies, when the c-index lacked 95% confidence interval (CI) and standard error, we followed the study by Debray et al[16]. The statistical model was selected based on the heterogeneity index (I^2). When $I^2 > 50\%$, the random-effects model was used; when $I^2 < 50\%$, the fixed-effects model was used. Considering the variations in model features among studies, a random-effects model was utilized to conduct a c-index meta-analysis. A bivariate mixed-effects model was employed to conduct meta-analyses of specificity and sensitivity. Ideally, this analysis would use data from the diagnostic four-fold table, which was often missing in the original studies. Consequently, we employed two complementary approaches to estimate the four-fold table: (1) combining reported number of cases, precision, specificity, and sensitivity, and (2) extracting specificity and sensitivity based on the optimal Youden's Index and then calculating the number of cases. All meta-analyses were conducted using R version 4.3.3 (R development Core Team, Vienna, <http://www.R-project.org>).

Results

Study selection

A systematic search for relevant articles was conducted across major medical databases including PubMed, Cochrane, Embase, and Web of Science. The search included publications up to March 2025. Following the initial retrieval of 6228 articles, we identified and removed 3166 duplicates. Subsequently, 2948 irrelevant publications were removed by browsing the title and abstract. Following a full-text review, 31 articles were removed due to the publicly published conference abstracts without peer review (n=19), lack of evaluation indicators for prediction accuracy (n=9), and absence of complete models (n=3). Finally, 83 articles [17-99] were included. The flow chart of the selection process is shown in **Figure 1**.

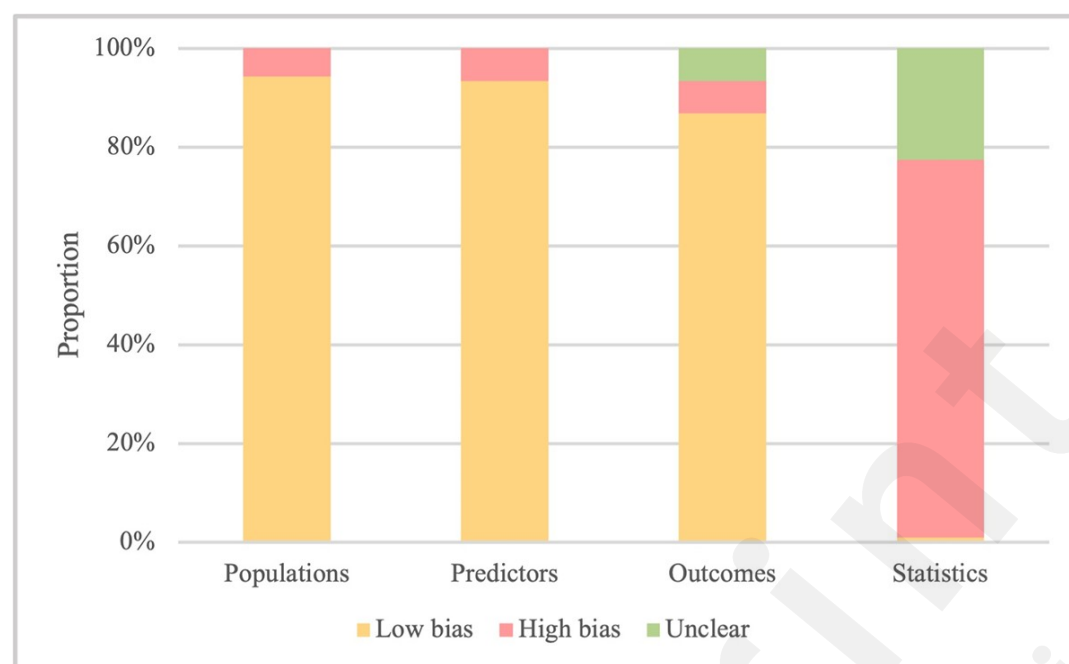
Figure 1 Flow chart of the literature selection process

Study characteristics

All the eligible articles were published from 2002 to 2025. The original studies included in our study were mainly cohort studies (77 studies), with additional 4 case-control studies[32, 36, 72, 76] and 2 studies with unclear study types[26, 45]. A total of 106 models were developed using five types of modeling methods, mainly logistic regression and radiomics. Of the included studies, 102 articles developed new prediction models and 44 articles validated the mature models. Details about these studies, including their characteristics, are provided in **Table S2**[17-99].

Quality assessment

The quality of studies was analyzed using the PROBAST checklists. The risk of bias was determined based on four dimensions, including populations, predictors, outcomes, and statistics. Notably, 6 models from 3 articles, which were case-control studies, were considered at a risk of bias in the choice of subjects. The predictors of 7 models in 4 studies were selected on the premise of knowing the outcome, which increased the risk of bias in predictor selection and outcome ascertainment. Our analysis revealed that, overall, the statistical handling of data was the most common source of potential bias. Among the 19 models developed in the 19 articles, 14 models had an events per variable (EPV) of less than 10, and 5 models had a sample size of less than 100. Our analysis identified several potential shortcomings in how some of the studies incorporated the data into their models. In 59 models from 42 articles, data with missing values were simply removed without any explanation. Additionally, variables were selected based solely on univariate analysis in one model, and 30 studies failed to consider the goodness of fit during development. All these issues can increase the risk of biased results. A detailed breakdown of these biases is presented in **Figure 2** and **Table S3**

Figure 2 The risk of bias assessment of the included models

The results of meta-analysis

The assessment of predictive value

This meta-analysis included 88197 AIS patients, among whom there were 9323 cases of HT. A total of 101 new machine learning models were developed using 101 training sets and 104 validation sets. All studies reported the c-index for predicting HT in AIS patients. The overall c-index, calculated by a random-effects model, was 0.845 (95% CI: 0.816-0.873) in the training sets. Furthermore, diagnostic fourfold tables were available from 81 models, showing an overall sensitivity of 0.84 (95% CI: 0.81-0.86) and specificity of 0.81 (95% CI: 0.79-0.84). In the validation sets, the pooled c-index was 0.832 (95%CI: 0.814-0.849) in 104 sets and the overall sensitivity and specificity, obtained from 89 sets, were 0.82 (95%CI: 0.79-0.84) and 0.78 (95%CI: 0.74-0.81), specifically. The details of the analysis of newly developed models are presented in **Table 1** and **Table 2**. The c-index, sensitivity, and specificity of each included model are shown in **Table S4**.

Subgroup analysis

The newly developed models were classified into three categories based on their predictors:

models that utilized only clinical features, models that used only radiomics, and models that combined clinical features with radiomics. In the training datasets, there were 64 models that utilized clinical features, achieving an overall c-index of 0.819 (95%CI: 0.788-0.851). Among these models, 48 included a diagnostic fourfold table, which indicated a pooled sensitivity of 0.81 (95%CI: 0.79-0.84) and specificity of 0.79 (95%CI: 0.75-0.83). Within the validation datasets, which consisted of 75 models, the overall c-index for models based on clinical features was 0.812 (95%CI: 0.791-0.833). Moreover, the pooled sensitivity and specificity of 61 models were 0.81 (95%CI: 0.78-0.84) and 0.74 (95%CI: 0.69-0.79), respectively. Notably, 18 radiomics-based models in the training sets had an overall c-index of 0.909 (95%CI: 0.885-0.932), with sensitivity of 0.88 (95%CI: 0.80-0.93) and specificity of 0.84 (95%CI: 0.79-0.89) in 16 models of them. 15 models in the validation sets had a pooled c-index of 0.880 (95%CI: 0.842-0.918), sensitivity of 0.80 (95%CI: 0.73-0.86), and specificity of 0.86 (95%CI: 0.80-0.90).

In terms of models based on clinical features combined with radiomics, 19 models in the training sets and 14 models in the validation sets achieved an overall c-index of 0.887 (95%CI: 0.852-0.921) and 0.915 (95%CI: 0.892-0.938), respectively. Within this subgroup, 17 models in the training sets reported a pooled sensitivity of 0.86 (95%CI: 0.81-0.89) and specificity of 0.84 (95%CI: 0.79-0.88), while 13 models in the validation sets demonstrated an overall sensitivity of 0.86 (95%CI: 0.82-0.89) and specificity of 0.81 (95%CI: 0.76-0.86). Moreover, we analyzed the predictive performance of these newly developed models across different treatment backgrounds, diagnostic criteria, and types of HT within three subgroups. Detailed meta-analysis results of subgroup analysis are presented in **Figure 3, Figure 4, Table 1, and Table 2.**

Figure 3 Forest plot of c-index for newly developed models in the training set

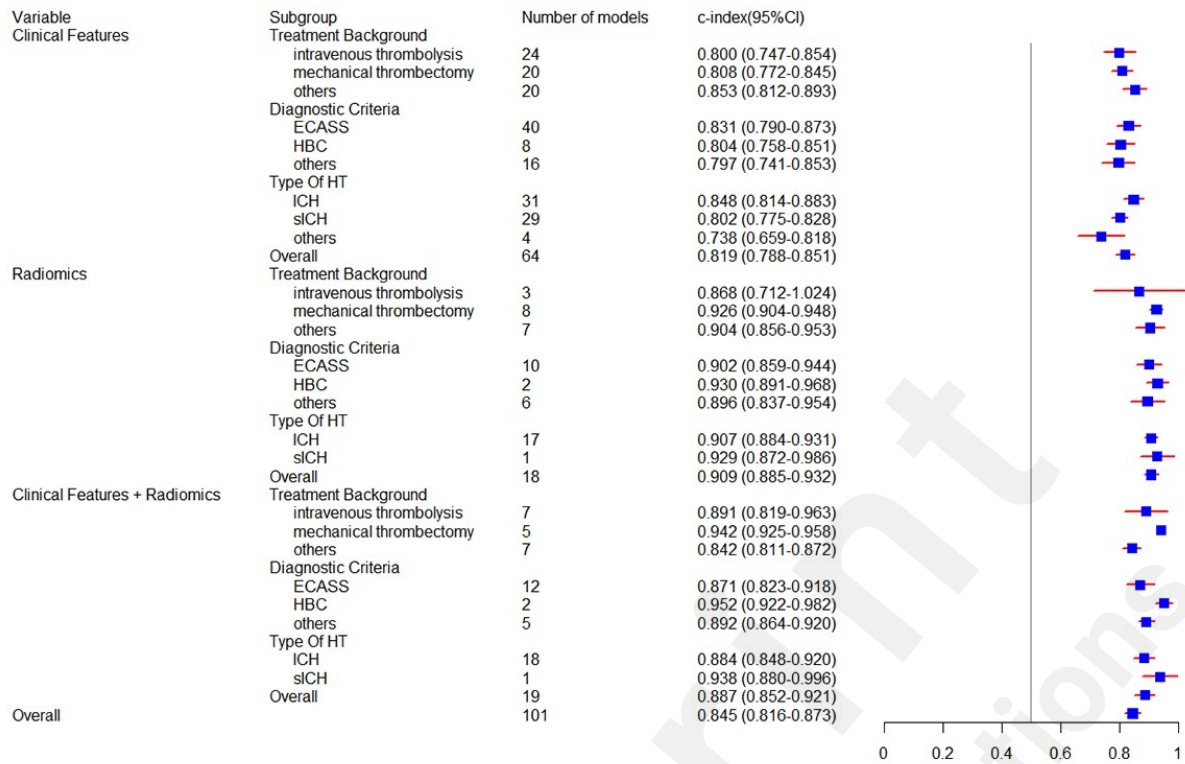


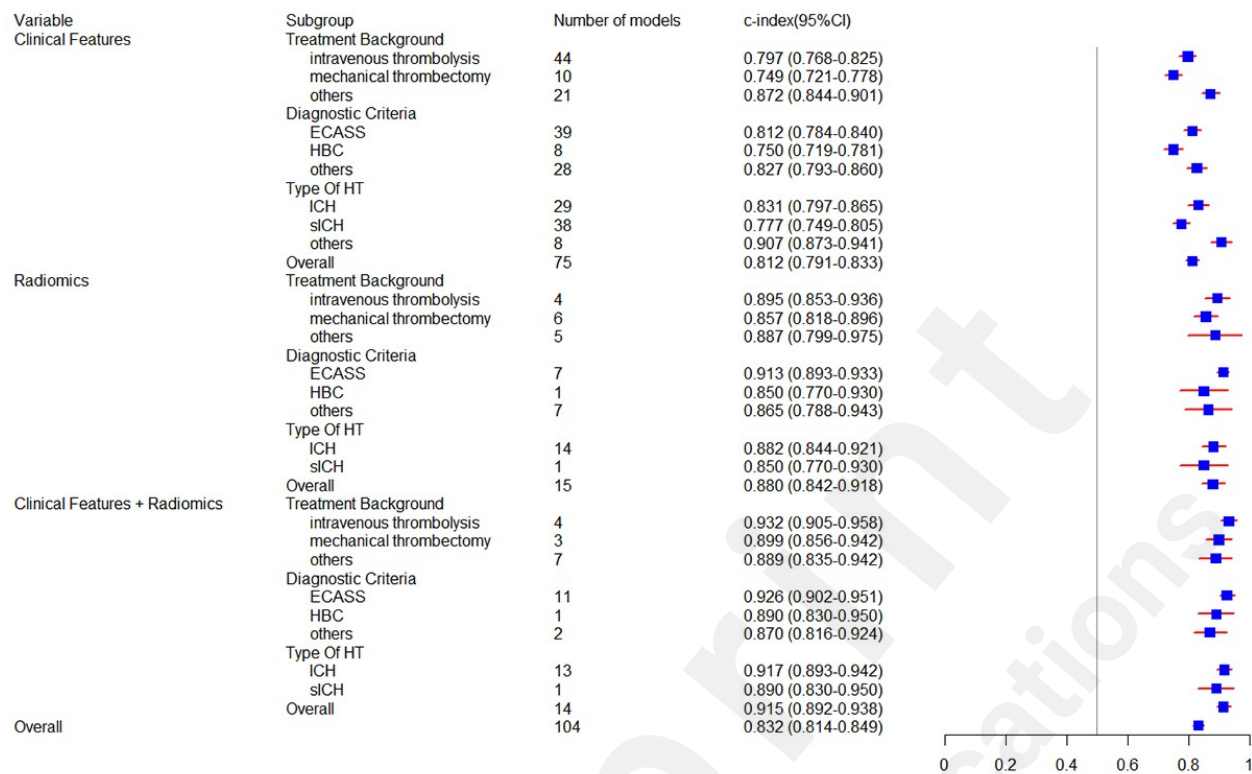
Figure 4 Forest plot of c-index for newly developed models in the validation set

Table 1 The c-index of newly developed models

Subgroup Analysis	Training Set					Validation Set				
	N ^a	Events	Sample Size ^b	C-index (95%CI)	I ²	N	Events	Sample Size	C-index (95%CI)	I ²
Clinical Features										
Treatment Background										
intravenous thrombolysis	24	1706	42342	0.800 (0.747-0.854)	99.3	44	1971	21536	0.797 (0.768-0.825)	95.6
mechanical thrombectomy	20	1818	8674	0.808 (0.772-0.845)	93.3	10	478	3943	0.749 (0.721-0.778)	30.0
others	20	1141	6812	0.853 (0.812-0.893)	93.9	21	420	3519	0.872 (0.844-0.901)	82.8
Diagnostic Criteria										
ECASS	40	2975	26257	0.831 (0.790-0.873)	99.5	39	1366	14422	0.812 (0.784-0.840)	92.0
HBC	8	542	5100	0.804 (0.758-0.851)	88.0	8	373	3369	0.750 (0.719-0.781)	32.5
others	16	941	25081	0.797 (0.741-0.853)	95.4	28	1178	14720	0.827 (0.793-0.860)	95.3
Type Of HT										
ICH	31	1649	6761	0.848 (0.814-0.883)	96.0	29	1112	6314	0.831 (0.797-0.865)	93.2
sICH	29	1734	35305	0.802 (0.775-0.828)	92.9	38	1117	21839	0.777 (0.749-0.805)	87.2
others	4	1075	3732	0.738 (0.659-0.818)	95.6	8	773	2142	0.907 (0.873-0.941)	93.7
Overall of Clinical Features										
	64	4251	44408	0.819 (0.788-0.851)	99.2	75	2812	28044	0.812 (0.791-0.833)	94.0
Radiomics										
Treatment Background										
intravenous thrombolysis	3	293	950	0.868 (0.712-1.024)	98.0	4	149	388	0.895 (0.853-0.936)	61.4
mechanical thrombectomy	8	359	935	0.926 (0.904-0.948)	49.6	6	142	368	0.857 (0.818-0.896)	0.0
others	7	345	746	0.904 (0.856-0.953)	91.2	5	176	334	0.887 (0.799-0.975)	85.1
Diagnostic Criteria										

ECASS	10	590	1666	0.902 (0.859-0.944)	94.1	7	238	511	0.913 (0.893-0.933)	0.0
HBC	2	36	102	0.930 (0.891-0.968)	0.0	1	15	102	0.850 (0.770-0.930)	NA ^c
others	6	371	863	0.896 (0.837-0.954)	94.5	7	214	477	0.865 (0.788-0.943)	89.6
Type Of HT										
ICH	17	997	2631	0.907 (0.884-0.931)	94.1	14	452	988	0.882 (0.844-0.921)	83.9
sICH	1	15	102	0.929 (0.872-0.986)	NA	1	15	102	0.850 (0.770-0.930)	NA
Overall of Radiomics										
	18	997	2631	0.909 (0.885-0.932)	93.8	15	467	1090	0.880 (0.842-0.918)	83.8
Clinical Features +Radiomics										
Treatment Background										
intravenous thrombolysis	7	382	1820	0.891 (0.819-0.963)	90.9	4	149	388	0.932 (0.905-0.958)	39.9
mechanical thrombectomy	5	175	522	0.942 (0.925-0.958)	0.0	3	52	192	0.899 (0.856-0.942)	0.0
others	7	158	326	0.842 (0.811-0.872)	34.1	7	115	220	0.889 (0.835-0.942)	59.4
Diagnostic Criteria										
ECASS	12	528	2148	0.871 (0.823-0.918)	94.0	11	245	537	0.926 (0.902-0.951)	39.3
HBC	2	36	102	0.952 (0.922-0.982)	0.0	1	15	102	0.890 (0.830-0.950)	NA
others	5	151	418	0.892 (0.864-0.920)	0.0	2	56	161	0.870 (0.816-0.924)	0.0
Type Of HT										
ICH	18	715	2668	0.884 (0.848-0.920)	92.4	13	301	698	0.917 (0.893-0.942)	44.2
sICH	1	15	102	0.938 (0.880-0.996)	NA	1	15	102	0.890 (0.830-0.950)	NA
Overall of Clinical Features +Radiomics										
	19	715	2668	0.887 (0.852-0.921)	92.0	14	316	800	0.915 (0.892-0.938)	43.6

Overall

10 1	5004	46914	0.845 (0.816-0.873)	99. 6	10 4	3082	28697	0.832 (0.814- 0.849)	93.3
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^aN: the number of models.

^bSample Size: total number of AIS cases included.

^cNA: not applicable.

Table 2 The sensitivity and specificity of newly developed models

Subgroup	Training Set			Validation Set		
Analysis	N ^a	Sen ^b (95%CI)	Spe ^c (95%CI)	N	Sen (95%CI)	Spe (95%CI)
Clinical Features						
Treatment Background						
intravenous thrombolysis	13	0.84 (0.76-0.90)	0.82 (0.75-0.87)	33	0.78 (0.75-0.81)	0.80 (0.76-0.85)
mechanical thrombectomy	17	0.78 (0.73-0.82)	0.76 (0.72-0.80)	8	0.73 (0.67-0.79)	0.69 (0.62-0.75)
others	18	0.82 (0.80-0.84)	0.79 (0.71-0.86)	20	0.90 (0.84-0.94)	0.64 (0.49-0.76)
Diagnostic Criteria						
ECASS	33	0.83 (0.79-0.86)	0.81 (0.76-0.85)	35	0.82 (0.78-0.85)	0.66 (0.57-0.74)
HBC	6	0.79 (0.71-0.85)	0.70 (0.63-0.77)	6	0.76 (0.70-0.81)	0.65 (0.59-0.70)
others	9	0.78 (0.73-0.83)	0.79 (0.73-0.84)	20	0.83 (0.76-0.88)	0.86 (0.83-0.88)
Type Of HT						
ICH	28	0.83 (0.79-0.86)	0.81 (0.76-0.86)	27	0.84 (0.80-0.87)	0.65 (0.53-0.76)
sICH	18	0.77 (0.73-0.81)	0.77 (0.73-0.81)	27	0.77 (0.73-0.80)	0.76 (0.72-0.80)
others	2	0.80-0.88	0.51-0.80	7	0.85 (0.71-0.93)	0.90 (0.85-0.94)
Overall of Clinical Features						
	48	0.81 (0.79-0.84)	0.79 (0.75-0.83)	61	0.81 (0.78-0.84)	0.74 (0.69-0.79)
Radiomics						
Treatment Background						
intravenous thrombolysis	3	0.81-0.99	0.68-0.95	4	0.84 (0.74-0.91)	0.86 (0.76-0.92)
mechanical thrombectomy	8	0.88 (0.81-0.93)	0.85 (0.79-0.89)	6	0.71 (0.60-0.80)	0.87 (0.78-0.93)
others	5	0.76 (0.66-0.83)	0.85 (0.76-0.91)	5	0.85 (0.72-0.92)	0.85 (0.71-0.92)
Diagnostic Criteria						
ECASS	10	0.90 (0.77-0.96)	0.86 (0.79-0.91)	7	0.82 (0.71-0.90)	0.89 (0.82-0.93)

HBC	2	0.86-0.94	0.82-0.91	1	0.93	0.77
others	4	0.82 (0.76-0.86)	0.77 (0.66-0.85)	7	0.77 (0.66-0.85)	0.85 (0.73-0.92)
Type Of HT						
ICH	15	0.87 (0.79-0.92)	0.84 (0.79-0.89)	14	0.80 (0.72-0.86)	0.87 (0.81-0.91)
sICH	1	0.94	0.82	1	0.93	0.77
Overall of Radiomics						
	16	0.88 (0.80-0.93)	0.84 (0.79-0.89)	15	0.80 (0.73-0.86)	0.86 (0.80-0.90)
Clinical Features +Radiomics						
Treatment Background						
intravenous thrombolysis	6	0.92 (0.83-0.96)	0.85 (0.71-0.93)	4	0.86 (0.78-0.92)	0.87 (0.80-0.91)
mechanical thrombectomy	5	0.86 (0.82-0.90)	0.88 (0.86-0.90)	3	0.77-0.93	0.77-0.87
others	6	0.79 (0.75-0.82)	0.79 (0.74-0.83)	6	0.87 (0.82-0.90)	0.76 (0.68-0.82)
Diagnostic Criteria						
ECASS	10	0.85 (0.77-0.90)	0.83 (0.75-0.89)	10	0.86 (0.82-0.90)	0.82 (0.75-0.88)
HBC	2	0.89-0.93	0.82-0.89	1	0.93	0.77
others	5	0.86 (0.79-0.90)	0.84 (0.75-0.91)	2	0.77-0.82	0.79-0.81
Type Of HT						
ICH	16	0.85 (0.81-0.89)	0.84 (0.79-0.89)	12	0.86 (0.82-0.89)	0.82 (0.76-0.87)
sICH	1	0.93	0.82	1	0.93	0.77
Overall of Clinical Features +Radiomics						
	17	0.86 (0.81-0.89)	0.84 (0.79-0.88)	13	0.86 (0.82-0.89)	0.81 (0.76-0.86)
Overall						
	81	0.84 (0.81-0.86)	0.81 (0.79-0.84)	89	0.82 (0.79-0.84)	0.78 (0.74-0.81)

^aN: the number of models.

^bSen: sensitivity.

^cSpe, specificity.

For subgroups with fewer than three models, the range of sensitivity or specificity for that subgroup analysis is presented

Validation of mature tools

In our study, we evaluated six established tools: GRASPS (Glucose, Race, Age, Sex, systolic blood Pressure at presentation, and Severity of stroke at presentation), Multicenter rt-PA Stroke Survey score (MSS), SEDAN (baseline blood Sugar, Early infarct signs, hyper Dense cerebral artery sign, Age, NIH Stroke Scale), Safe Implementation of Treatments in

Stroke (SITS), Stroke Prognostication using Age and NIH Stroke Scale (SPAN-100), and thrombolysis in cerebral ischaemia-Alberta stroke program early CT-glucose score (TAG) [56, 58, 60, 76, 100, 101]. Eleven data sets were used to validate the GRASPS, showing an overall c-index of 0.694 (95%CI: 0.642-0.746), and the pooled sensitivity [0.71 (95%CI: 0.60-0.80)] and specificity [0.68 (95%CI: 0.58-0.76)] were calculated using seven of these data sets. The overall c-index [0.702 (95%CI: 0.677-0.727)] of MSS was validated by 9 data sets, and its sensitivity [0.71 (95%CI: 0.66-0.75)] and specificity [0.67 (95%CI: 0.64-0.71)] were validated by 5 data sets. To validate SEDAN, the combined c-index across 11 datasets was 0.707 (95% CI: 0.647-0.766), with sensitivity and specificity reported from 6 datasets as 0.75 (95% CI: 0.65-0.82) and 0.69 (95% CI: 0.58-0.77), respectively. In studies validating SITS, the pooled c-index across 12 datasets was 0.663 (95% CI: 0.628-0.699). Sensitivity ranged from 0.4679 to 0.6159, and specificity ranged from 0.6957 to 0.6997 across 3 datasets. The overall c-index of 17 data sets to validate SPAN-100 was 0.606 (95%CI: 0.568-0.644), and the sensitivity and specificity of 10 data sets were 0.42 (95%CI: 0.26-0.59) and 0.86 (95%CI: 0.76-0.93). Furthermore, from the 6 data sets which validated TAG, we could only obtain the pooled c-index of 0.686 (95%CI: 0.649-0.723). Similarly, the predictive value of these mature tools under different backgrounds of treatments, diagnostic criteria, and HT types was also explored. Detailed meta-analysis results for these mature models are presented in **Figure 5, Figure 6, Table 3, and Table 4.**

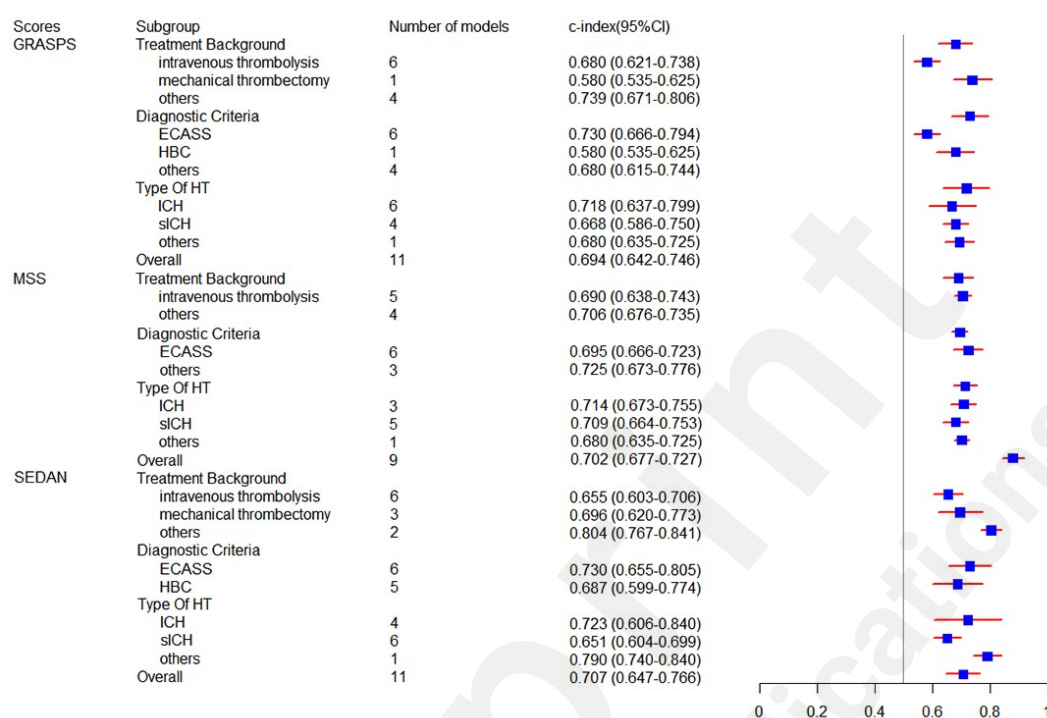
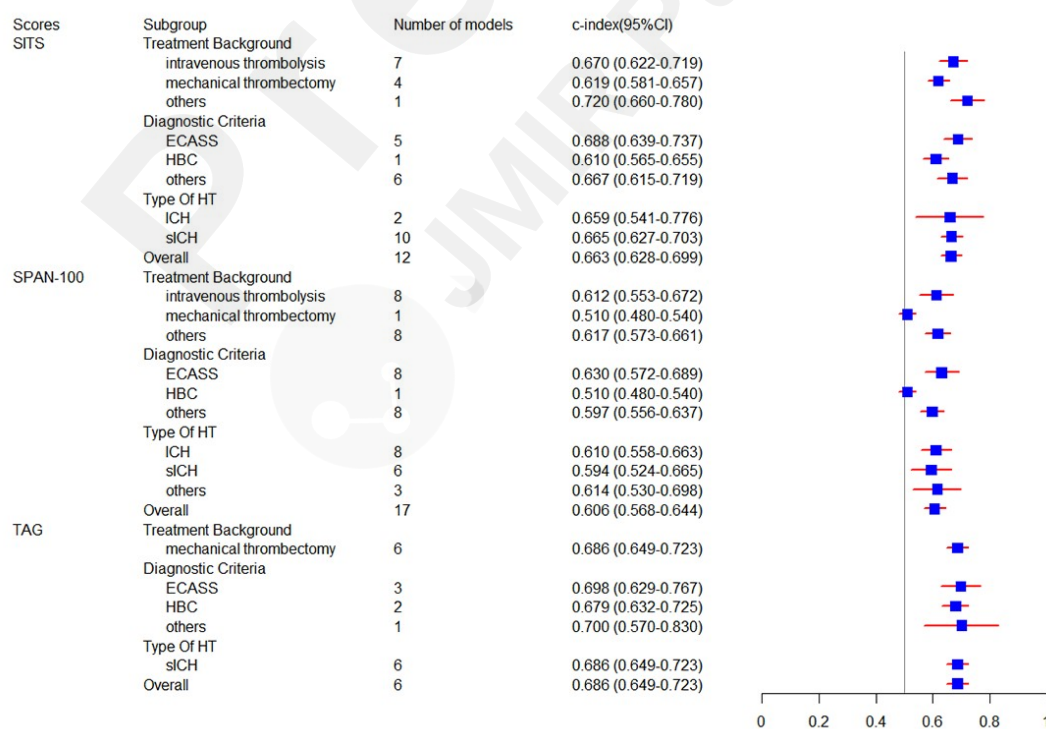
Figure 5 Forest plot of c-index for mature tools (GRASPS, MSS, and SEDAN)**Figure 6** Forest plot of c-index for mature tools (SITS, SPAN-100, and TAG)

Table 3 The c-index of mature models

Subgroup Analysis	Validation Set			
	N ^a	Events ^b	Sample Size ^c	C-index (95%CI)
GRASPS				
Treatment Background				
intravenous thrombolysis	6	276	2112	0.680 (0.621-0.738)
mechanical thrombectomy	1	188	3180	0.580 (0.535-0.625)
others	4	433	2132	0.739 (0.671-0.806)
Diagnostic Criteria				
ECASS	6	346	2879	0.730 (0.666-0.794)
HBC	1	188	3180	0.580 (0.535-0.625)
others	4	363	3249	0.680 (0.615-0.744)
Type Of HT				
ICH	6	249	2360	0.718 (0.637-0.799)
sICH	4	435	6429	0.668 (0.586-0.750)
others	1	213	1884	0.680 (0.635-0.725)
Overall of GRASPS				
	11	897	7424	0.694 (0.642-0.746)
MSS				
Treatment Background				
intravenous thrombolysis	5	171	642	0.690 (0.638-0.743)
others	4	433	2132	0.706 (0.676-0.735)
Diagnostic Criteria				
ECASS	6	374	2774	0.695 (0.666-0.723)
others	3	230	1973	0.725 (0.673-0.776)
Type Of HT				
ICH	3	111	801	0.714 (0.673-0.755)
sICH	5	280	1973	0.709 (0.664-0.753)
others	1	213	1884	0.680 (0.635-0.725)
Overall of MSS				
	9	604	2774	0.702 (0.677-0.727)
SEDAN				
Treatment Background				
intravenous thrombolysis	6	345	1648	0.655 (0.603-0.706)
mechanical thrombectomy	3	51	258	0.696 (0.620-0.773)
others	2	151	787	0.804 (0.767-0.841)

Diagnostic Criteria

ECASS	6	171	789	0.730 (0.655-0.805)
others	5	376	2251	0.687 (0.599-0.774)

Type Of HT

ICH	4	198	1807	0.723 (0.606-0.840)
sICH	6	258	1712	0.651 (0.604-0.699)
others	1	91	539	0.790 (0.740-0.840)

Overall of SEDAN

	11	547	2693	0.707 (0.647-0.766)
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SITS**Treatment Background**

intravenous thrombolysis	7	407	1994	0.670 (0.622-0.719)
mechanical thrombectomy	4	239	3438	0.619 (0.581-0.657)
others	1	60	248	0.720 (0.660-0.780)

Diagnostic Criteria

ECASS	5	178	1143	0.688 (0.639-0.737)
HBC	1	188	3180	0.610 (0.565-0.655)
others	6	340	2252	0.667 (0.615-0.719)

Type Of HT

ICH	2	174	1605	0.659 (0.541-0.776)
sICH	10	532	5432	0.665 (0.627-0.703)

Overall of SITS

	12	706	5680	0.663 (0.628-0.699)
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SPAN-100**Treatment Background**

intravenous thrombolysis	8	428	2343	0.612 (0.553-0.672)
mechanical thrombectomy	1	188	3180	0.510 (0.480-0.540)
others	8	682	3389	0.617 (0.573-0.661)

Diagnostic Criteria

ECASS	8	502	3241	0.630 (0.572-0.689)
HBC	1	188	3180	0.510 (0.480-0.540)
others	8	608	4464	0.597 (0.556-0.637)

Type Of HT

ICH	8	387	2975	0.610 (0.558-0.663)
sICH	6	570	6660	0.594 (0.524-0.665)
others	3	341	2668	0.614 (0.530-0.698)

Overall of SPAN-100

	17	1298	8912	0.606 (0.568-0.644)
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TAG**Treatment Background**

mechanical thrombectomy	6	209	1499	0.686 (0.649-0.723)
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Diagnostic Criteria

ECASS	3	56	367	0.698 (0.629-0.767)
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HBC	2	141	1132	0.679 (0.632-0.725)
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others	1	12	258	0.700 (0.570-0.830)
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Type Of HT

sICH	6	209	1499	0.686 (0.649-0.723)
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Overall of TAG

	6	209	1499	0.686 (0.649-0.723)
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^aN: the number of models.^bEvents, Patients with HT^cSample Size: total number of AIS cases included.**Table 4** The sensitivity and specificity of mature models

Subgroup Analysis	Validation Set		
	N	Sen (95%CI)	Spe (95%CI)
GRASPS			
Treatment Background			
intravenous thrombolysis	4	0.77 (0.50-0.92)	0.67 (0.49-0.80)
others	3	0.67-0.76	0.62-0.75
Diagnostic Criteria			
ECASS	5	0.67 (0.55-0.77)	0.65 (0.52-0.77)
others	2	0.70-0.76	0.68-0.75
Type Of HT			
ICH	4	0.77 (0.50-0.92)	0.67 (0.49-0.80)
sICH	2	0.70-0.76	0.68-0.75
others	1	0.67	0.62
Overall of GRASPS	7	0.71 (0.60-0.80)	0.68 (0.58-0.76)
MSS			
Treatment Background			
intravenous thrombolysis	2	0.65-0.77	0.63-0.68
others	3	0.68-0.76	0.63-0.73
Diagnostic Criteria			
ECASS	3	0.65-0.77	0.63-0.68
others	2	0.68-0.76	0.68-0.73

Type Of HT

ICH	2	0.65-0.77	0.63-0.68
sICH	2	0.68-0.76	0.68-0.73
others	1	0.69	0.63

Overall of MSS

5	0.71 (0.66-0.75)	0.67 (0.64-0.71)
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SEDAN**Treatment Background**

intravenous thrombolysis	2	0.50-0.75	0.68-0.73
mechanical thrombectomy	3	0.62-0.89	0.41-0.73
others	1	0.71	0.78

Diagnostic Criteria

ECASS	4	0.74 (0.56-0.86)	0.64 (0.50-0.76)
others	2	0.67-0.71	0.73-0.78

Type Of HT

ICH	2	0.50-0.75	0.67-0.74
sICH	3	0.62-0.89	0.41-0.73
others	1	0.71	0.78

Overall of SEDAN

6	0.75 (0.65-0.82)	0.69 (0.58-0.77)
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SITS**Treatment Background**

mechanical thrombectomy	3	0.47-0.62	0.69-0.70
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Diagnostic Criteria

ECASS	2	0.47-0.62	0.69-0.70
others	1	0.58	0.70

Type Of HT

sICH	3	0.47-0.62	0.69-0.70
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Overall of SITS

3	0.47-0.62	0.69-0.70
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SPAN-100**Treatment Background**

intravenous thrombolysis	4	0.50 (0.20-0.80)	0.86 (0.72-0.94)
others	6	0.41 (0.21-0.63)	0.87 (0.71-0.95)

Diagnostic Criteria

ECASS	5	0.46 (0.27-0.66)	0.82 (0.67-0.92)
others	5	0.37 (0.16-0.63)	0.89 (0.74-0.96)

Type Of HT

ICH	5	0.44 (0.19-0.72)	0.89 (0.78-0.95)
sICH	2	0.65-0.76	0.63-0.70
others	3	0.15-0.65	0.65-0.98

Overall of SPAN-100

10	0.42 (0.26-0.59)	0.86 (0.76-0.93)
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TAG

Treatment Background			
mechanical thrombectomy	4	0.78 (0.62-0.89)	0.55 (0.46-0.64)
Diagnostic Criteria			
ECASS	3	0.71-0.93	0.40-0.66
others	1	0.75	0.57
Type Of HT			
sICH	4	0.78 (0.62-0.89)	0.55 (0.46-0.64)
Overall of TAG			
	4	0.78 (0.62-0.89)	0.55 (0.46-0.64)

N, the number of models; Sen, sensitivity; Spe, specificity

For subgroups with fewer than three models, the range of sensitivity or specificity for that subgroup analysis is presented

Discussion

The main findings

Our systematic review and meta-analysis identified several existing tools for predicting HT risk in AIS patients. However, the predictive performance of these currently available tools remains controversial. In recent studies, some machine learning models were built mainly based on clinical features, radiomics, and clinical features combined with radiomics, which similarly had a relatively ideal predictive value. The validation sets yielded c-index values of 0.812 (95% CI: 0.791-0.833) for models based on clinical features, 0.880 (95% CI: 0.842-0.918) for models based on radiomics, and 0.915 (95% CI: 0.892-0.938) for models integrating clinical features with radiomics. These findings suggest that the models based on both clinical features and radiomics demonstrated superior predictive accuracy to those using either clinical features or radiomics alone. This study provided evidence-based evidence for the use of machine learning to develop models based on different modeling variables (clinical features, radiomics, and radiomics combined with clinical features). In the future, with the help of the well-developed prediction model, the high-risk population of HT can be screened, according

to which, doctors can take active treatment and intervention, increase the density and attention of follow-up to reduce the risk of HT of AIS patients.

Subgroup evaluation

In addition to summarizing the overall accuracy of machine learning models for HT prediction, we also conducted subgroup analyses to explore potential variations in model performance. Notably, Tan et al.[102] performed a separate meta-analysis on 21 studies encompassing 4473 AIS patients. Their analysis focused on comparing the efficacy and safety of endovascular treatment and intravenous thrombolysis, finding no significant difference in HT risk between the two methods. In our study, detailed subgroup analyses were also performed by different treatment backgrounds. The c-index of these models for predicting HT after thrombolysis and thrombectomy was similar, while the models for predicting thrombolysis showed better sensitivity and specificity. However, we cannot rule out the influence of the fewer models for predicting thrombectomy. Overall, under the contexts of all these treatment backgrounds, machine learning models can be established to predict HT.

Currently, the diagnostic criteria for HT primarily encompass ECASS[67, 103, 104] and HBC[105]. ECASS defines sICH strictly, focusing on significant increases in NIHSS score (≥ 4) from baseline and neurological deterioration. However, the definition of sICH in HBC is broader and more flexible, and sICH can be identified when any of the following criteria are satisfied: a NIHSS score exceeding baseline value (≥ 4), an increase in one NIHSS category (≥ 2), requiring a major medical/surgical intervention or disease progression without known causes. In contrast, asymptomatic intracerebral hemorrhage

and other types of hemorrhage are mainly defined based on imaging. Among the included newly developed models, out of the 27 models for thrombolysis, 17 models adopted ECASS criteria, whereas among the 21 models for thrombectomy, 11 adopted ECASS criteria and 8 adopted HBC criteria. In this study, we found that the ECASS models had higher predictive accuracy for HT compared to the model based on HBC. However, this result is concluded only based on limited evidence. To assess its generalizability across different hemorrhage subtypes, we conducted a subgroup analysis stratified by the type of HT. The HT categories included sICH, intracerebral hemorrhage (ICH) without further subtype classification, and other types of intracerebral hemorrhage distinct from sICH. This analysis revealed that the machine learning models maintained relatively stable predictive performance across the various HT subtypes. Our analysis included studies that evaluated clinical feature-based models, radiomics-based models, and combination models. All model types demonstrated a degree of predictive ability. Notably, clinical feature-based models offer clear advantages in interpretability due to the use of well-defined variables. However, the meta-analysis revealed the lowest pooled c-index (0.812 in the validation set) for models based solely on interpretable clinical features. Conversely, radiomics-based models exhibited improved predictive accuracy, reflected by an overall c-index of 0.880. Notably, the segmentation of medical imaging, feature extraction and difference of imaging time points can potentially cause heterogeneity during model establishment. Additionally, the type of medical imaging selected can significantly impact the model's results. These limitations underscore the need for further research to solidify the predictive power of radiomics models. Our

analysis revealed that models based on both clinical features and radiomics achieved the best overall performance (c-index of 0.915 in the validation set), suggesting their potential utility in future clinical practice.

Comparison with other studies

Previous investigations have focused on the early prediction of HT in AIS patients. In a meta-analysis by Suh et al.[106] assessing perfusion CT for predicting HT risk in AIS, they reported a c-index of 0.84 (95%CI: 0.81-0.87), sensitivity of 0.84 (95%CI: 0.71-0.91), and specificity of 0.74 (95%CI: 0.67-0.81). This meta-analysis comprised 15 original studies that reported CT perfusion parameters. The results showed that high blood-brain barrier permeability and low perfusion were associated with HT. Moreover, another meta-analysis of 9 studies obtained a c-index of models based on magnetic resonance imaging (MRI) parameters of 0.85 (95%CI: 0.82-0.88), sensitivity of 0.92 (95%CI: 0.70-0.98), and specificity of 0.78 (95%CI: 0.65-0.87) to predict the risk of HT[107]. Increased permeability, hypoperfusion, reduced ADC values, and FLAIR hyperintensity are known to elevate the risk of HT. Interestingly, radiomics leverages high-throughput computing to extract numerous quantitative image-derived features, thereby enhancing diagnostic, prognostic, and predictive accuracy[108].

Furthermore, clinical features have been used to develop accurate prediction models. Interpretable clinical features of HT were analyzed in a previous study[109], with the c-index ranging from 0.67 to 0.79 in the included original studies and the c-index ranging from 0.59 to 0.88 in the external validation studies. The present results indicated that the prediction models based on these common clinical features possess promising

predictive value.

Although all of previously developed models have certain effect on HT prediction, the predictive value of the models based on either conventional imaging parameters or clinical features is not as good as that based on machine learning. Our study shows that the c-index of the prediction models built based on clinical features and radiomics can even reach 0.812 and 0.880 in the validation set, respectively, which largely demonstrates the potential of prediction models based on machine learning to be applied in clinical practice. In addition, the prediction model developed by clinical features combined with radiomic features had the best predictive value with a c-index of 0.915, which provides an important reference for the development of subsequent HT prediction models and is in line with our conventional knowledge. Since radiomics only considers the characteristics of the lesion itself, and demographics, which are part of the clinical characteristics, can also influence the risk of developing HT[110, 111], only a combination of the two can predict HT more comprehensively. The predictive efficacy of radiomics is affected by various factors, and there is currently no uniform specification and supervision for the establishment of predictive models based on radiomics[112], which poses a challenge to its clinical application. Overall, compared with other studies, our study provides stronger references for subsequent HT prediction models.

Strengths and limitations

This is the first systematic review encompassing all types of machine learning-based predictive models for HT in patients with AIS. In addition, robust subgroup analysis was conducted by different treatment backgrounds, diagnostic criteria, and HT types.

Moreover, we analyzed the external validation results of mature models, and found that the machine learning models had good performance, indicating they are promising tools for the establishment of new HT prediction models in future.

The limitations of this analysis need to be acknowledged. First, the number of included models did not allow us to directly compare the performance of various machine learning algorithms using the same set of model features. Second, most original studies validated their models internally rather than externally, thus probably impacting the interpretation of the results. And our detailed subgroup analysis also resulted in too few externally validated models in each subgroup. Moreover, radiomics-based studies may be more dependent on imaging parameters and the experience of the segmenter. Therefore, future studies should incorporate patients from multicenter and different population backgrounds to construct models with wider applicability and higher robustness under standard operation process for accurate treatment and prevention. Third, treatment backgrounds were diverse among the involved models. Despite the comprehensive discussion of treatment contexts, there is a large variation in the number of cases included in different treatment contexts (thrombolysis, thrombectomy) and the number of models. Hence, these results still need to be interpreted with caution. Fourth, the limitation of our research also lies in the lack of stratified analysis on geographical and demographic differences. Additionally, for some studies with too small a sample size, prediction models developed using deep learning cannot completely avoid the risk of overfitting. Moreover, publication bias was not assessed in our study because publication bias is more inclined to be assessed in the same model. Finally, fewer studies validated

existing mature models and, some of the tools were not designed to predict HT, such as SITS, which was built to predict the prognosis of stroke patients[101]. Therefore, these results should be interpreted with caution.

Future prospect

Nowadays, although machine learning has a wide range of applications in the research of AIS, it still faces certain challenges for its promotion in clinical practice. First, in the process of machine learning development, a large number of models tend to be developed based on a small number of cases, which raises some concerns about the robustness of the models. In the screening process of variables, the process of obtaining some variables is not clear, especially the findings based on demographic information that involves private information, which may compromise the accuracy of the variables. In the process of model construction, particularly for models based on radiomics, there is a lack of standards for the process of image selection, image segmentation, and texture extraction and screening, which makes model development heavily dependent on experience. In addition, existing models are predominantly internally validated, and only a few studies have carried out external validation in different regions, which poses a challenge to model promotion and accuracy. Especially in radiomics-based models, there may be large differences in images from different institutions, and there is still a lack of standardized criteria in clinical practice. Moreover, a large number of existing models only consider the accuracy of the model without considering risk stratification of the population, especially the variability of healthcare resources in different regions, which also poses a challenge to the clinical application of the model. In addition, the ethical

issues involved in models developed based on machine learning are also worth noting. Although the prediction model has an ideal application prospect, it is after all a means based on artificial intelligence. In the future, clinical diagnosis and treatment can not completely rely on the model established by machine learning. We should also pay attention to humanistic care and personalized diagnosis and treatment in clinical practice, especially for patients identified as low-risk by predictive models, we should not ignore the systematic management of them. In summary, in the future, we should carry out external validation of multicenter, large-sample, and different population-based predictive models to truly extend machine learning models into clinical practice. Furthermore, we should develop standardized operational procedures for building machine learning models, and the application of developed models in clinical practice should be regulated by authoritative organizations (e.g., the FDA).

Conclusion

Our analysis revealed limitations in the performance of current tools for predicting HT in AIS patients, highlighting the lack of a well-established clinical prediction model. However, the meta-analysis demonstrated promising results for machine learning models, particularly those combining clinical features and radiomics. These findings provide encouraging evidence supporting the development and improvement of clinical prediction tools based on machine learning approaches.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the study conception and design. Writing - original draft preparation: Benqiao Wang; Writing - review and editing: Benqiao Wang, Bohao Jiang, Dan Liu, Ruixia Zhu; Conceptualization: Ruixia Zhu; Methodology: Benqiao Wang, Bohao Jiang; Formal analysis and investigation: Bohao Jiang, Benqiao Wang, Liu Dan; Resources: Bohao Jiang; Supervision: Ruixia Zhu, Benqiao Wang, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Table S1 Literature search strategy

Multimedia Appendix 2

Table S2 Basic characteristics of the included studies

Multimedia Appendix 3

Table S3 The result of PROBAST assessment

Multimedia Appendix 4

Table S4 The c-index, sensitivity, and specificity of each included model

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Abbreviations

AF: atrial fibrillation

AIS: acute ischemic stroke

ALP: alkaline phosphatase

ALT: alanine aminotransferase

AUC: area under the curve

CBF: cerebral blood flow

CBS: clot burden score

CI: confidence interval

DBP: diastolic blood pressure

DM: diabetes mellitus

DWI: diffusion weighted imaging

ECASS: European Cooperative Acute Stroke Study

EIS: early infarct signs

EPV: events per variable

EVT: endovascular treatment

FDA: Food and Drug Administration

HBC: Heidelberg Bleeding Classification

HDL: high density lipoprotein

HT: hemorrhagic transformation

ICH: intracranial hemorrhage

LDL: low density lipoprotein

MMP-9: matrix metalloproteinase-9

MRI: magnetic resonance imaging

MSS: Multicenter rt-PA Stroke Survey score

NCCT: non-contrast computed tomography

NLR: neutrophil to lymphocyte ratio

OTT: onset-to-treatment

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROBAST: Prediction Model Risk of Bias Assessment Tool

rLMC: regional leptomeningeal collateral

SBP: systolic blood pressure

sICH: symptomatic intracranial hemorrhage

SITS: Safe Implementation of Treatments in Stroke

SPAN-100: Stroke Prognostication using Age and NIH Stroke Scale

TAG: thrombolysis in cerebral ischaemia-Alberta stroke program early CT-glucose score

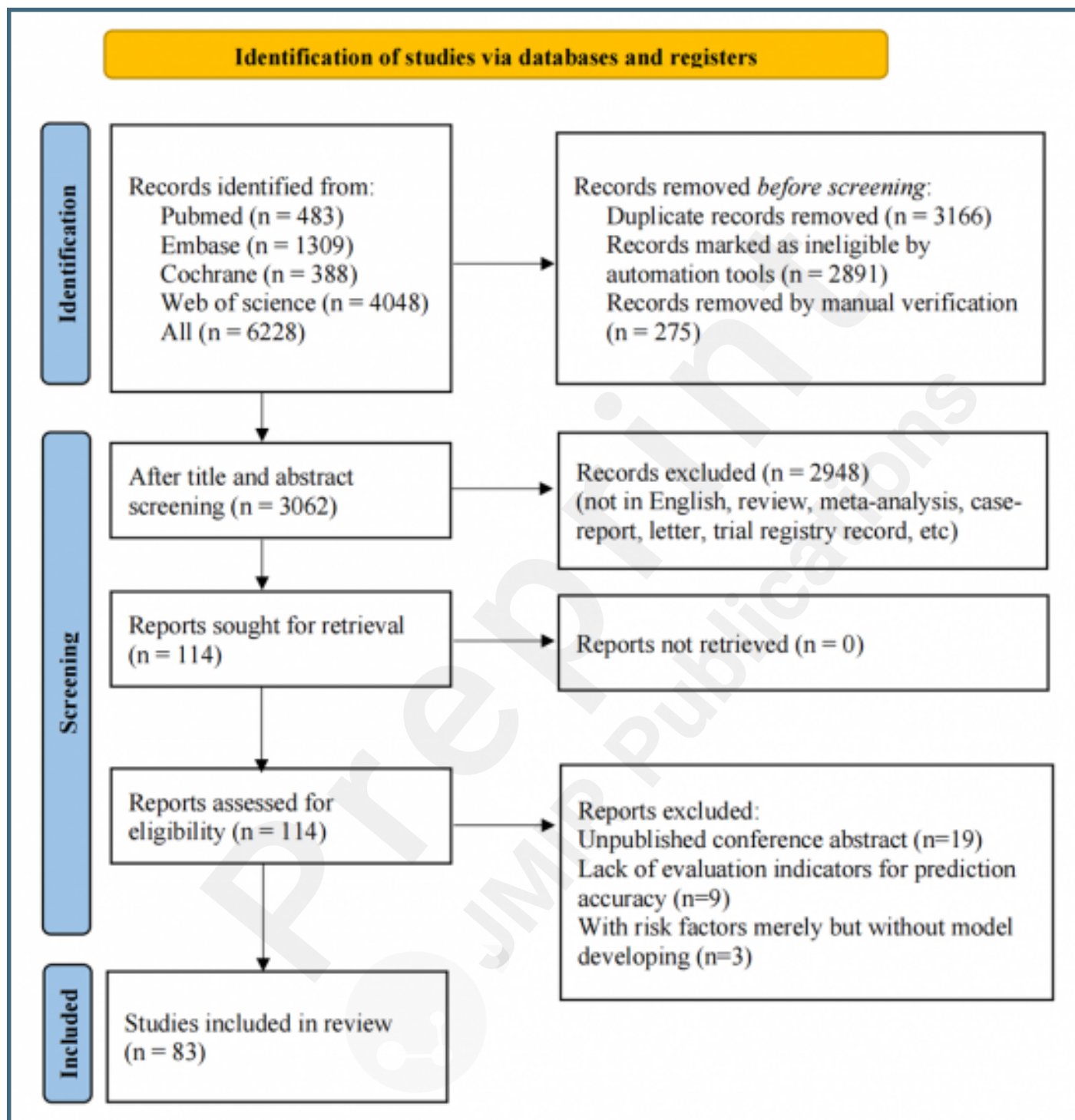
TOAST: Trial of ORG 10172 in Acute Stroke Treatment

UA: uric acid

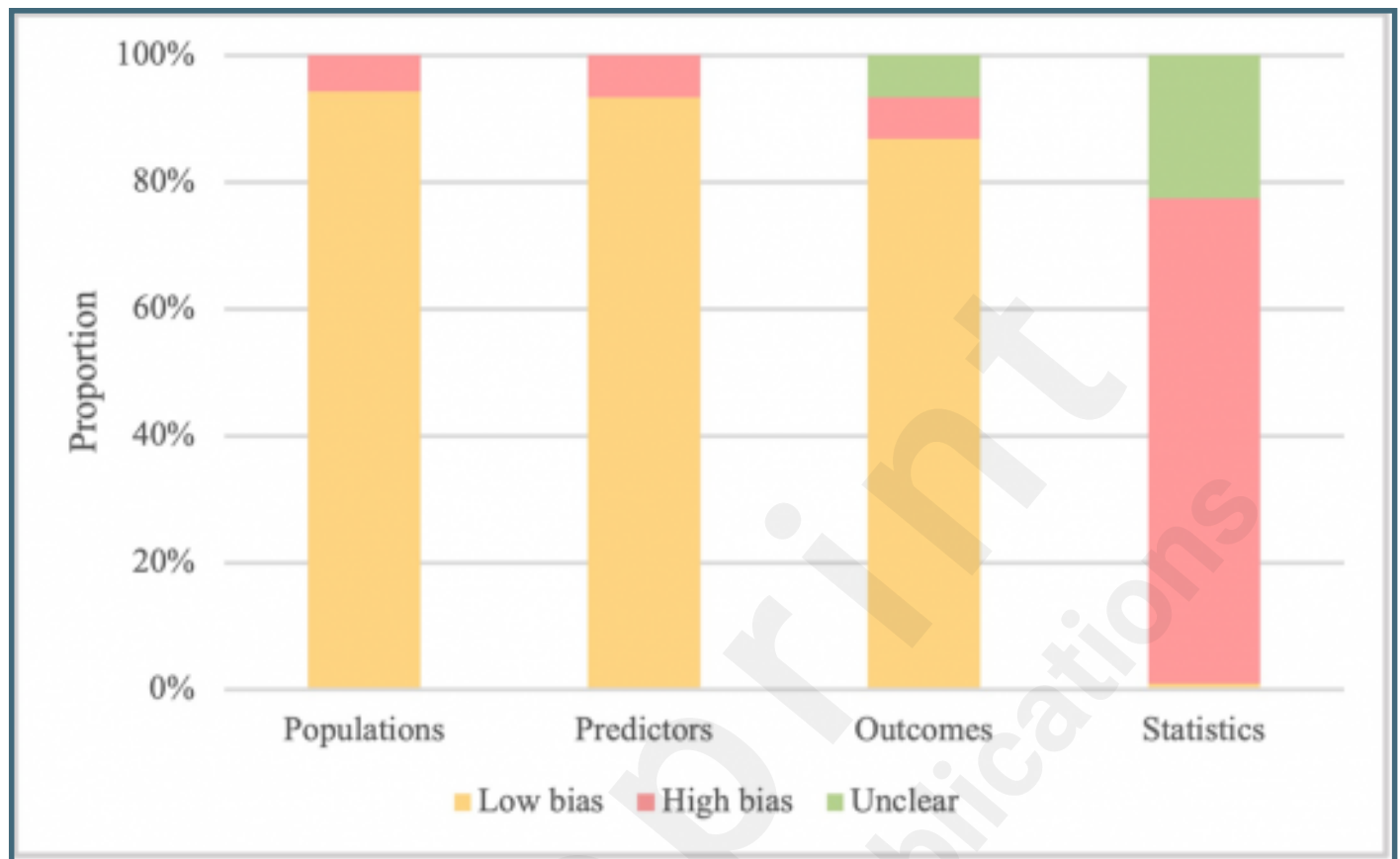
Supplementary Files

Figures

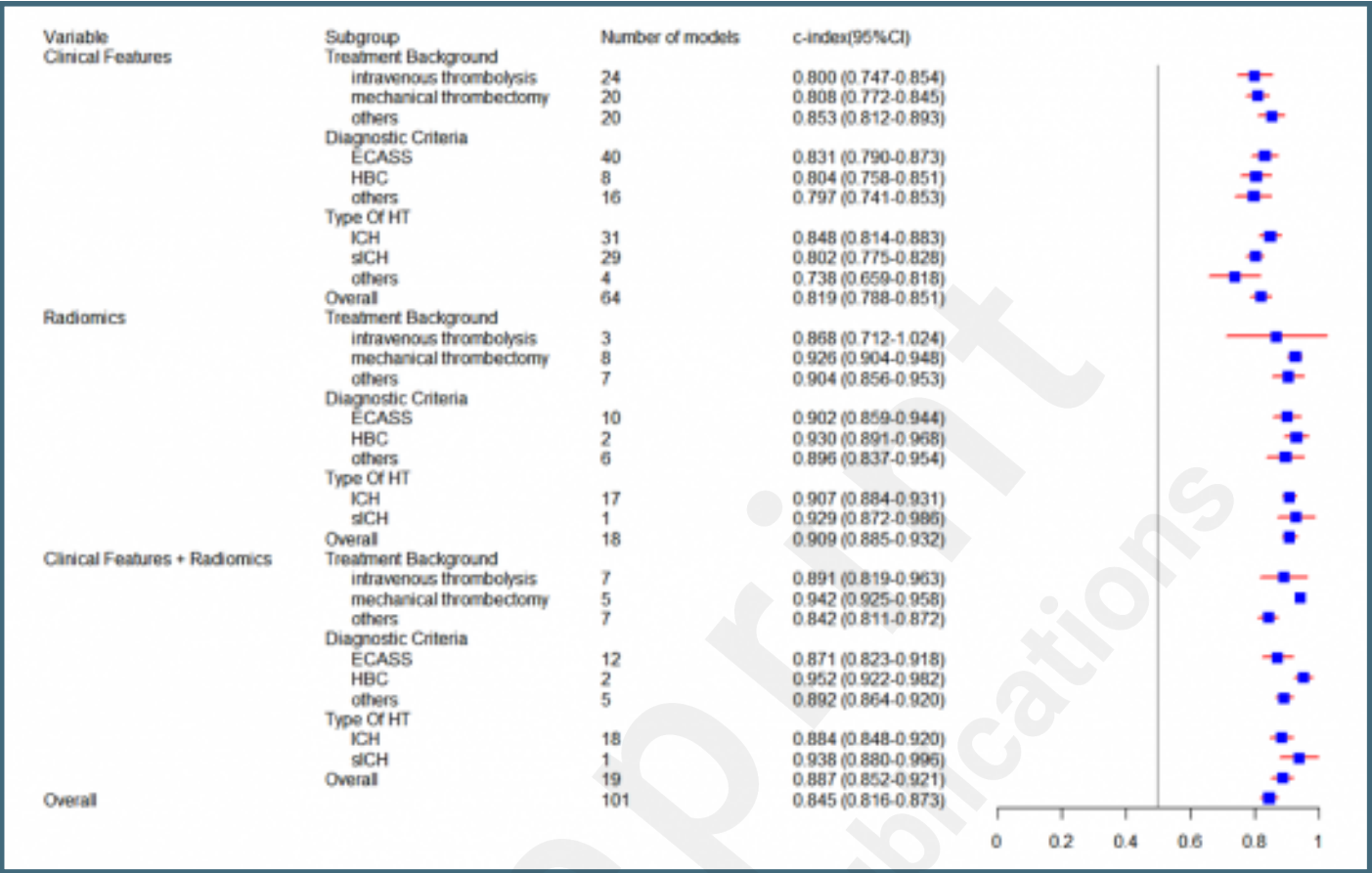
Flow chart of the literature selection process.



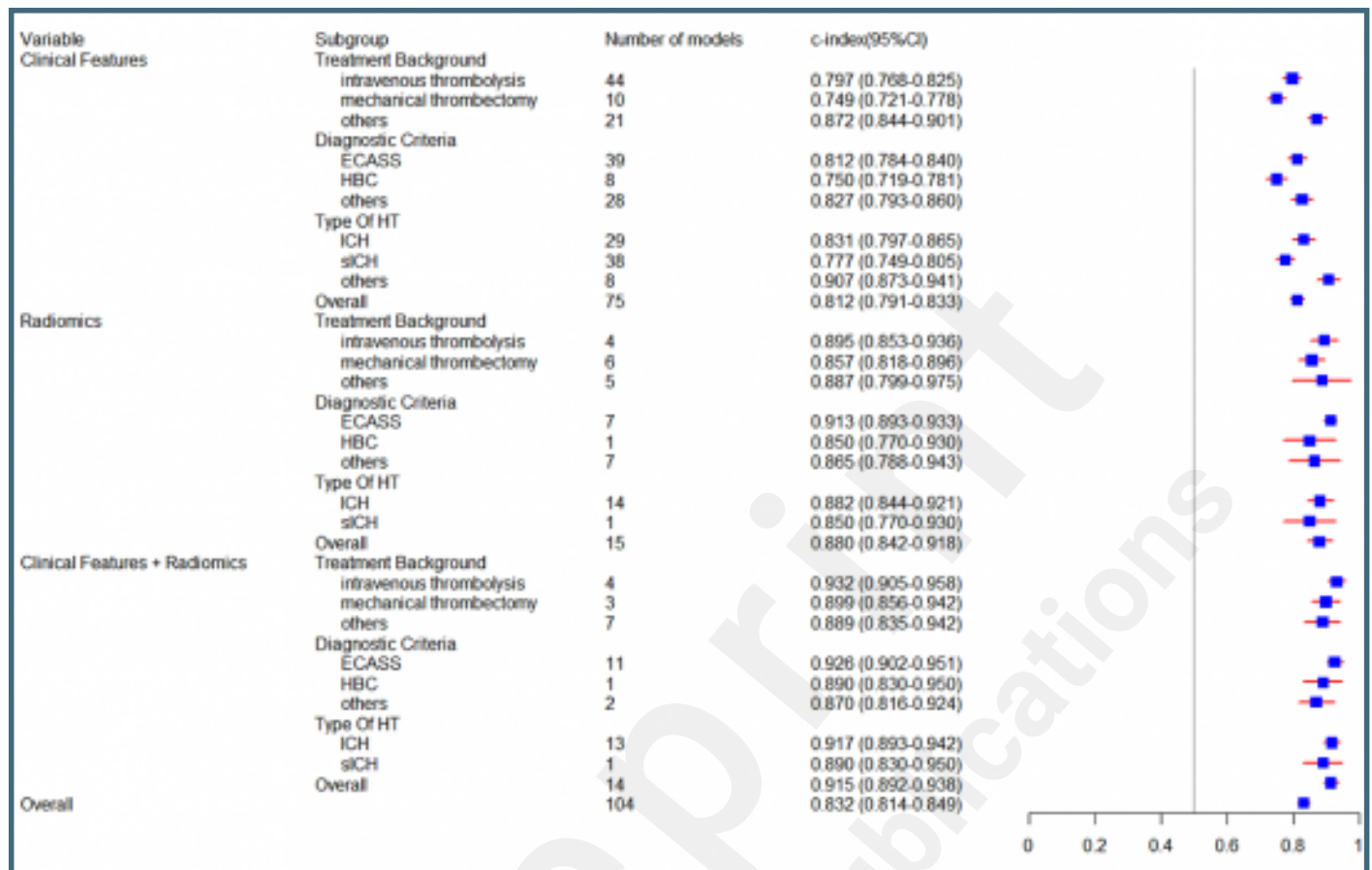
The risk of bias assessment of the included models.



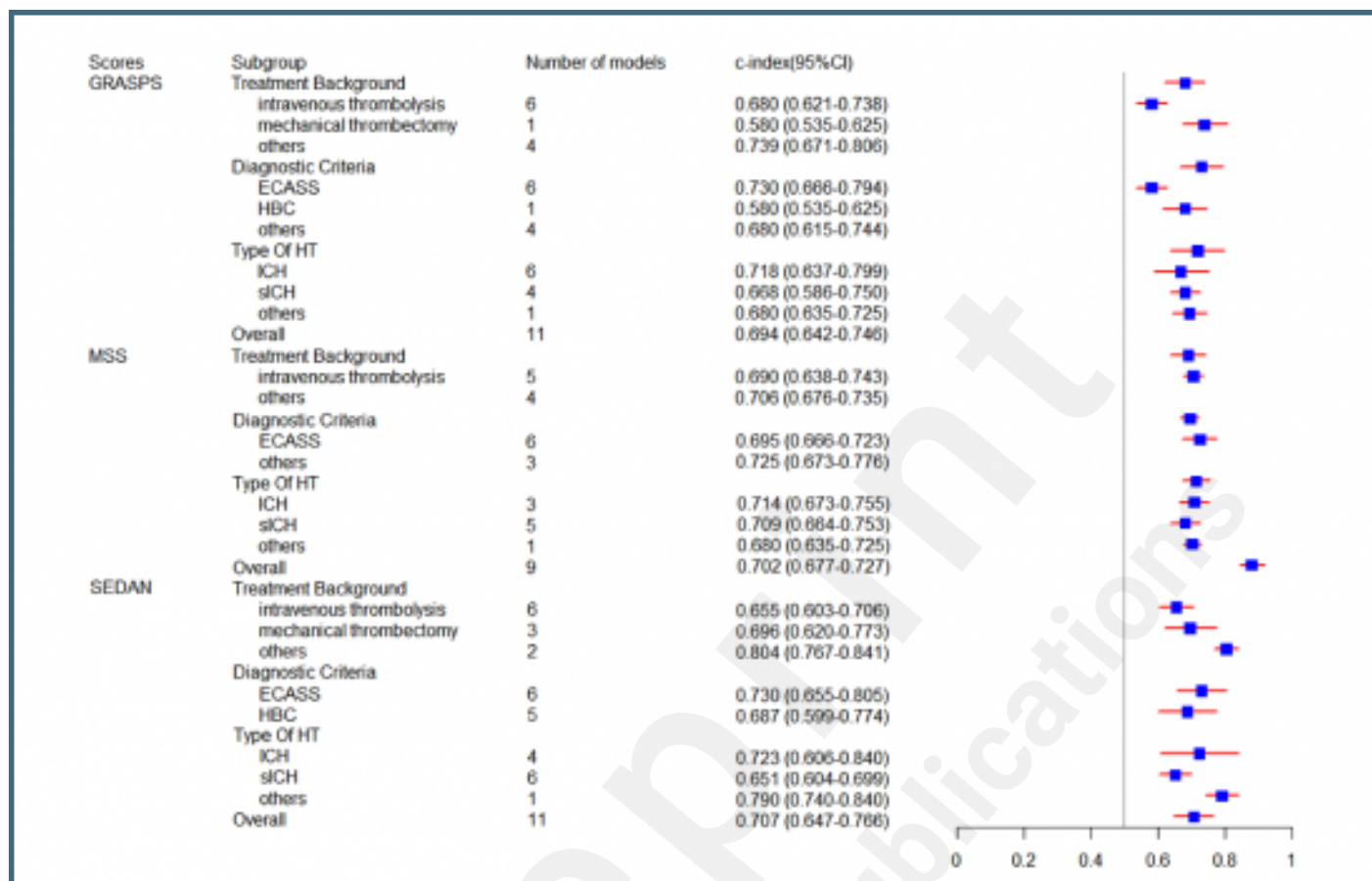
Forest plot of c-index for newly developed models in the training set.



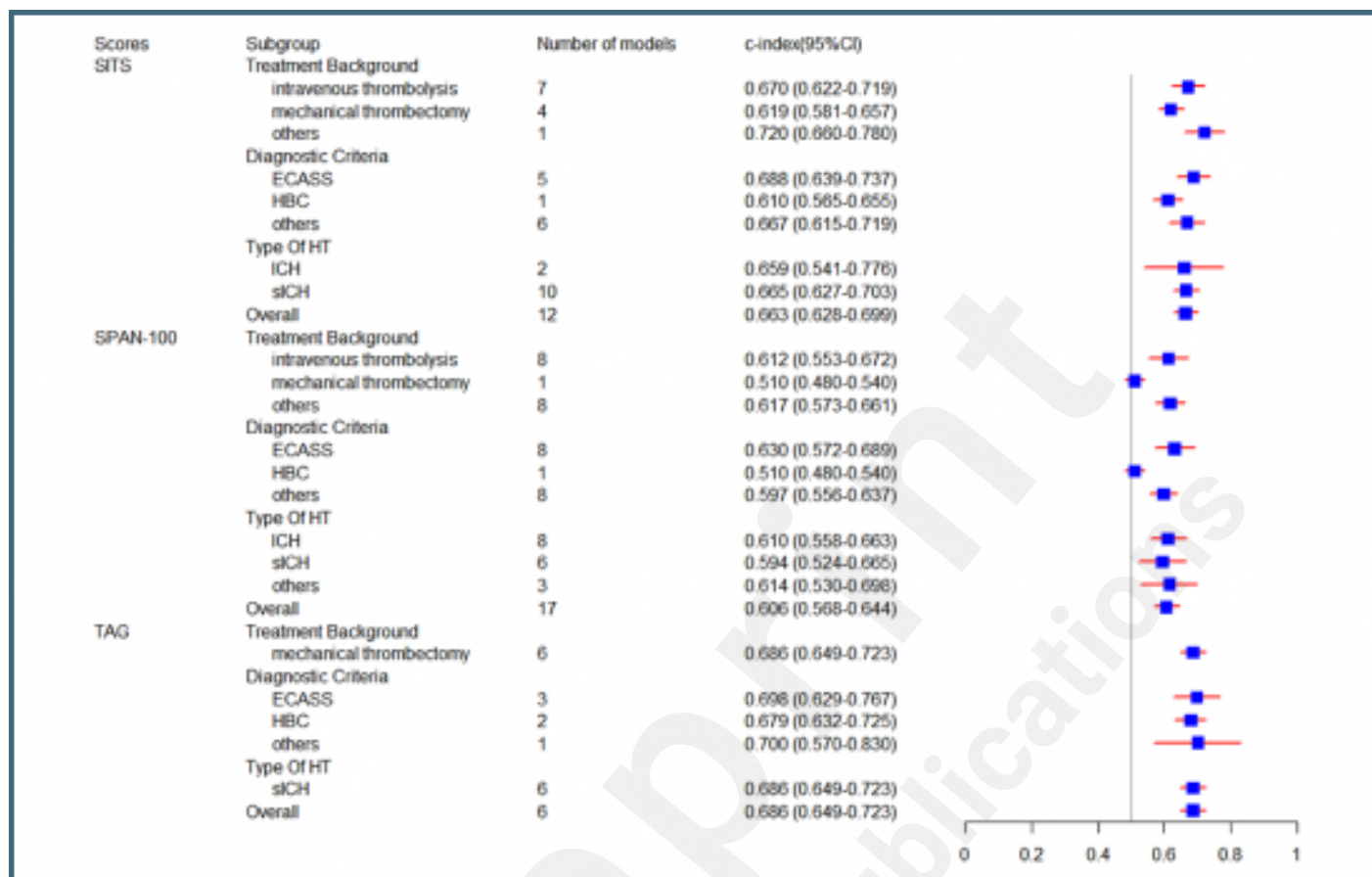
Forest plot of c-index for newly developed models in the validation set.



Forest plot of c-index for mature tools (GRASPS, MSS, and SEDAN).



Forest plot of c-index for mature tools (SITS, SPAN-100, and TAG).



Multimedia Appendixes

Table S1. Literature search strategy.

URL: <http://asset.jmir.pub/assets/e0bb8573e40b98169170c306840dcff7.docx>

Table S2. Basic characteristics of the included studies.

URL: <http://asset.jmir.pub/assets/25dac880ef3473960926198ee7a28e5e.xlsx>

Table S3. The result of PROBAST assessment.

URL: <http://asset.jmir.pub/assets/5b934ac33443c562e1936ac0c6dc85a7.xlsx>

Table S4. The c-index, sensitivity, and specificity of each included model.

URL: <http://asset.jmir.pub/assets/9f5075145a47dc60182a53415083f06d.xlsx>

