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The value of predictive instruments in the screening of acute stroke: an umbrella review on previous systematic reviews

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Abstract: **Objective:** Although various predictive instruments have been introduced for early stroke diagnosis, there is no consensus on their performance. Therefore, we decided to assess the value of predictive instruments in the detection of stroke by conducting an umbrella review.

Method: A search was performed in the Medline, Embase, Scopus and Web of Science databases by the end of August 2021 for systematic reviews and meta-analyses. Original articles included in the systematic reviews were retrieved, summarized and pooled sensitivity, specificity and diagnostic odds ratio were calculated. The level of evidence was divided into five groups: convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV) and non-significant.

Results: The value of 33 predictive instruments was evaluated. The sample size included in these scoring systems' assessments varied between 182 and 47072 patients. The level of evidence was class I in one tool, class II in 18 tools, class III in 2 tools, class IV in 11 tools, and non-significant in one tool. Apart from Med PACS, which had a low diagnostic value, other tools appeared to be able to detect a stroke. The optimum performance for diagnosis of stroke was for ROSIER, NIHSS, PASS, FAST, LAMS, RACE and CPSS.

Conclusion: Convincing to suggestive evidence shows that ROSIER, NIHSS, PASS, FAST, LAMS, RACE and CPSS have the optimum performance in identifying stroke. Since ROSIER's calculation is simple and has the highest sensitivity and specificity among those predictive instruments, it is recommended for stroke diagnosis in pre-hospital and in-hospital settings.

Keywords: Decision Support Techniques; Diagnosis; Emergency Medical Service; Stroke

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1. Introduction

Stroke is one of the main causes of mortality and morbidity with an annual incidence rate of 25 million cases (1). Stroke is one of the top 10 causes of death worldwide (1, 2) and is the cause of 5 to 10 percent of acute deaths. Based on the responsible pathophysiological processes, stroke is divided into two types: hemorrhagic and ischemic. The prevalence of ischemic stroke is much higher than the hemorrhagic type; However, mortality due to hemorrhagic stroke is much higher than the ischemic type (1).

The most well-known treatment for ischemic stroke is the use of intravenous thrombolytics such as tissue plasminogen activator (tPA), which should be administrated in 3.5 to 4 hours after the onset of stroke symptoms (3). Another treatment mentioned in recent studies is thrombectomy. Endovascular thrombectomy in great vessels is one of the most effective treatments for ischemic stroke (4-6). While surgery and endovascular embolization are used to treat strokes, the effectiveness of these treatments could be reduced in many cases due to delayed diagnosis. If the response team is able to quickly diagnose cerebrovascular accidents, the onset-to-door time could be substantially decreased.

Computed tomography scan (CT scan) and magnetic resonance imaging (MRI) are reliable modalities to detect strokes (7), but the lack of access to these imaging techniques in pre-hospital settings and even in some hospitals has led researchers to look for other alternatives. One of these alternative methods is using clinical screening tools. Various predictive instruments have been introduced to detect stroke, such as the Cincinnati Prehospital Stroke Severity Scale (CPSS); Los Angeles Motor Scale (LAMS); National In-

stitutes of Health Stroke Scale (NIHSS); Rapid Arterial Occlusion Evaluation; the Stroke Vision, Aphasia, Neglect assessment (VAN); Melbourne Ambulance Stroke Screen (MASS); Medic Prehospital Assessment for Code Stroke (Med PACS); Ontario Prehospital Stroke Screening Tool (OPSS); Recognition of Stroke in the Emergency Room (ROSIER) and Face Arm Speech Test (FAST) (8-11). Several systematic reviews have evaluated the value of these tools in stroke diagnosis, but there are substantial differences in their conclusions. Some believe that the value of these predictive instruments is equivalent in the diagnosis of stroke, but others do not have such an opinion (8, 10). Therefore, we decided to assess the value of predictive instruments in stroke detection by conducting an umbrella review to find the optimum diagnostic tools for early stroke detection.

2. Methods

2.1. Study design

The protocol of the present study has been registered and approved by Tehran University of Medical Sciences. The university ethics committee oversaw the study process. In the present study, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations (12) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (13) were used. All steps of searching, screening and summarizing the articles were performed by at least two independent researchers and any disagreements were resolved by discussion with a third researcher.

2.2. Search strategy

The purpose of this umbrella review is to compare the value of scoring systems in identifying stroke. For this purpose, an extensive search was initially conducted in the electronic resources of Medline, Embase, Scopus, and Web of Science by the end of August 2021. Then, with the appropriate combination of keywords related to stroke and predictive instruments, systematic reviews and meta-analyses were searched. The full search strategies for these databases have been reported in Appendix 1. PICO definition of the present study is as follows: diagnostic value of clinical decision rules (I) in stroke diagnosis (P). Comparisons (C) were done with a gold standard modality (CT scan and/or MRI) and the outcome (O) was considered the diagnostic value of these tools in detection of stroke. In addition to the systematic search, a manual search was also performed on Google search engine, and Google scholar.

Articles were screened based on title and abstract and systematic reviews and meta-analyses were studied in full text subsequently. Inclusion criteria were systematic reviews and meta-analysis that were conducted to assess the diagnostic value of scoring systems in identifying strokes. Exclusion criteria included studies with a pediatric population, narrative reviews, non-stoke studies, radiology-based decision tools and non-diagnostic reviews.

2.3. Data extraction

Data collection and summarization were performed by at least two independent researchers. Following the acquisition of the full text of systematic review and meta-analysis articles, information related to the name of the first author, year of publication, number of articles included in the systematic review/meta-analysis, samples' size and setting of study (in-hospital or pre-hospital) were recorded. Since in some cases, systematic reviews and meta-analyses included identical articles and some eligible reviews did not report pooled results, it was decided to obtain the full text of included original articles and extract the required data from them. Four independent researchers attained the papers and extracted the required data. If a study stratified the analysis by different subgroups, we also recorded the findings separately. In some studies, the diagnostic value of several predictive instruments was examined and therefore, the data were recorded separately for each tool. The quality of the methodology of systematic reviews and meta-analyses was assessed using AMSTAR (A Measurement Tool to Assess systematic Reviews) version 2 (14).

2.4. Data synthesis, certainty of evidence and statistical analyses

In the present umbrella review, True Positive (TP), True Negative (TN), False Positive (FP) and False Negative (FN) values were extracted from the articles. If the values of TP, TN, FP and FN were not reported, these values were calculated based on sensitivity, specificity and sample size. Since most of the review articles reported only sensitivity and specificity, all the original studies included in these review articles were investigated and data were extracted as required. Data were entered only once if a study was reported in two or more systematic reviews.

For each tool a sensitivity, specificity, Diagnostic Odds Ratio (DOR), Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR) were calculated. The "metandi" package in STATA 17.0 statistical software was used to calculate the values. Since this package is only able to perform analyses in cases where there are at least 4 articles, in cases that the number of imported original articles was less than 4, the "meta" package was used to report pooled effect size. For this purpose, the values of sensitivity, specificity, DOR, PLR and NLR and its 95% confidence interval (95% CI) were calculated and then the analyses were pooled with the meta command. Heterogeneity between studies was assessed using the I^2 statistics and I^2 above 50% was considered as heterogeneity. Deek's asymmetry plot was used to examine the publication bias and small-study effect. Excess significance bias was also investigated using the method proposed by Ioannidis and Trikalinos (15) and $p < 0.05$ indicated excess significant bias.

Level of evidence was assessed based on the method proposed in the previous article (16). Since DOR is a representative value for sensitivity and specificity, it was used for as-

sessment of certainty of evidence. The level of evidence was divided into four groups: convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV) and non-significant. Convincing level of evidence was in cases where the sample size was more than 1000 patients, p value obtained for pooled DOR in random effect model was less than 10-6, no evidence of heterogeneity was present (I^2 <50%), prediction interval did not cross the null and no evidence of small-study effect and excess significance was present. Highly suggestive level was in cases where the sample size was more than 1000 patients, random effect p value for effect size was lower than 10^{-6}, the largest included study had a significant effect whilst class I criteria were not met. The level of evidence was suggestive when the sample size was more than 1000 patients, p value of random effect model was lower than 10^{-3}, the largest included study had a significant effect whilst class I-II criteria were not met. The level of evidence was poor when the p value was <0.05 and no Class I-III criteria were met. Finally, non-significant was reported when the p value of effect size was higher than 0.05. This approach has been done based on the previous umbrella review (16).

3. Results

3.1. Search results

The search eventually resulted in 4,936 records. After removing duplicates, the abstract and title of 3496 articles were evaluated. Finally, 22 full-text articles were studied and 11 systematic reviews/meta-analyses were included in the present study (8-10, 17-24) (Figure 1).

3.2. Summary of data

Table 1 shows a summary of the included articles. 8 systematic reviews and 3 meta-analyses were included. The risk of bias assessment according to AMSTAR-2 showed that the quality of evidence from all 11 studies was critically low (Table 2). In these 11 articles, the diagnostic value of a total of 33 predictive instruments was examined. The number of articles included in the review articles ranged from 6 to 25. The list of scoring systems is reported in tables 3 and 4. CPSS (in 32 original articles), NIHSS (in 32 original articles), ROSIER (in 18 original articles) and 3-item stroke scale (3I-SS; in 15 original articles) were the most studied tools, respectively. Based on the number of articles included in each clinical assessment tool, the analyses were performed in two parts. A) predictive instruments that at least 4 articles have examined their diagnostic value in identifying stroke (Table 3) and B) predictive instruments that less than 4 studies have examined their diagnostic value (Table 4).

The number of people included in the diagnostic value of scoring systems varied between 182 and 47072 patients. The largest sample sizes were related to NIHSS, CPSS, Rapid Arterial Occlusion Evaluation (RACE), 3I-SS, FAST, Postural Assessment Scale for Stroke (PASS), and Los Angeles Pre-Hospital Stroke Screen (LAPSS) systems. The sample size in the evaluation of 9 tools was less than 1000 patients. Except for the Vision, Aphasia, Neglect (VAN) scale and Med PACS, significant DOR for stroke was observed in studied predictive instruments. Out of 33 analyses, the p-value for 28 tools (82.86%) was less than 10^{-6}. Significant heterogeneity was observed in 51.51% of the analyses. Prediction interval in 24.24% of the analyses included null. In three scoring systems (9.09%) evidence of small study effect and 5 analyses (15.15%) evidence of excess significant bias was observed (Tables 5 and 6). In general, the level of evidence was class I in 1 tool, class II in 18 tools, class III in 2 tools, class IV in 11 tools and non-significant in 1 tool. All tools reported in at least 4 studies were class I-III (Tables 5 and 6).

3.3. Diagnostic performance of clinical instruments that have been reported in at least 4 studies

The level of evidence of predictive instruments reported in at least 4 studies was between classes I-III. There was no class IV in this group. Therefore, the evidence obtained is between convincing to suggestive. Level of evidence of Balance, Eyes, Face, Arm, Speech, Time (BE-FAST) tools was also in class I and the sensitivity and specificity of this clinical tool were 0.62 (95% CI: 0.38, 0.86) and 0.79 (95% CI: 0.62, 0.96), respectively. As can be seen, the diagnostic performance of BE-FAST is not very high.

Among class II evidence, the highest sensitivity and specificity were for ROSIER (sensitivity = 0.88, specificity = 0.67), NIHSS (sensitivity = 0.83, specificity = 0.69), PASS (sensitivity = 0.80, specificity = 0.72), FAST (sensitivity = 0.80, specificity = 0.62), LAMS (sensitivity = 0.76, specificity = 0.87), shortened NIHSS-8 (sNIHSS8) (sensitivity = 0.75, specificity = 0.77), Rapid Arterial Occlusion Evaluation (RACE) (sensitivity = 0.73, specificity = 0.80), CPSS (sensitivity = 0.75, specificity = 0.75) and Bernese score (sensitivity = 0.71, specificity = 0.82). The sensitivity of other tools was less than 0.70. In class III evidence, there were three tools of Cincinnati Stroke Triage Assessment Tool (C-STAT) and LAPSS, which LAPSS had the best performance (sensitivity = 0.79, specificity = 0.91) (Table 5).

3.4. Diagnostic performance of predictive instruments that have been reported in less than 4 studies

Four predictive instruments of Aphasia/ Neglect/ Gaze Deviation (ANGD), shortened NIHSS-5 (sNIHSS-5), Ambulance Clinical Triage for Acute Stroke Treatment (ACT-FAST), modified NIHSS (mNHISS) and shortened NIHSS-1 (sNIHSS-1) were in class II level of evidence. The optimum performance in stroke diagnosis was for ACT-FAST (sensitivity = 0.91, specificity = 0.89), ANGD (sensitivity = 0.94, specificity = 0.58) and sNIHSS-5 (sensitivity = 0.73, specificity = 0.79) (Table 6).

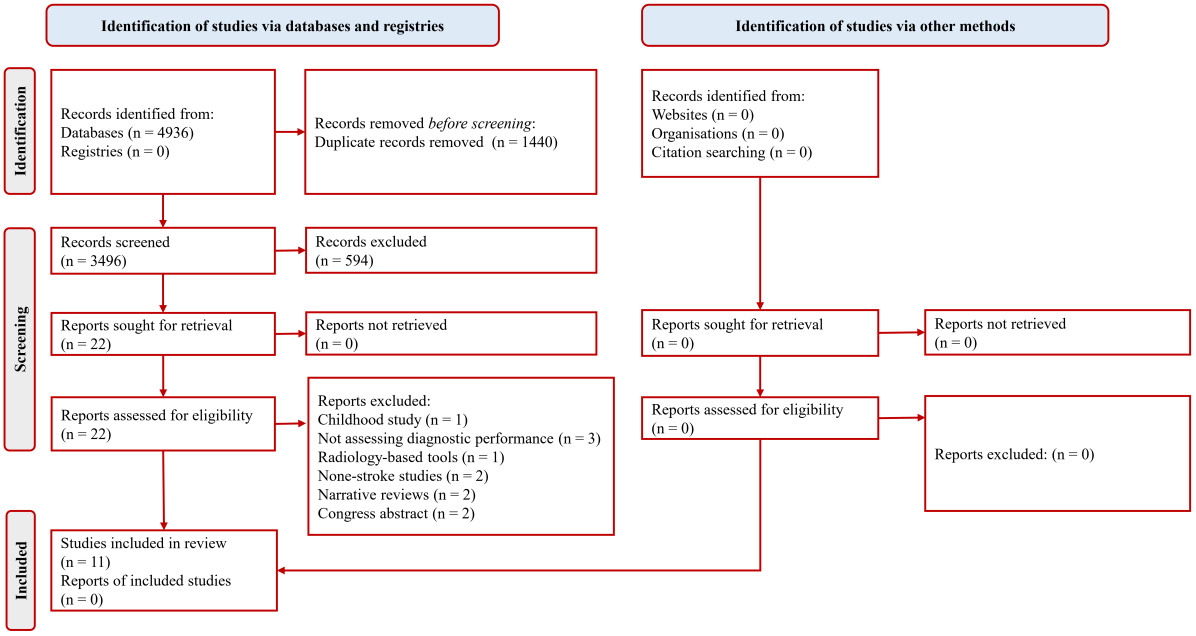

Figure 1 Flow diagram of current umbrella review.

Table 1 Summary of included studies

First author	Year	Type of review	Number of included studies	Number of included instruments	Setting of studies	Type of stroke	Reference
Antipova	2019	Systematic	25	33	Hospital & pre-hospital	Ischemic; TIA	(17)
Brandler	2014	Systematic	8	7	Pre-hospital	Ischemic; hemorrhagic; TIA	(8)
De Luca	2019	Meta-analysis	11	1	Hospital & pre-hospital	Ischemic; hemorrhagic; TIA	(18)
Han	2020	Meta-analysis	14	1	Pre-hospital	Ischemic; hemorrhagic; TIA	(19)
Krebs	2017	Systematic	8	6	Pre-hospital	Ischemic	(20)
Loudon	2019	Systematic	6	11	Pre-hospital	Ischemic	(21)
Meyran	2020	Meta-analysis	24	10	Pre-hospital	Ischemic; hemorrhagic; TIA	(22)
Oostema	2016	Systematic	7	3	Pre-hospital	Ischemic; TIA	(23)
Rudd	2015	Systematic	21	7	Hospital & pre-hospital	Ischemic; TIA	(24)
Smith	2018	Systematic	36	5	Hospital & pre-hospital	Ischemic; hemorrhagic; TIA	(9)
Vidale	2018	Systematic	13	19	Pre-hospital	Ischemic	(10)

TIA: Transient ischemic stroke

4. Discussion

Based on our knowledge, this study is the first umbrella review performed on the value of predictive instruments in stroke diagnosis. In the present study, 33 scoring systems were examined and the evidence obtained for 21 tools were in class I-III. Apart from Med PACS, whose DOR was non-significant for stroke diagnosis, other tools appear to be able to detect a stroke. Among these tools, the optimum performance was seen for ROSIER, NIHSS, PASS, FAST, LAMS, RACE and CPSS. Although the highest sensitivity and specificity in stroke diagnosis belonged to ACT-FAST, the number of studies included in the assessment of this clinical tool was two (sample size 1130), pointing to a need for further comprehensive studies.

ROSIER tool consists of 7 variables including the level of consciousness, seizure activity, asymmetric weakness (facial,

Table 2 AMSTAR risk of bias assessment of included studies

Item	Antipova, 2019	Brandler, 2014	De Luca, 2019	Han, 2020	Krebs, 2017	Loudon, 2019	Meyran, 2020	Oostema, 2016	Rudd, 2015	Smith, 2018	Vidale, 2018
1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	No
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	No	No	No	No	No	No	Yes	No	No	No	No
8	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	P/Y	Yes	Yes
10	No	No	No	No	No	No	No	No	No	No	No
11	No meta	No meta	Yes	Yes	No meta	No meta	Yes	No meta	No meta	No meta	No meta
12	No meta	No meta	No	Yes	No meta	No meta	No	No meta	No meta	No meta	No meta
13	No	No	No	No	No	No	No	No	No	No	No
14	No	No	Yes	Yes	No	No	No	No	No	No	No
15	No meta	No meta	No	Yes	No meta	No meta	No	No meta	No meta	No meta	No meta
16	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low

P/Y: Partial yes; No meta: No meta-analysis conducted

Table 3 Diagnostic performance of scoring systems in detection of stroke in analyses with a minimum 4 included studies

Score	Number of studies	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	PLR (95% CI)	NLR (95% CI)
CPSS	32	22996	0.75 (0.68, 0.81)	0.75 (0.68, 0.82)	9.27 (6.56, 13.09)	3.05 (2.38, 3.90)	0.33 (0.26, 0.41)
NIHSS	32	47072	0.82 (0.75, 0.86)	0.69 (0.63, 0.75)	10.0 (7.66, 13.10)	2.66 (2.26, 3.13)	0.26 (0.21, 0.34)
ROSIER	18	7223	0.88 (0.84, 0.91)	0.67 (0.55, 0.77)	15.24 (9.07, 25.60)	2.69 (1.93, 3.75)	0.18 (0.13, 0.24)
3I-SS	15	16421	0.59 (0.43, 0.73)	0.87 (0.77, 0.93)	9.71 (6.89, 13.68)	4.57 (3.06, 6.84)	0.47 (0.35, 0.64)
FAST	12	14965	0.80 (0.66, 0.90)	0.62 (0.39, 0.81)	6.77 (5.16, 8.91)	2.12 (1.36, 3.32)	0.31 (0.24, 0.41)
RACE	12	16535	0.73 (0.65, 0.81)	0.80 (0.72, 0.85)	10.73 (7.24, 15.91)	3.58 (2.68, 4.78)	0.33 (0.26, 0.44)
PASS	9	14075	0.80 (0.68, 0.88)	0.72 (0.53, 0.85)	10.27 (6.78, 15.55)	2.83 (1.77, 4.52)	0.28 (0.20, 0.39)
C-STAT	7	10660	0.71 (0.59, 0.81)	0.77 (0.60, 0.87)	8.64 (3.78, 19.71)	3.18 (1.74, 5.80)	0.37 (0.25, 0.54)
FAST-ED	7	5716	0.61 (0.54, 0.67)	0.86 (0.82, 0.89)	9.48 (6.50, 13.82)	4.32 (3.40, 5.50)	0.46 (0.38, 0.54)
aNIHSS	7	7433	0.75 (0.62, 0.85)	0.64 (0.53, 0.73)	5.37 (3.86, 7.45)	2.07 (1.74, 2.46)	0.39 (1.74, 2.46)
LAMS	6	5587	0.76 (0.65, 0.84)	0.87 (0.81, 0.91)	21.16 (9.04, 49.51)	5.81 (3.68, 9.18)	0.27 (0.18, 0.43)
LAPSS	6	13988	0.79 (0.76, 0.83)	0.91 (0.74, 0.97)	40.03 (9.28, 172.66)	8.92 (2.70, 29.47)	0.22 (0.17, 0.29)
Bernese score	5	5425	0.71 (0.68, 0.74)	0.82 (0.80, 0.84)	11.38 (9.58, 13.5)	3.99 (3.57, 4.48)	0.35 (0.32, 0.39)
sNIHSS-8	5	4237	0.75 (0.73, 0.77)	0.83 (0.81, 0.84)	12.0 (10.05, 14.02)	3.53 (3.22, 3.84)	0.32 (0.29, 0.35)
BE-FAST	4	1436	0.62 (0.38, 0.86)	0.79 (0.62, 0.96)	8.38 (5.78, 10.97)	3.19 (1.71, 4.67)	0.44 (0.22, 0.67)
MPDS	4	12925	0.58 (0.40, 0.75)	0.95 (0.79, 0.99)	28.10 (11.0, 71.32)	12.0 (3.40, 43.20)	0.44 (0.31, 0.62)

3I-SS: 3-item stroke scale; aNIHSS: Abbreviated National Institutes of Health Stroke Scale, or NIH Stroke Scale; BE-FAST: BE-FAST: Balance, Eyes, Face, Arm, Speech, Time; C-STAT: Cincinnati Stroke Triage Assessment Tool; CPSS: Cincinnati Pre-Hospital Stroke Scale; FAST: Face Arm Speech Test; FAST-ED: Field Assessment Stroke Triage for Emergency Destination; LAMS: Los Angeles Motor Scale; LAPSS: Los Angeles Pre-Hospital Stroke Screen; MPDS: Medical Priority Dispatch Software; NIHSS: National Institutes of Health Stroke Scale; PASS: Postural Assessment Scale for Stroke; RACE: Rapid Arterial oCclusion Evaluation; ROSIER: Recognition of Stroke in the Emergency Room; sNIHSS: Shortening National Institutes of Health Stroke Scale.

arm, leg), speech disturbance and visual field defect, which are much easier to calculate than NIHSS. The NIHSS is an 11-domain tool that is time-consuming to evaluate. The current umbrella review demonstrates that ROSIER performance is better than all NIHSS versions (full and abbreviated version) and may be used as an effective tool in emergency settings to diagnose stroke.

In the present study, there was no evidence of excess significance bias present. Since in all included tools, the largest studies demonstrated significant findings, therefore, it was expected that there would be no excess significance bias in the studies. Since in Ioannidis and Trikalinos method (15), the power is calculated based on the effect size of the largest study and regarding the fact that the sample size was very high in these studies, the expected number of significant studies was very similar to the observed number of significant studies. Nevertheless, the Cochrane guideline states that caution should be exercised on the use of the Ioannidis and Trikalinos method, considering that its accuracy has not yet been properly evaluated.

There was significant heterogeneity among the included studies in the assessment of the value of predictive instru-

Table 4 Diagnostic performance of scoring systems in detection of stroke in analyses less than 4 included studies

Score	Number of studies	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	PLR (95% CI)	NLR (95% CI)
ANGD	3	1841	0.94 (0.91, 0.97)	0.58 (0.39, 0.76)	21.93 (11.29, 32.57)	2.39 (1.53, 3.24)	0.11 (0.06, 0.15)
MASS	3	981	0.85 (0.83, 0.87)	0.82 (0.78, 0.86)	27.19 (20.62, 35.87)	4.85 (3.86, 6.10)	0.17 (0.15, 0.20)
sNIHSS-5	3	2830	0.73 (0.71, 0.76)	0.79 (0.77, 0.82)	10.15 (8.30, 11.99)	3.50 (3.13, 3.87)	0.34 (0.30, 0.37)
ACT-FAST	2	1130	0.91 (0.81, 1.0)	0.89 (0.83, 0.96)	80.87 (8.0, 153.74)	9.24 (4.14, 14.35)	0.10 (0.01, 0.20)
VAN	2	838	0.96 (0.91, 1.00)	0.73 (0.39, 1.00)	22.69 (1.0, 46.40)	4.22 (1.68, 10.14)	0.08 (0.00, 0.17)
mNHISS	2	2089	0.78 (0.75, 0.80)	0.77 (0.74, 0.79)	11.23 (8.80, 13.65)	3.31 (2.93, 3.68)	0.29 (0.26, 0.33)
sNIHSS-1	2	2089	0.64 (0.61, 0.67)	0.81 (0.78, 0.83)	7.34 (5.80, 8.88)	3.31 (2.88, 3.75)	0.44 (0.40, 0.48)
M-DIRECT	1	327	0.74 (0.65, 0.83)	0.92 (0.88, 0.96)	33.0 (9.7, 56.34)	9.33 (4.90, 13.76)	0.28 (0.18, 0.38)
EMSA	1	1663	0.74 (0.67, 0.81)	0.50 (0.48, 0.52)	2.92 (1.86, 3.98)	1.49 (1.34, 1.64)	0.51 (0.37, 0.64)
FAST PLUS	1	435	0.93 (0.88, 0.98)	0.47 (0.41, 0.53)	11.31 (2.54, 20.08)	1.75 (1.55, 1.95)	0.15 (0.04, 0.26)
FPSS	1	856	0.54 (0.40, 0.64)	0.91 (0.89, 0.93)	12.25 (6.46, 18.04)	6.15 (4.35, 7.95)	0.50 (0.40, 0.60)
LEGS	1	182	0.86 (0.77, 0.95)	0.96 (0.92, 1.00)	127.44 (41.6, 390.36)	19.32 (9.60, 30.13)	0.15 (0.06, 0.24)
MPSS	1	1004	0.84 (0.80, 0.88)	0.65 (0.61, 0.69)	9.83 (6.47, 13.19)	2.40 (2.12, 2.68)	0.24 (0.18, 0.30)
Med PACS	1	416	0.74 (0.68, 0.80)	0.33 (0.26, 0.40)	1.42 (0.79, 2.05)	1.11 (1.00, 1.24)	0.78 (0.54, 1.0)
OPSS	1	554	0.87 (0.82, 0.92)	0.59 (0.54, 0.64)	9.61 (5.12, 14.01)	2.13 (1.84, 242)	0.22 (0.14, 0.30)
rNIHSS	1	1004	0.73 (0.68, 0.78)	0.39 (0.35, 0.43)	1.72 (1.22, 2.22)	1.2 (1.09, 1.31)	0.69 (0.55, 0.83)
sNIHSS-EMS	1	741	0.70 (0.65, 0.75)	0.81 (0.77, 0.85)	9.90 (6.57, 13.34)	3.37 (2.89, 4.55)	0.37 (0.30, 0.44)

CI: Confidence Interval; DOR: Diagnostic Odds Ratio; PLR: Positive Likelihood Ratio; NLR: Negative Likelihood Ratio. FAST PLUS: ACT-FAST: Ambulance Clinical Triage for Acute Stroke Treatment; ANGD: Aphasia; Neglect/gaze deviation; The first part is the FAST test and the second part evaluates only the presence of severe arm or leg motor deficit; FPSS: Finnish Prehospital Stroke Scale; LEGS: Lower extremity strength, Eyes/visual fields, Gaze deviation, Speech difficulty; M-DIRECT: Madrid-Direct Referral to Endovascular Center; MASS: Melbourne Ambulance Stroke Screen; Med PACS: Medic Prehospital Assessment for Code Stroke; mNHISS: Modified National Institutes of Health Stroke Scale; MPSS: Maria Prehospital Stroke Scale; OPSS: Ontario Prehospital Stroke Screening Tool; rNIHSS: Revised National Institutes of Health Stroke Scale; sNIHSS: Shortening National Institutes of Health Stroke Scale; sNIHSS-EMS: Shortening National Institutes of Health Stroke Scale for Emergency Medical Services; VAN: Vision, Aphasia, Neglect

Table 5 Level of evidence among included scoring systems in detection of stroke in analyses with a minimum 4 included studies

Score	Number of studies	Sample size	DOR (95% CI)	P value for random effect	Prediction interval	I^2	LS	Small study effect	Excess significance bias	Level of evidence
CPSS	32	22996	9.27 (6.56, 13.09)	<1.0 × 10-50	1.26, 67.61	95.45	Yes	0.133	No	II
NIHSS	32	47072	10.0 (7.66, 13.10)	<1.0 × 10-50	2.49, 35.24	95.85	Yes	0.337	No	II
ROSIER	18	7223	15.24 (9.07, 25.60)	<1.0 × 10-50	1.52, 162.25	93.15	Yes	0.110	No	II
3I-SS	15	16421	9.71 (6.89, 13.68)	<1.0 × 10-50	2.70, 32.73	88.49	Yes	0.713	No	II
FAST	12	14965	6.77 (5.16, 8.91)	<1.0 × 10-50	2.85, 17.69	77.17	Yes	0.126	No	II
RACE	12	16535	10.73 (7.24, 15.91)	<1.0 × 10-50	2.27, 49.43	95.45	Yes	0.993	No	II
PASS	9	14075	10.27 (6.78, 15.55)	<1.0 × 10-50	2.47, 41.30	91.19	Yes	0.342	No	II
C-STAT	7	10660	8.64 (3.78, 19.71)	2.1 × 10-6	0.35, 208.40	97.82	Yes	0.600	No	III
FAST-ED	7	5716	9.48 (6.50, 13.82)	<1.0 × 10-50	2.29, 39.81	86.08	Yes	0.872	No	II
aNIHSS	7	7433	5.37 (3.86, 7.45)	<1.0 × 10-50	1.57, 17.97	90.03	Yes	0.190	No	II
LAMS	6	5587	21.16 (9.04, 49.51)	3.0 × 10-11	0.95, 513.86	94.74	Yes	0.151	No	II
LAPSS	6	13988	40.03 (9.28, 172.66)	1.6 × 10-5	0.09, 2000	98.04	Yes	0.785	No	III
Bernese score	5	5425	11.38 (9.58, 13.5)	<1.0 × 10-50	6.37, 20.38	50.25	Yes	<0.001	No	II
sNIHSS-8	5	4237	12.0 (10.05, 14.02)	<1.0 × 10-50	9.34, 15.77	0.00	Yes	0.418	No	II
BE-FAST	4	1436	8.38 (5.78, 10.97)	<1.0 × 10-50	4.16, 20.76	10.82	Yes	0.458	No	I
MPDS	4	12925	28.10 (11.0, 71.32)	8.5 × 10-8	0.08, 7400.9	97.37	Yes	0.044	No	II

CI: Confidence Interval; DOR: Diagnostic Odds Ratio; LS: Largest study with significant effect.
3I-SS: 3-item stroke scale; aNIHSS: Abbreviated National Institutes of Health Stroke Scale, or NIH Stroke Scale; BE-FAST: BE-FAST: Balance, Eyes, Face, Arm, Speech, Time; C-STAT: Cincinnati Stroke Triage Assessment Tool; CPSS: Cincinnati Pre-Hospital Stroke Scale; FAST: Face Arm Speech Test; FAST-ED: Field Assessment Stroke Triage for Emergency Destination; LAMS: Los Angeles Motor Scale; LAPSS: Los Angeles Pre-Hospital Stroke Screen; MPDS: Medical Priority Dispatch Software; NIHSS: National Institutes of Health Stroke Scale; PASS: Postural Assessment Scale for Stroke; RACE: Rapid Arterial oCclusion Evaluation; ROSIER: Recognition of Stroke in the Emergency Room; sNIHSS: Shortening National Institutes of Health Stroke Scale.

Table 6 Level of evidence among included scoring systems in detection of stroke in analyses less than 4 included studies

Score	Number of studies	Sample size	DOR (95% CI)	P value for random effect	Prediction interval	I^2	LS	Small study effect	Excess significance bias	Level of evidence
ANGD	3	1841	21.93 (11.29, 32.57)	<1.0 × 10-50	1.42, 388.29	0.00	Yes	0.737	No	II
MASS	3	981	27.19 (20.62, 35.87)	2.3 × 10-14	0.006, 7100,0	48.3	Yes	0.431	No	IV
sNIHSS-5	3	2830	10.15 (8.30, 11.99)	<1.0 × 10-50	3.20, 32.36	0.00	Yes	0.030	No	II
ACT-FAST	2	1130	80.87 (8.0, 153.74)	<1.0 × 10-50	NA	0.00	Yes	NA	No	II
VAN	2	838	22.69 (1.0, 46.40)	3.3 × 10-4	NA	53.5	Yes	NA	No	IV
mNHISS	2	2089	11.23 (8.80, 13.65)	<1.0 × 10-50	NA	0.00	Yes	NA	No	II
sNIHSS-1	2	2089	7.34 (5.80, 8.88)	<1.0 × 10-50	NA	0.00	Yes	NA	No	II
M-DIRECT	1	327	33.0 (9.7, 56.34)	<1.0 × 10-50	NA	NA	NA	NA	NA	IV
EMSA	1	1663	2.92 (1.86, 3.98)	4.4 × 10-9	NA	NA	NA	NA	NA	IV
FAST PLUS	1	435	11.31 (2.54, 20.08)	2.8 × 10-11	NA	NA	NA	NA	NA	IV
FPSS	1	856	12.25 (6.46, 18.04)	<1.0 × 10-50	NA	NA	NA	NA	NA	IV
LEGS	1	182	127.44 (41.60, 390.36)	<1.0 × 10-50	NA	NA	NA	NA	NA	IV
MPSS	1	1004	9.83 (6.47, 13.19)	<1.0 × 10-50	NA	NA	NA	NA	NA	IV
Med PACS	1	416	1.42 (0.79, 2.05)	0.11	NA	NA	NA	NA	NA	NS
OPSS	1	554	9.61 (5.12, 14.01)	<1.0 × 10-50	NA	NA	NA	NA	NA	IV
rNIHSS	1	1004	1.72 (1.22, 2.22)	2.2 × 10-4	NA	NA	NA	NA	NA	IV
sNIHSS-EMS	1	741	9.90 (6.57, 13.34)	<1.0 × 10-50	NA	NA	NA	NA	NA	IV

CI: Confidence Interval; DOR: Diagnostic Odds Ratio; LS: Largest study with significant effect.
ACT-FAST: Ambulance Clinical Triage for Acute Stroke Treatment; ANGD: Aphasia; Neglect/gaze deviation; FAST PLUS: The first part is the FAST test and the second part evaluates only the presence of severe arm or leg motor deficit; FPSS: Finnish Prehospital Stroke Scale; LEGS: Lower extremity strength, Eyes/visual fields, Gaze deviation, Speech difficulty; M-DIRECT: Madrid-Direct Referral to Endovascular Center; MASS: Melbourne Ambulance Stroke Screen; Med PACS: Medic Prehospital Assessment for Code Stroke; mNHISS: Modified National Institutes of Health Stroke Scale; MPSS: Maria Prehospital Stroke Scale; OPSS: Ontario Prehospital Stroke Screening Tool; rNIHSS: Revised National Institutes of Health Stroke Scale; sNIHSS: Shortening National Institutes of Health Stroke Scale; sNIHSS-EMS: Shortening National Institutes of Health Stroke Scale for Emergency Medical Services; VAN: Vision, Aphasia, Neglec

ments in stroke diagnosis. It is worth mentioning that the diagnostic value studies are often heterogeneous due to significant differences in the methodology, different gold standards and variation in the expertise of operators conducting the index test. Therefore, as a resort, it is suggested that random effect models be used in all meta-analyses of diagnostic value studies, even if heterogeneity is not observed.

Finally, it should be noted that the study of heterogeneity in studies of diagnostic values is difficult and is associated with numerous pitfalls (25). Inspecting Table 6, it becomes clear that the reason behind most studies being in class II of evidence is due to high heterogeneity among them. Accordingly, if we ignore the existence of heterogeneity in the evaluation of certainty of the evidence, the evidence obtained in most predictive instruments is classified as convincing (class I). Therefore, it may be necessary to omit heterogeneity as a criterion in the certainty of evidence assessment of diagnostic accuracy studies, or at least not consider it for class I of evidence, regarding that the power of analysis for assessment of heterogeneity among diagnostic accuracy studies is low (25). In the present umbrella review, it was found that 17 predictive instruments were only evaluated in less than 4 studies. In other words, the available systematic reviews and meta-analyses evaluating these tools included a maximum of 3 studies. Although new studies have been performed on these predictive instruments in recent years, (26-30) the need for more comprehensive systematic reviews and probable meta-analyses is felt for the clinical decision rules presented in Table 6.

5. Limitations

The risk of bias assessment of included systematic reviews/meta-analyses was critically low. Although this is a possible limitation of the current umbrella review, since we pooled data of original studies, therefore, the low quality of systematic reviews/meta-analyses did not consider as a significant limitation. In addition, we assessed the level of evidence for each tool, separately.

6. Conclusion

Convincing to suggestive evidence shows that ROSIER, NIHSS, PASS, FAST, LAMS, RACE and CPSS have the optimum performance in identifying stroke. Since ROSIER's calculation is simple and has the highest sensitivity and specificity, it is recommended as an effective tool in identifying strokes in pre-hospital and in-hospital settings. Moreover, it was found that the diagnostic value of 17 scoring systems was examined in less than 4 studies, pointing to the need for more comprehensive systematic reviews on these scoring systems.

7. Declarations

7.1. Acknowledgment

None.

7.2. Authors' contribution

Study design and conception: AB and MY; Data gathering: All the authors; Analysis: MY; Drafting and revise: All the au-

thors.

7.3. Conflict of Interest

The authors declare that there is no conflict of interest.

7.4. Funding

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Appendix 1 Full search strategy for all databases

PubMed
((("Stroke"[mh] OR "Brain Infarction"[mh] OR "Brain Stem Infarctions"[mh] OR "Infarction, Anterior Cerebral Artery"[mh] OR "Cerebral Infarction"[mh] OR "Hypoxia-Ischemia, Brain"[mh] OR "Brain Ischemia"[mh] OR "Arterial Occlusive Diseases"[mh] OR Stroke[tiab] OR Brain Infarction[tiab] OR Brain Stem Infarctions[tiab] OR Cerebral Infarction[tiab] OR Brain Ischemia[tiab] OR Cerebrovascular Accident[tiab] OR Brain Vascular Accident[tiab] OR Cerebrovascular Stroke[tiab] OR Arterial Occlusive Disease[tiab] OR Arterial Obstructive Diseases[tiab] OR Arterial Obstructive Disease[tiab])) AND ("Predictive Value of Tests"[mh] OR "Sensitivity and Specificity"[mh] OR "Severity of Illness Index"[mh] OR "Early Diagnosis"[mh] OR Cincinnati Prehospital Stroke Severity Scale[tiab] OR CPSSS[tiab] OR Los Angeles Motor Scale[tiab] OR LAMS[tiab] OR National Institutes of Health Stroke Scale[tiab] OR NIHSS[tiab] OR Rapid Arterial Occlusion Evaluation[tiab] OR RACE[tiab] OR Stroke Vision, Aphasia, Neglect[tiab] OR vision, aphasia, and neglect[tiab] OR Melbourne Ambulance Stroke Screen[tiab] OR MASS[tiab] OR Medic Prehospital Assessment for Code Stroke[tiab] OR Med PACS[tiab] OR MPACS[tiab] OR MedPACS[tiab] OR Ontario Prehospital Stroke Screening Tool[tiab] OR OPSS[tiab] OR Recognition of Stroke in the Emergency Room[tiab] OR ROSIER[tiab] OR Face Arm Speech Test [tiab] OR Face Arm Speech Time test[tiab] OR decision rule[tiab] OR Decision Aids[tiab] OR Decision Aid[tiab])) AND ((((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt])
Embase
1- 'cincinnati prehospital stroke severity scale'/exp OR 'cincinnati prehospital stroke severity scale' OR 'los angeles motor scale'/exp OR 'los angeles motor scale' OR 'national institutes of health stroke scale'/exp OR 'national institutes of health stroke scale' OR 'national institutes of health stroke scale score'/exp OR 'national institutes of health stroke scale score' OR 'rapid arterial occlusion evaluation scale'/exp OR 'rapid arterial occlusion evaluation scale' OR 'cpsss':ab,ti OR 'lams':ab,ti OR 'nihss':ab,ti OR 'race':ab,ti OR 'stroke vision, aphasia, neglect':ab,ti OR 'vision, aphasia, and neglect':ab,ti OR 'melbourne ambulance stroke screen':ab,ti OR 'mass':ab,ti OR 'medic prehospital assessment for code stroke':ab,ti OR 'med pacs':ab,ti OR 'mpacs':ab,ti OR 'medpacs':ab,ti OR 'ontario prehospital stroke screening tool':ab,ti OR 'opss':ab,ti OR 'recognition of stroke in the emergency room':ab,ti OR 'rosier':ab,ti OR 'face arm speech test':ab,ti OR 'face arm speech time test':ab,ti OR 'decision rule':ab,ti OR 'decision aids':ab,ti OR 'decision aid':ab,ti 2- 'cerebrovascular accident'/exp OR 'cerebrovascular accident' OR 'stroke patient'/exp OR 'stroke patient' OR 'brain infarction'/exp OR 'brain infarction' OR 'brain stem infarction'/exp OR 'brain stem infarction' OR 'cerebral artery disease'/exp OR 'cerebral artery disease' OR 'hypoxic ischemic encephalopathy'/exp OR 'hypoxic ischemic encephalopathy' OR 'brain ischemia'/exp OR 'brain ischemia' OR 'peripheral occlusive artery disease'/exp OR 'peripheral occlusive artery disease' OR 'Stroke' 3- 'systematic review'/de OR 'meta analysis'/exp OR 'meta analysis' OR 'meta analysis (topic)'/exp OR 'meta analysis (topic)' OR 'systematic review'/exp OR 'systematic review' OR 'systematic review (topic)'/exp OR 'systematic review (topic)' 4- #1 AND #2 AND #3

Appendix 1 Full search strategy for all databases

Scopus
(((TITLE-ABS-KEY ("Stroke") OR TITLE-ABS-KEY ("Brain Infarction") OR TITLE-ABS-KEY ("Brain Stem Infarctions") OR TITLE-ABS-KEY ("Infarction, Anterior Cerebral Artery") OR TITLE-ABS-KEY ("Cerebral Infarction") OR TITLE-ABS-KEY ("Hypoxia-Ischemia, Brain") OR TITLE-ABS-KEY ("Brain Ischemia") OR TITLE-ABS-KEY ("Arterial Occlusive Diseases") OR TITLE-ABS-KEY ("Stroke") OR TITLE-ABS-KEY ("Brain Infarction") OR TITLE-ABS-KEY ("Brain Stem Infarctions") OR TITLE-ABS-KEY ("Cerebral Infarction") OR TITLE-ABS-KEY ("Brain Ischemia") OR TITLE-ABS-KEY ("Cerebrovascular Accident") OR TITLE-ABS-KEY ("Brain Vascular Accident") OR TITLE-ABS-KEY ("Cerebrovascular Stroke") OR TITLE-ABS-KEY ("Arterial Occlusive Disease") OR TITLE-ABS-KEY ("Arterial Obstructive Diseases") OR TITLE-ABS-KEY ("Arterial Obstructive Disease"))) AND ((TITLE-ABS-KEY ("Cincinnati Prehospital Stroke Severity Scale") OR TITLE-ABS-KEY ("CPSSS") OR TITLE-ABS-KEY ("Los Angeles Motor Scale") OR TITLE-ABS-KEY ("LAMS") OR TITLE-ABS-KEY ("National Institutes of Health Stroke Scale") OR TITLE-ABS-KEY ("NIHSS") OR TITLE-ABS-KEY ("Rapid Arterial Occlusion Evaluation") OR TITLE-ABS-KEY ("RACE") OR TITLE-ABS-KEY ("Stroke Vision, Aphasia, Neglect") OR TITLE-ABS-KEY ("vision, aphasia, and neglect") OR TITLE-ABS-KEY ("Melbourne Ambulance Stroke Screen") OR TITLE-ABS-KEY ("MASS") OR TITLE-ABS-KEY ("Medic Prehospital Assessment for Code Stroke") OR TITLE-ABS-KEY ("Med PACS") OR TITLE-ABS-KEY ("MPACS") OR TITLE-ABS-KEY ("MedPACS") OR TITLE-ABS-KEY ("Ontario Prehospital Stroke Screening Tool") OR TITLE-ABS-KEY ("OPSS") OR TITLE-ABS-KEY ("Recognition of Stroke in the Emergency Room") OR TITLE-ABS-KEY ("ROSIER") OR TITLE-ABS-KEY ("Face Arm Speech Test ") OR TITLE-ABS-KEY ("Face Arm Speech Time test") OR TITLE-ABS-KEY ("decision rule") OR TITLE-ABS-KEY ("Decision Aids") OR TITLE-ABS-KEY ("Decision Aid")))) AND (TITLE-ABS-KEY ("systematic review" OR "meta-analysis" OR "metaanalysis" OR "meta analysis"))
Web of Science
1- TS= ("Stroke" OR "Brain Infarction" OR "Brain Stem Infarctions" OR "Infarction, Anterior Cerebral Artery" OR "Cerebral Infarction" OR "Hypoxia-Ischemia, Brain" OR "Brain Ischemia" OR "Arterial Occlusive Diseases" OR "Stroke" OR "Brain Infarction" OR "Brain Stem Infarctions" OR "Cerebral Infarction" OR "Brain Ischemia" OR "Cerebrovascular Accident" OR "Brain Vascular Accident" OR "Cerebrovascular Stroke" OR "Arterial Occlusive Disease" OR "Arterial Obstructive Diseases" OR "Arterial Obstructive Disease") 2- TS=("Cincinnati Prehospital Stroke Severity Scale" OR "CPSSS" OR "Los Angeles Motor Scale" OR "LAMS" OR "National Institutes of Health Stroke Scale" OR "NIHSS" OR "Rapid Arterial Occlusion Evaluation" OR "RACE" OR "Stroke Vision, Aphasia, Neglect" OR "vision, aphasia, and neglect" OR "Melbourne Ambulance Stroke Screen" OR "MASS" OR "Medic Prehospital Assessment for Code Stroke" OR "Med PACS" OR "MPACS" OR "MedPACS" OR "Ontario Prehospital Stroke Screening Tool" OR "OPSS" OR "Recognition of Stroke in the Emergency Room" OR "ROSIER" OR "Face Arm Speech Test " OR "Face Arm Speech Time test" OR "decision rule" OR "Decision Aids" OR "Decision Aid") 3- TS=("systematic review" OR "meta-analysis" OR "metaanalysis" OR "meta analysis") 4- #1 AND #2 AND #3