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The Evaluation of Risk Assessment Tools in Patients with Atrial Fibrillation to Prevent Stroke

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ABSTRACT:

THE EVALUATION OF RISK ASSESSMENT TOOLS TO PREVENT STROKE BY AF

BACKGROUND: Many clinical risk assessment tools are used to assess the risk of stroke in patients with atrial fibrillation (AF). Using a clinical risk assessment tool with low efficacy leads to avoidable healthcare costs. Several studies have investigated the efficacy of such tools. To date, there is still no review in which most commonly used tools are evaluated systematically for the broadest scope of patients. To ensure a high standard of clinical care to all patients, the best clinical risk assessment tool should be determined. This review aims to contribute to this determination and thus contribute to new guidelines.
OBJECTIVE: The goal of the study was to choose the most efficacious risk assessment tool of those most commonly used in clinical practice: Framingham, SPAF, CHADS2, CHA2DS2-VASc and R2CHADS2 for risk evaluation of stroke in people with AF.
METHODS: Pubmed was searched with the aim to find articles reporting on quality analysis of clinical risk assessment tools. Relevant articles were given critical appraisal . With meta-analysis c-statistics were pooled for each tool. The weighted means were subsequently subjected to t-tests, in which two random tools were compared, to obtain p-values. The p-values were then evaluated on level of significance.
RESULTS: received critical appraisal. Results from 8 articles were included in the meta-analysis. The analysis resulted in pooled c-statistics of 0,665 for CHADS2, 0,652 for CHA2DS2-VASc, 0,659 for SPAF and 0,618 for Framingham. The lowest p-value was 0.22, when comparing Framingham with CHA2DS2-VASc, and the highest was 0.95, when comparing CHADS2 with SPAF.
CONCLUSION: From the resulting p-values we cannot conclude a significant difference between the efficacy of the different clinical risk assessment tools.

WHAT IS KNOWN: Several clinical risk assessment tools are in use to assess the various risk factors for stroke in patients with AF. By means of classification preventive measures can be implemented when a certain risk of stroke is present. Several studies have evaluated the efficacy of clinical risk assessment tools.

WHAT IS NEW: This review compares the most commonly used assessment tools that predict the risk of stroke for the broadest scope of patients with AF. After pooling data from all identified articles, no significant difference was found. This review has thus not clarified which

KEYWORDS: Atrial Fibrillation, Stroke Risk, Classification Systems tool has the largest predictive value.

Introduction

Patients with atrial fibrillation (AF) have a high risk of developing an ischemic cardiovascular accident: stroke. Approximately 35 percent of patients with AF will develop stroke (1). AF is a condition in which the atria contract fast and incoherently. These contractions may result in arterial embolisms which in turn can block the cerebral arteries (2,3). Several risk factors can contribute to classify, and thereby assess, the risk for stroke in patients with AF. By implementing this clinical risk assessment, preventive measures such as administering anticoagulants, can be taken in patients with a given risk for stroke. In patients with a low risk for stroke, preventive administration of anticoagulants is unfavourable and therefore undesired. The risk of complications turns the balance over the preventive effect in these low risk patients. Adequate classification and subsequent risk assessment is therefore imperative (4).

Several clinical risk assessment tools are in use. The most commonly used tools are: Framingham, Stroke Prevention in Atrial Fibrilation (SPAF), CHADS2 [cardiac failure, hypertension, age >74, diabetes, stroke/TIA/thromboembolism (double)], CHA2DS2-VASc [cardic failure, hypertension, age >74 (double), diabetes, stroke/TIA/thromboembolism (double), vascular disease, age 65-74, sex-category (female)] en R2CHAD2 [Renal failure (double), cardiac failure, hypertension, age >74, diabetes, stroke/TIA/thromboembolism (double)] (table 1). CHA2DS2-VASc and R2CHAD2 are the successors of CHADS2, and are designed to assess patients more adequately for their risk for stroke. All clinical assessment tools are easy to use and inexpensive, according to the authors of this review. However, using a clinical risk assessment tool with low efficacy leads to avoidable healthcare costs. These avoidable costs emerge from both patients who develop adverse effects of preventive coagulants, while they should not be treated according to their genuine risk, as well as patients who will get a stroke and are not treated with preventive coagulants, while they should be according to their genuine risk.

Several studies evaluated the efficacy of each of the clinical risk assessment tools mentioned above, however no review is known in which these most commonly used systems are compared for the broadest scope of patients. To contribute to a high standard of clinical care for patients with AF, the most efficacious clinical assessment tool

should be chosen. This review aims to contribute to this search and thus contribute to new guidelines.

Methods

Pubmed was searched with a predetermined search and selection strategy. First, relevant synonyms were formulated for the determinant (clinical risk assessment tools), the domain (patients with AF) and the outcome (stroke). The synonyms were combined in the search strategy (table 2). Secondly, the 490 studies found were screened on title and abstract in accordance with our inclusion criteria. Studies were included when the study population consisted of AF patients and patient were not a member of a specific subpopulation, when c-statistics and one of the clinical risk assessment tools were mentioned. The study had to be focussed on the evaluation of the clinical risk assessment tools. After this selection, 15 relevant articles were included. Thirdly, the full text of these articles were screened. Three articles were subsequently excluded based on the following exclusion criteria: review, no full text or English version available (figure 1).

After this procedure, 12 articles remained which were evaluated individually by two researchers. The articles were evaluated for quality with the aid of a checklist designed by the researchers. This checklist evaluated relevance and validity of the patient selection, the time interval between risk assessment and the diagnosis of stroke, and validity of both the methods used and the results. The complete checklist is available online (5). The checklist was based on QUADAS-2, Offringa et al. (18) and information obtained from a senior investigator (Prof. Rovers, Radboudumc). Differences resulting from this evaluation were discussed together with a third researcher. The result of the critical appraisal is stated in a risk of bias summary. This summary shows in which topics the included studies systematically deviated. In the summary of findings table, the scale of the study population, the c-statistics with according 95% CI, and quality score are stated for each study..

Meta-analysis of the c-statistics was performed with StatsDirect and discussed with a statistician. Only the eight studies which provided 95% CI were included in the meta-analysis. Analysis consists of pooling the c-statistics of each individual risk assessment tool. When pooling the c-statistic data, it was assumed c-statistics were normally distributed. Studies were weighed based on the standard error of the mean, calculated using the 95% CI of the provided c-statistic. A random effects model was used to compare the different risk assessment scores. This model takes both difference between individuals within a study and differences between studies into account. The 95% CI resulting from different studies belonging to the same classification system have minimal overlap, which points to heterogeneity between different studies. Therefore, a random effects-model is more suitable than a fixed effects-model.

To determine whether or not a significant difference was present in the predicted values between two random clinical risk assessment tools, an independent sample t-test was performed. Executing a test in which all of the systems were compared at once would deliver a hard-to-interpret outcome. On top of that, this test would take much longer to execute properly and it would lead to the same outcome and conclusions as the simple-to-use t-tests. Therefore, this test was not performed.

Results

The risk of bias summary summarises the results from the critical appraisal and shows different levels of validity amongst included articles (figure 2). In each study the population was well documented. Selection of patients however, was of more variable quality. In seven studies bias could have resulted from this selection. In one study this could not be determined. In five studies results were gathered in one medical centre or results came from a single country only. Studies that were included in the analysis showed great differences in time interval between clinical risk assessment and stroke as well. Little or no information was available about patients that were lost to follow-up in eleven studies. Clinical risk assessment was impartial and often clear definitions for certain risk factors were stated. Stroke itself is a hard and dichotomous outcome. A clear definition for stroke was stated by the investigators before the studies were performed. In most studies MRI images were evaluated by blinded experts.

Outcomes of each study are shown as a c-statistic. Included studies had no results for the clinical risk assessment tool R2CHADS2. Four out of twelve studies did not report 95% CI's apart from the c-statistics. These studies were not included in the meta-analysis. This resulted in only two studies for SPAF and Framingham included in the meta-analysis. For CHADS2 there were seven included studies and for CHA2DS2-VASc six. C-statistics are close to 0,65 and most 95% CI's do not contain 0,50 (table 3). Different studies give comparable results for the respective clinical assessment tool they focussed on. Only the study of Gage BF et al. show outliners.
In the meta-analysis the following pooled c-statistics were found per clinical risk assessment tool. For CHADS2 a pooled c-statistic of 0,66 (95% CI; 0,59-0,74) for Framingham a pooled c-statistic of 0,62 (95% CI; 0,59-0,65), for CHA2DS2-VASc a pooled c-statistic of 0,65 (95% CI; 0,61-0,70) and SPAF a pooled c-statistic of 0,66 (95% CI; 0,48-0,83) (figure 3).
Comparing the c-statistics stated above the following p-values were calculated. P-value was lowest when comparing Framingham and CHA2DS2-VASc; 0.22. Comparing Framingham and CHA2DS2-VASc; 0.22, comparing Framingham and CHADS2; 0.26, comparing Framingham and SPAF; 0.65, comparing CHA2DS2-VASc and CHADS2; 0.77, comparing CHA2DS2-VASc and SPAF; 0.94 and comparing CHADS2 and SPAF it was 0.95.

Discussion

This review aims to contribute to the guidelines of preventative measures taken to reduce the incidence of stroke. These measures are aimed at the entire population of patients with AF. To accomplish this aim, the most efficacious clinical assessment tool should be pointed out.

By excluding subgroups within populations when selecting studies, a large measure of heterogeneity was prevented. The resulting selection does, however, include populations from different continents. Since a conclusion applicable on the broadest scope of patients was desired, no limitation was made regarding this distribution. Another risk for heterogeneity are different time intervals between classification of clinical risk assessments and confirmation of stroke diagnosis. In three studies included in the meta-analysis, the timespan of this time interval was scored unsatisfactory on the checklist used for critical appraisal. Possibly this led to confounding in the meta-analysis.

Further heterogeneity between studies was present because some studies investigated only patients treated with anticoagulants. Other studies only looked at patients without anticoagulants and there were some studies which investigated both patients with and without anticoagulants. Although clinical assessment tools are designed for patients not currently receiving anticoagulants, it was difficult to include studies with this population. These studies are not frequently executed because of the ethical objections since patients assessed with a high risk should not have been withheld preventive, anticoagulant medication.

Coppens M. et al. have selected patients with a score of 1 for CHADS2. This studies gives a lower c-statistic for CHA2DS2-VASc than other studies. Although this study focuses on a subpopulation, it wasincluded in the meta-analysis, which may have led to confounding. Because of insufficient homogeneity between studies, a meta-analysis with a random effects model was performed(see Methods section). Only studies that mentioned a 95% CI were included in the meta-analysis.

Taken into account that the aim of the study was to give an overview of the clinically most frequently used risk assessment tools, we included all of these tools in our search strategy. After careful selection of articles we concluded no studies were available evaluating the quality of R2CHADS2. The most probable explanation for this would be that R2CHADS2 is a relatively new clinical assessment tool and consequently no studies have yet been performed that met our inclusion criteria.

The outcome used to perform the meta-analysis was the c-statistic. Studies without c-statistic were excluded for this purpose (see Methods section). Since different guidelines are used in various parts of the world, anticoagulant therapy is not started according to the same cut off points. In our review, we should have calculated sensitivity and specificity for every score. Not every study reported sensitivity and specificity for every score. Therefore we chose c-statistics as outcome measure. This measure can be discriminative for each cut off value. Studies reporting on the quality of the clinical assessment tools, but did not report a c-statistic are, however, excluded by this choice.

In our study a risk of bias arises because studies were included that include patients either with or without anticoagulant therapy or included both groups. Studies with a study population receiving anticoagulant therapy will have relatively fewer strokes, given the therapeutic effect of this intervention. If this reduction of strokes occurs predominantly in patients assessed as being high risk patients, this will result in an underestimation of the actual predictive value of the clinical assessment tool used. Differences in anticoagulant use thus lead to confounding of the results that are depicted in the summary of findings table. This is an imperfection of our study.

In our review only studies published on Pubmed were included. Because of practical considerations we had to choose a more specific domain, a more specific outcome, fewer determinants or the use of Pubmed alone. Given the aim of this review we could not suffice exclude some clinical assessment tools or use a more specific domain or outcome. This would compromise the external validity and relevance of this review.

Baruch L. et al. and Lip GY. Frison L. et al. appeared to have used the same dataset (SPORTIF 3). The same patients with atrial fibrillation were included in these studies. The outcomes for the same tools are, however, different. Baruch L. et al. state for CHADS2 a c-statistic of 0.665 and for Framingham 0.64. Lip GY. et al. state a c-statistic for CHADS2 of 0.637 and for Framingham 0.621 respectively. These differences are most likely to be explained due to differences in the length of follow-up. The study of Baruch L. et al. is not included in the meta-analysis because no 95% CI were reported.

Since stroke is a commonly occurring event in patients with AF and no test with a clearly proven superior predictive value, the different clinical assessment tools are all being used in current clinical practice. The reasonably low predictive qualities of the tools are compensated by starting preventive interventions with anticoagulants when only two points are scored on the respective scales (4). The cut-off value is thus being kept low. Therefore a high sensitivity can be calculated. The specificity is reasonably low in that case, because many patients that would never have developed a stroke are treated. These patients are, however, at risk for adverse effects of the preventive interventions.

Conclusion

It could not be clarified which clinical risk assessment tool has the largest predictive value and is, therefore, the most efficacious. No significant difference was found among the individual tools regarding the predictive value for stroke in patients with AF. All tools have a mediocre score. C-statistics were approximately 0,65 for all studies included, indicating the clinical assessment tools have a somewhat superior predictive value over no assessment at all.

The 95% CI show some overlap (figure 3). The Framingham assessment tool appears to deviate most from CHA2DS2-VASc with a p-value of 0.22. Framingham can, based on this information alone, not be advised against since the evidence for such a statement did not show a significant p-value.

Furthermore, CHA2DS2-VASc is a successor of the CHADS2, with the intention to assess patients better for their risk of developing a stroke. However, this does not result from the performed t-test given the p-value of 0,77.

For Framingham and SPAF more relevant and well documented research should be performed. In the meta-analysis of this review only two studies concerning the Framingham and SPAF tools could be included. More studies addressing these clinical assessment tools could possibly prove the inferiority of this tools over the others discussed here.

To decide on the superiority of one tool over the other, more research needs to be performed. Since R2CHADS2 could not be evaluated, for reasons discussed above, no statement concerning all, most frequently used clinical assessment tool can be made. To draw a conclusion on the quality of R2CAHDS2 compared to that of those clinical assessment tools discussed in this review more comparative research should be done into R2CHADS2. The authors of this review stress the need for this research since only then a valid choice for either of these assessment tools can be made.

Given the low c-statistics values for every risk assessment tool, we encourage new investigations to be performed aiming to develop a new, superior, clinical risk assessment tool.

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Critical appraisal: composed checklist

Patients:
Has the patients population mentioned clear? (2)
Could the selection of patients create bias? (1)
Do the patients deviate from our domain? (1,2)

Time interval:
Could the time interval between classification of the risk and determine an eventual stroke created bias? i.e. was the interval long enough? (1,2)

Method:
Could the type of research created bias? (3)
Is the classification objective and blinded? (2)

Results:
Are the results imprecise? (2)
Has selective loss of results occured? (3)

(1) QUADAS-2
(2) Offringa et al.
(3) Lecture Critical Appraisal Prof. Maroeska Rovers

In articles about diagnostic devises/checklists, often sensitivity and specificity is used. However, this is only possible when the outcome of the test is binary (e.g. sick v.s. not sick). For diagnostic assessments with a continuous outcome an equivalent of the sensitivity and specificity is the c-statistic. In case of the c-statistic, for every possible cut-off value in the continuous outcome, the sensitivity and specificity is calculated. These values are then stated into a diagram where sensitivity is plotted against 1-specificity. When a line is drawn between the points, the area under this curve can be calculated. This is named the c-statistic which has a value between 0,5-1. This means, 0,5: there is no predictive value of the diagnostic device used(e.g. tossing a coin). 1: the diagnostic device predicts the health status perfectly.

Tables

Table 1: Risk factors by each risk assessment tools

Risk factors	risk assessment tools				
	$CHADS_2$	CHA_2DS_2-VASc	R_2CHADS_2	Framingham	SPAF
Hypertension	✓	✓	✓	✓ x0-4 a)	✓
Age between 65 and 75	×	✓	×	✓ x0-10 b)	×
Age above 74	✓	✓ x2	✓	✓ x0-10 b)	✓ c)
Female gender	×	✓	×	✓ x6	✓ c)
Clinical history of heart failure	✓	✓	✓	×	✓
Clinical history of diabetes	✓	✓	✓	✓ x4	×
Clinical history of stroke/TIA/ thromboembolism	✓ x2	✓ x2	✓ x2	✓ x6	✓
Clinical history of vascular disease	×	✓	×	×	×
Clinical history of renal failure	×	×	✓ x2	×	×

a) Framingham score 0 (<120); 1 (120-139); 2 (140-159); 3 (160-179); 4 (>180) for systolic blood pressure (mmHg) b) Framingham score 0 (<60); 1 (60-62); 2 (63-66); 3 (67-71); 4 (72-74); 5 (75-77); 6 (78-81); 7 (82-85); 8 (86-90); 9 (91-93); 10 (>93) for ages (years) c) SPAF combines age >74 and female gender as one risk factor.

Table 2: Brachial artery characteristics and arterial stiffness parameters

Pubmed hits	490 (date: 03/17/2014)
Determinant	risk classification system[Title/Abstract] OR chads2[Title/Abstract] OR SPAF[Title/Abstract] OR cha2ds2 vasc[Title/Abstract] OR r2chads2[Title/Abstract] OR risk classification[Title/Abstract] OR Framingham[Title/Abstract]
Domain	atrial fibrillation[Title/Abstract] OR "Atrial Fibrillation"[Mesh] OR af[Title/Abstract] OR a-fib[Title/Abstract]
Outcome	"Stroke"[Mesh] OR stroke[Title/Abstract) OR cerebrovascular accident[Title/Abstract] OR cva[Title/Abstract] OR cerebrovascular insult[Title/Abstract] OR cvi[Title/Abstract] OR brain attack[Title/Abstract]
Total	((risk classification system[Title/Abstract] OR chads2[Title/Abstract] OR SPAF[Title/Abstract] OR cha2ds2 vasc[Title/Abstract] OR r2chads2[Title/Abstract] OR risk classification[Title/Abstract] OR Framingham[Title/Abstract]) AND ("Stroke"[Mesh] OR stroke[Title/Abstract) OR cerebrovascular accident[Title/Abstract] OR cva[Title/Abstract] OR cerebrovascular insult[Title/Abstract] OR cvi[Title/Abstract] OR brain attack[Title/Abstract]) AND (atrial fibrillation[Title/Abstract] OR "Atrial Fibrillation"[Mesh] OR af[Title/Abstract] OR a-fib[Title/Abstract]))

Table 3: summary of findings-table

Study	*Patients*	*risk assessment tools*	*c-statistic (95%-CI)*	*Quality (GRADE)*	*Anticoagulants*
[6] Lip GY, Frison L	N = 7329	$CHADS_2$ Framingham CHA_2DS_2-VASc	0,637 (0.607-0.674) 0.621 (0.589-0.658) 0.647 (0.613-0.678)	++	Yes
[7] Lip GY, Nieuwlaat R	N = 1084 from the Euro Heart Survey	$CHADS_2$ Framingham SPAF	0.549 (0.435-0.662) 0.586 (0.477-0.695) 0.561 (0.450-0.672)	++	Yes
[8] Poli D, Lip GY	N = 662 'elderly' from Italy	$CHADS_2$ CHA_2DS_2-VASc	0.524 (0.435-0.614) 0.683 (0.606-0.759)	++	Yes
[9] Wang TJ, Massaro JM	N = 868 from the Framingham cohort	$CHADS_2$ SPAF Framingham	0.62 0.62 0.66	+	No
[10] Gage BF, Waterman AD	N = 1733 from seven states of the USA (California, Connecticut, Louisiana, Maine, Missouri, New Hampshire and Vermont)	SPAF $CHADS_2$	0,74 (0,71-0,76) 0,82 (0,80-0,84)	+	No
[11] Guo Y, Apostolakis S	N = 1034 chinese people from the PLA general hospital, Beijing	$CHADS_2$ CHA_2DS_2-VASc	0,72 (0,64-0,81) 0,58 (0,50-0,67)	-	No
[12] Li SY, Zhao XQ	N = 1297 from the Chinese National Prospective Registry	$CHADS_2$ CHA_2DS_2-VASc	0,551 0,532	-	No
[13] Zuo ML, Liu S	N = 528 from the Queen Mary Hospital, Hong Kong	$CHADS_2$ CHA_2DS_2-VASc	0,69 (0,65-0,73) 0,69 (0,65-0,73)	+	Yes
[14] Baruch, L, Gage BF	N = 7329	Framingham $CHADS_2$ SPAF	0.64 0.65 0.61	+	Yes
[15] Cha, MJ, Lee HS	N = 1733 From a Korean cohort	$CHADS_2$ CHA_2DS_2-VASc	0.668 (0.641-0.696) 0.710 (0.683-0.737)	--	No
[16] Coppens M, Eikelboom JW	N = 4670	CHA_2DS_2-VASc	0.587 (0.550–0.624)	+	Yes
[17] Fang, MC, Go AS	N = 13559	SPAF $CHADS_2$ Framingham	0.60 0.58 0.62	++	Yes

Figures

Figure 1: process of searching and selection studies for inclusion

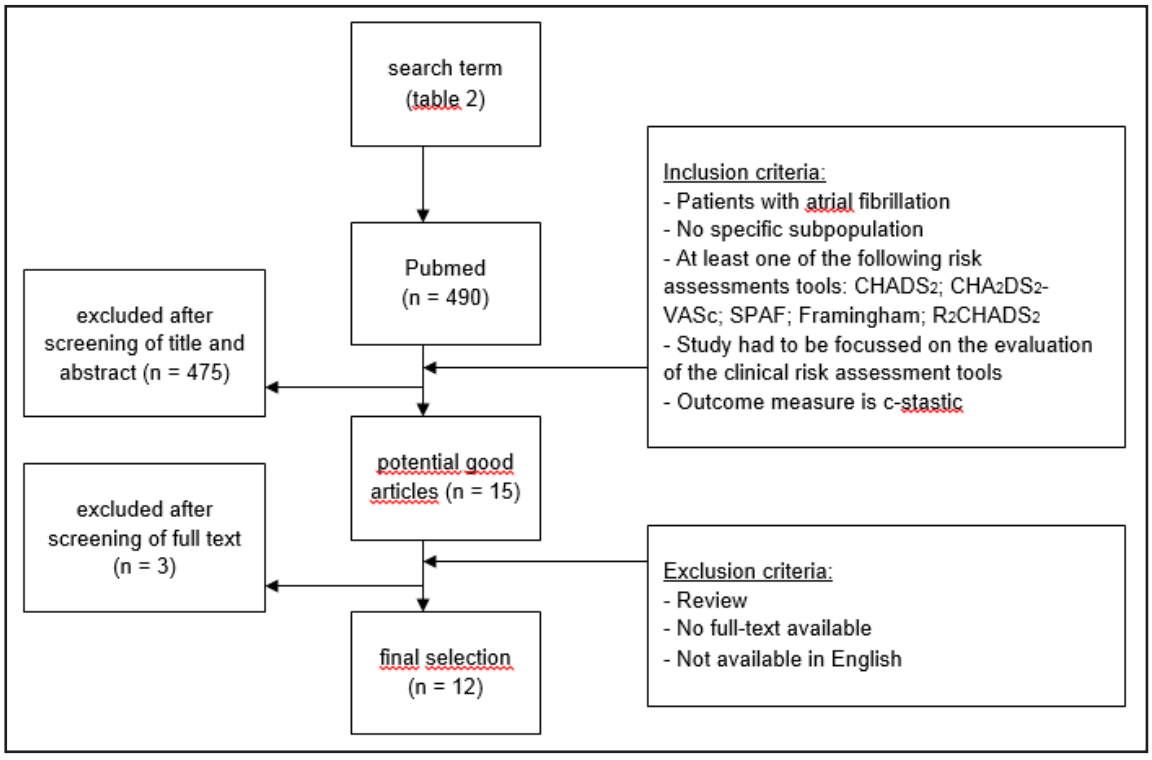

Figure 2: Risk of bias summary

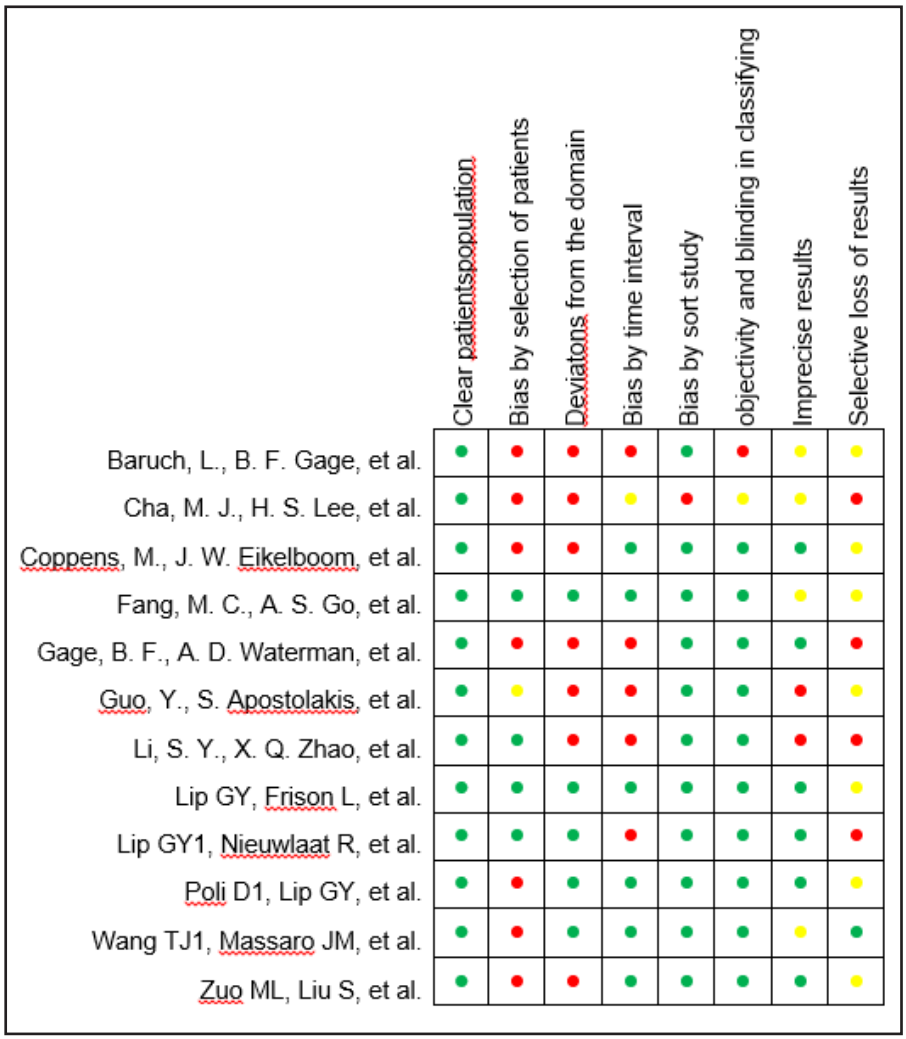

Figure 3: results of the meta-analysis