

Use of microvascular retinal changes on retinal photographs to predict stroke recurrence

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Abstract

Background/Objectives: Changes in retinal microvasculature has been associated with the stroke severity and incident stroke risk. However, its role in predicting stroke recurrence, which results in higher mortality and poorer functional recovery, remains uncertain. This study aims to determine the association of retinal microvascular changes with recurrent ischemic stroke.

Subjects/Methods: We conducted a systematic search of the PubMed and Embase databases up to August 2024. Prospective studies that investigated the use of retinal biomarkers as predictors of recurrent stroke risk were included. The odds ratio (OR), hazard ratio (HR) and mean difference (MD) of various retinal biomarkers were then pooled using a random-effect model.

Results: 7 studies evaluating retinal microvasculature in 2938 stroke patients with or without recurrence were included. Our analysis revealed higher mean arterial branching angle (OR = 0.80; 95% CI: 0.71 - 0.90; $p = 0.0002$) and retinopathy consisting of only retinal haemorrhages (OR = 0.59, 95% CI: 0.41 - 0.87, $p = 0.0069$) to be significantly associated with lower stroke recurrence. Additionally, mean venous branching angle was found to be significantly lower in patients with stroke recurrence compared to stroke patients with no recurrence (MD = -0.44; 95% CI: -0.85 - -0.02; $p = 0.0395$).

Conclusions: Our study identifies features of retinal microvasculopathy that may be able to identify patients at a higher risk of recurrent stroke. Given the accessibility of retinal imaging, our findings reinforce retinal microvasculature as a promising biomarker for risk stratification and monitoring of stroke recurrence.

Introduction

Recurrent strokes constitute a significant proportion of all incident strokes, resulting in higher morbidity and mortality [1]. Despite improvements in stroke recurrence rates, progress has plateaued in recent years according to global studies. The rate of recurrence has remained largely unchanged over the last 20 years despite advances in stroke prevention [2]. Currently, the prediction of stroke recurrence is based on well-validated risk factors such as hypertension, atrial fibrillation and diabetes mellitus. However, these risk factors only explain a portion of recurrent strokes and may sometimes have a heterogenous effect on risk [3, 4]. While commonly used clinical risk scores offer valuable information on predicting the risk of recurrent stroke, their predictive performance has limited generalizability across different populations and timeframes [5]. This suggests that supplementing these scores and clinical risk factors with additional biomarkers could enhance long-term risk stratification [6].

Retinal imaging allows for a non-invasive evaluation of the retinal microvasculature. Given that the retinal and intracranial circulations have a common origin and drainage and share similar physiological properties, retinal imaging can potentially serve as a window into cerebrovascular health [7, 8]. In fact, research has suggested that retinal imaging can be a powerful tool in predicting incident stroke [9]. There have been promising studies for the use of retinal microvascular changes in predicting stroke in

healthy individuals, even after adjusting for known metabolic risk factors such as blood pressure and cholesterol [10–12].

Recently, there has been a growing interest in the association of retinal microvascular changes with recurrent ischemic stroke. This systematic review and meta-analysis aim to appraise and synthesise the existing evidence of each of these microvascular changes, with the goal of informing future risk stratification and prevention strategies.

Methodology

Protocol Registration

This review was prospectively registered to PROSPERO. The registration number for this review is CRD42025641778.

Literature Search Strategy

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [13]. Details of the search strategy can be found in Supplementary material 1. As the study was conducted through screening of previously published articles, ethical approval was not needed. Two independent authors comprehensively searched all published studies in electronic databases, including PubMed and Embase, from inception through 19 August 2024. The eligible studies were limited to those in the English language and conducted in human subjects.

Inclusion and Exclusion Criteria

Included studies satisfied the following criteria: (1) The article discussed the use of retinal biomarkers as predictors of recurrent stroke risk. (2) The study was prospective or used data from biobanks involving prospective recruitment. (3) The study was conducted using human subjects. (4) The article was written in English.

We excluded animal studies, non-original articles, case reports, conference abstracts, duplicates, preprint studies from our review. Articles for which the full text could not be extracted were also excluded.

Risk of bias and Quality Assessment

The risk of bias was assessed using the Joanna Briggs Institute (JBI) checklist [14], which can be found in Supplementary Table 1.

Statistical Analysis

We performed all quantitative analyses in R (version 4.1.2) using the meta package. Statistical significance was determined by a two-sided p-value of <0.05. Using random-effects models, we performed aggregate data meta-analysis of the study-reported mean difference and OR, retinal

biomarkers in participants with stroke recurrence and compared that against that in participants with no stroke recurrence. Heterogeneity was evaluated with I² statistics, where I² values below 30% were considered low, 30–60% moderate, and above 60% substantial. Subgroup and sensitivity analyses by retinal biomarkers were conducted. Publication bias was checked visually through funnel plot asymmetry and quantitatively using the Egger's test, with a p-value < 0.10 considered indicative of significant bias.

Data Collection

Data extracted from each study included: study size, population characteristics, comorbidities, study type, methodology and retinal biomarkers assessed. All included studies were reviewed in full by 2 authors before documentation of findings.

Synthesis of Results

Seven studies investigated the association between retinal biomarkers and stroke recurrence. Of the included studies, three investigated retinopathy, four investigated central retinal arteriolar equivalent (CRAE) and central retinal venule equivalent (CRVE), two investigated the bifurcation coefficient of arterioles (BCA) and bifurcation coefficient of venules (BCV), four investigated mean arterial branching angle (MABA) and three investigated mean venous branching angle (MVBA).

Results

Study Design

The search strategy screened 687 possibly relevant studies after deduplication of titles. 10 records sought for retrieval after exclusion of reports. Three reports were conference abstracts and thus not retrieved. In all, seven reports were included in this analysis; four were prospective cohort studies, with the remaining three being a prospective observational cross-sectional study, retrospective cohort study and retrospective case control study. Across all the studies, 2938 participants were involved, of which 506 experienced a recurrent stroke episode, whereas 2432 participants did not. Detailed characteristics of all seven studies can be found in Supplementary table 2.

Retinal biomarker	Number of studies	Number of participants without recurrence	Number of participants with recurrence	Effect size (95% CI)	P value	I ² (%)
Retinopathy (any lesion)	3	1819	228	HR 1.26 (0.93 - 1.71)	0.14	0
Retinopathy (only retinal haemorrhages)	2	337	94	OR 0.59 (0.41 - 0.87)	0.0069	0
CRAE	2	497	149	MD 0.18 (-0.31 - 0.68)	0.4705	80.6
CRVE	2	497	149	MD 0.10 (-0.28 - 0.48)	0.6036	64
BCA	2	497	149	MD 0.01 (-0.01 - 0.02)	0.2086	0
BCV	2	497	149	MD -0.01 (-0.02 to 0.00)	0.1476	0
MABA	3	923	219	OR 0.80 (0.71 - 0.90)	0.0002	0
MABA	2	497	149	MD -0.18 (-0.56 - 0.21)	0.3690	0
MVBA	2	591	125	OR 0.81 (0.61 - 1.06)	0.1267	19.7
MVBA	2	497	149	MD -0.44 (-0.85 - -0.02)	0.0395	0

Table 1: Retinal microvasculature biomarkers in patients with and without stroke recurrence. Random-effects model is applied when heterogeneity is high.

Abbreviations: BCA, bifurcation coefficient of arterioles; BCV, bifurcation coefficient of venules; CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent; MABA, mean arterial branch angle; MVBA, mean venous branch angle

Retinopathy

Individual measures of retinopathy such as haemorrhages and exudates were included and compared between stroke patients who had a recurrent episode and those who did not.

Three studies (1819 stroke patients) investigated the relationship between retinopathy and stroke recurrence. These studies similarly defined retinopathy as the presence of any one or more lesions such as microhemorrhages, microaneurysms and cotton-wool spots. Analysis of the data revealed that retinopathy was not significantly associated with an increased risk of recurrent stroke (HR = 1.26, 95% CI: 0.93 - 1.71, P = 0.14, Table 1). Two studies (944 stroke patients) defined retinopathy as the presence of retinal haemorrhages. Analysis of these studies found stroke patients with retinopathy were significantly less likely to have a recurrent stroke (OR = 0.59, 95% CI: 0.41 - 0.87, P = 0.0069, Table 1), compared to patients without retinopathy.

Retinal vessel calibre

A total of two studies (662 stroke patients) investigated retinal vessel calibre as central retinal arteriolar (CRAE) and central retinal venular equivalent (CRVE) and their results were separately analysed.

Pooled results from two studies found that CRAE was not significantly different between stroke patients with and without recurrent strokes (MD = 0.18, 95% CI: -0.31 - 0.68, P = 0.4705, Table 1). CRVE was also not significantly different between patients with and without recurrent stroke (MD = 0.10, 95% CI: -0.28 - 0.48, P = 0.6036, Table 1).

Bifurcation coefficient of vessels

Pooled mean difference from two studies showed that higher bifurcation coefficient of arterioles was not significantly associated with an increase in likelihood of recurrent stroke (MD = 0.01, 95% CI: -0.01 - 0.02, P = 0.2086, Table 1). Mean difference of bifurcation coefficient of venules was also not significantly associated with stroke recurrence (MD = -0.01; 95% CI: -0.02 - 0.00; P = 0.1476, Table 1).

Branching angle

Three studies reporting MABA were included in the analysis. Pooling of results found that a higher MABA was significantly associated with a lower risk of stroke recurrence (OR = 0.80; 95% CI: 0.71 - 0.90; p = 0.0002, Table 1). On the other hand, a lower mean difference of mean arterial branching angle was not shown to be significantly associated with stroke recurrence (MD = -0.18; 95% CI: -0.56 - 0.21; p = 0.3690, Table 1).

MVBA was not significantly associated with stroke recurrence (OR = 0.81; 95% CI: 0.61 - 1.06; p = 0.1267, Table 1). Compared to stroke patients with no recurrence, mean venous branching angle was found to be significantly lower in patients with stroke recurrence (MD = -0.44; 95% CI: -0.85 - -0.02; p = 0.0395, Table 1).

Other retinal biomarkers

Arteriovenous nicking (AVN) and focal arteriolar narrowing (FAN) have been shown to predict recurrent cerebrovascular events. De Silva et al. (n = 652) found that severe AVN (HR = 2.28, 95% CI: 1.20–4.33) and severe FAN (HR = 2.75, 95% CI: 1.14–6.63) were predictors of recurrent stroke episodes after adjustment. In particular, severe FAN also predicted composite vascular events (HR = 2.77, 95% CI: 1.31–5.86), which encompassed cerebrovascular events and coronary events. However, the finding for AVN was not seen in a study by Zhuo et al. 2023 (n = 612) (no recurrence: 0.30±0.08, recurrence: 0.30±0.07, p = 0.83), where no adjustment was made for risk factors (Supplementary Table 3).

Asymmetry index of arterioles has been investigated by Zhuo et al. with varying results. While their 2017 found that asymmetry index of arterioles could predict recurrent stroke events (OR = 2.035, 95% CI: 1.152 - 3.597, p = 0.014), they were not able to replicate this finding in their 2023 study (no recurrence and recurrence: 0.83±0.01; p = 0.97). On the other hand, the asymmetry index of venules has been consistently found to be predictive of stroke recurrence in both their 2017 study (OR = 3.696, 95% CI: 1.582-8.633, p = 0.003) and 2023 study (no recurrence: 0.77±0.02, recurrence: 0.76±0.2, p = 0.01).

Zhuo et al. 2017 had found a decrease in bifurcation angle of arterioles (OR = 0.810, 95% CI: 0.711-0.923, p = 0.004) and venules (OR = 0.847, 95% CI: 0.767-0.936, p = 0.001) is associated with stroke recurrence. However, Zhuo et al. 2023 did not adjust for clinical risk factors and found that there was no significant relationship between bifurcation angle of arterioles (p = 0.74) or venules (p = 0.28) and stroke recurrence.

Zhao et al. had found that wider mean arteriolar diameter (MAD>74.14µm, OR = 2.80, 95% CI: 1.24-6.30, p = 0.013) is related to an increase in stroke recurrence. Mean venous diameters of larger than 83.91µm was found to be related to an increase in stroke recurrence (OR = 2.41, 95%CI: 1.09-5.33, p = 0.031).

Mean arterial-venous ratio, mean venous tortuosity (MVT) and mean arterial tortuosity (MAT) and fractal dimensions (FD) was not found to be significantly associated with stroke recurrence in studies. A detailed summary on each of these biomarkers can be found in Supplementary Table 3.

Discussion

Our systematic review and meta-analysis assessed retinal biomarkers in association with stroke recurrence in 2954 stroke patients to determine their association. Pooled data showed that retinal biomarkers significantly associated with stroke recurrence were mean arterial branch angle, mean venous branch angle, and isolated retinal haemorrhages

In our analysis, retinopathy was separately defined as either a broad measure of retinal findings including microhemorrhages, microaneurysms, cotton-wool spots or arteriolar narrowing, or more specifically defined by retinal haemorrhages. Pooled hazard ratios for the presence of any retinopathy irrespective of subtype did not yield a significant association of retinopathy with stroke recurrence. This contrasts with

findings in patients who have not had stroke before, where retinopathy was shown to be a good predictor for incident stroke [10]. However, retinopathy, defined specifically by the presence of retinal haemorrhages, was found to be significantly associated with a decreased stroke recurrence risk. This discrepancy could suggest that individual parameters of retinopathy may have distinct associations with recurrent stroke, which would explain the wide confidence intervals and variability. Future studies should explore retinopathy features with greater granularity to obtain a more robust idea of their association with stroke recurrence. Retinal haemorrhages may also reflect varying degrees of damage that occur at different timepoints. They may be a result of microvascular damage from diabetes and hypertension before stroke episodes, increased permeability and leakage, or an angiogenic drive secondary to ischemia post-stroke. New vessels that form after ischemic episodes are often more fragile and thus prone to hemorrhage [15]. Longitudinal studies that characterise the extent of retinal haemorrhages and other retinopathy markers before and after stroke could help to determine their utility in predicting recurrence risk more precisely.

Interestingly, Hjelmgren et al. studied only patients with type 2 diabetes mellitus with previous strokes and found that the presence of diabetic retinopathy was not a strong predictor of stroke recurrence in these patients. In contrast, studies on stroke risk in diabetic patients with no previous strokes indicate that diabetic retinopathy is a predictor for incident stroke [16, 17]. This suggests that diabetic retinopathy is implicated in the first stroke episode but is not a significant biomarker for recurrent stroke. Thus, it is possible that diabetic retinopathy primarily reflects underlying microvascular damage from long standing suboptimally controlled diabetes, which may contribute to the initial stroke event but has limited prognostic value thereafter. Longitudinal studies are warranted to identify any potential confounders, such as intensified diabetic control following the index stroke episode that may contribute to decreased risk of stroke recurrence.

Apart from focal measurements such as CRAE and CRVE, retinal vessel metrics such as BCA, BCV, MABA and MVBA provide a further quantitative measure of retinal vascular health. Our analysis found that higher MABA is significantly associated with a lower risk of stroke recurrence, and that MVBA was significantly lower in patients with recurrent stroke. A wider angle of arterial bifurcation between parent and daughter vessels reduces the maximum wall shear stress (WSS), which in turn reduces hemodynamic stress on the vessel wall [18]. This may potentially decrease endothelial injury, thereby lowering the likelihood of recurrent cerebrovascular events. Similarly, a lower angle of bifurcation in veins would increase maximum WSS, increasing the stroke recurrence risk. Existing evidence showed that vessels that follow Murray's law for bifurcation ratios were found to have a protective effect from thrombus formation, indicating that changes in bifurcation ratio from the optimal value affect the likelihood of thrombosis [19]. However, despite the potential relevance of BCA and BCV to stroke occurrence, we did not find any association of BCA and BCV with risk of stroke recurrence. One possible explanation is that bifurcation ratios may be less sensitive to the post-stroke vascular changes that contribute to precipitating another stroke episode. While both bifurcation angle and bifurcation ratio can affect shear stress and flow dynamics, it is unclear which feature is more prominently altered post-stroke. Certain morphological changes in cerebral vasculature post-stroke such as increased vessel

branches was associated with reduced risk of stroke recurrence [20]. It is plausible that this association of branch angle, but not bifurcation coefficient, with the risk of stroke recurrence could reflect the specific post-stroke changes in the vessels. However, further research is required to ascertain this hypothesis. Overall, these findings suggest that branching angle metrics may better capture the microvascular changes in relation to stroke recurrence than bifurcation coefficients. Future studies should continue to explore the clinical relevance of bifurcation angle retinal metrics and validate its utility in identifying patients at risk of recurrent stroke.

In addition, raised MABA and MVBA have been shown to attenuate the association between clinical factors and the risk of stroke recurrence. In a study of 196 participants, Zhuo et al. 2017 found that increased MABA weakens the association between other clinical factors and retinal vessel biomarkers with the risk of stroke recurrence. Compared to patients who did not experience recurrent stroke, Zhuo et al. 2017 noted that the positive association between higher BMI with higher risk of stroke recurrence as well as the negative association between higher BCA and stroke recurrence was compromised by an increase in MABA. Similar to MABA, Zhuo et al. 2017 noted that increased MVBA affects the association between clinical factors and the risk of stroke recurrence. Increased MVBA attenuates the negative association between stroke recurrence and atrial fibrillation. These findings suggest the possibility that MABA and MVBA may play a mediating or modifying role in the relationship between established clinical risk factors and stroke recurrence. Whilst exact mechanisms underpinning this is unknown, this may support the hypothesis that higher MABA and MVBA reflect the adaptive changes of the retinal vasculature in response to the previous stroke. Such changes may alter how traditional risk factors relate to the likelihood of recurrence.

While MVBA was significantly lower in patients who experienced stroke recurrence compared to those who did not, no statistical significance was found when odds ratios were analysed (OR = 0.81; 95% CI: 0.61 - 1.06; $p = 0.1267$, Figure 10). The lack of statistical significance in the analysis of OR may be attributable to the small number of studies included, which potentially reduces the power required to detect a meaningful effect. This discrepancy highlights the need for more well-powered studies to clarify the role of MVBA in predicting stroke recurrence.

In the same vein, FD, another parameter of the retinal vascular trees, describes the density and complexity of the retinal vascular, and hence how effectively blood flows in the retina [21]. It is expected that in theory, patients with recurrent stroke are likely to experience a reduction in fractal dimensions. With destructive processes such as atherosclerosis and arteriosclerosis acting on the vessel walls of small perforating vessels, the vessels lengthen and become more tortuous, resulting in increased vascular leakage. This reduces the ability of cerebral arterioles to regulate blood flow, leading to areas supplied by these vessels becoming vulnerable to ischemic damage. Similarly, in the retina, this translates to vascular rarefaction and collapse, hence a reduction in fractal dimensions [22]. This is consistent with a recent systematic review on first stroke patients which found that decreased FD is associated with stroke [23]. However, Zhuo et al. 2023 noted that there is no significant difference between fractal dimensions of the retinal arterioles and venules in patients with or without stroke

recurrence. The heterogeneity in results could be attributed to not only Zhuo having a smaller sample size but also the difference in methodology used to measure FD such as the region of interests of FD.

Retinal vascular diameters indirectly affect blood flow and hence metabolism of the retina [24]. Zhao et al. found that mean venous diameters of larger than $83.91\mu\text{m}$ was found to be related to an increase in stroke recurrence, which is consistent with previous findings in first-time stroke patients [25]. The study also found that wider mean arteriolar diameter is related to an increase in stroke recurrence. This is inconsistent with studies on first-time stroke patients that showed no association between wider mean arteriolar diameter and stroke events [25]. One possible reason for the difference could be that retinal arterioles widen due to maladaptive remodelling after a stroke, making them more susceptible to recurrent stroke [9].

Limitations:

One limitation of our study is the variability in follow-up periods across the included studies, which may affect the assessment of retinal microvascular changes over time. Reported follow-up ranged from 1 year to 6 years. Potential longitudinal progression of microvascular changes may not be fully captured in studies with shorter follow-up periods.

In our analysis, the included studies had variations in method of fundus image acquisition, such as differences in camera models, software for image analysis, and whether mydriatic or non-mydriatic imaging was performed. The exact imaging protocols were also only reported in some of the studies. This may have introduced heterogeneity in the measurement of retinal parameters.

Additionally, all included studies utilised color fundus photography to assess retinal features. As optical coherence tomography angiography (OCTA) becomes more widely adopted, future research should consider leveraging this advanced imaging modality. OCTA offers more detailed and different measures of retinal microvasculature, which offers the potential to identify further parameters or biomarkers of interest.

Our analysis also focused solely on ischemic stroke due to the limited availability of studies examining retinal microvascular changes in other stroke subtypes. Consequently, our findings may not be generalizable to haemorrhagic stroke or other cerebrovascular events, highlighting the need for future research to explore these associations more comprehensively.

Lastly, the small number of papers investigating each individual biomarker limited the statistical power of our meta-analysis, reducing the ability to detect significant associations. More research is needed to validate the associations of each of these biomarkers and clarify their prognostic value in recurrent stroke risk.

Conclusion

Our meta-analysis identified key retinal microvascular biomarkers such as MABA, MVBA and retinal haemorrhages that are significantly associated with recurrent strokes. These biomarkers may reflect morphological adaptations that occur post-stroke as a physiological response and suggest that retinal imaging may be a promising tool for risk stratification of recurrent stroke.

Declarations

Author Contributions:

Y.C, R.S.Y.C, Y.C.E, C.X.Y.G, Y.K.T, J.Y, C.H.L.L and B.Y.Q.T. were responsible in writing, reviewing and editing. C.H.L.L, B.Y.Q.T. helped with supervision. All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest:

The authors declare no conflicts of interest for this study.

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Figures

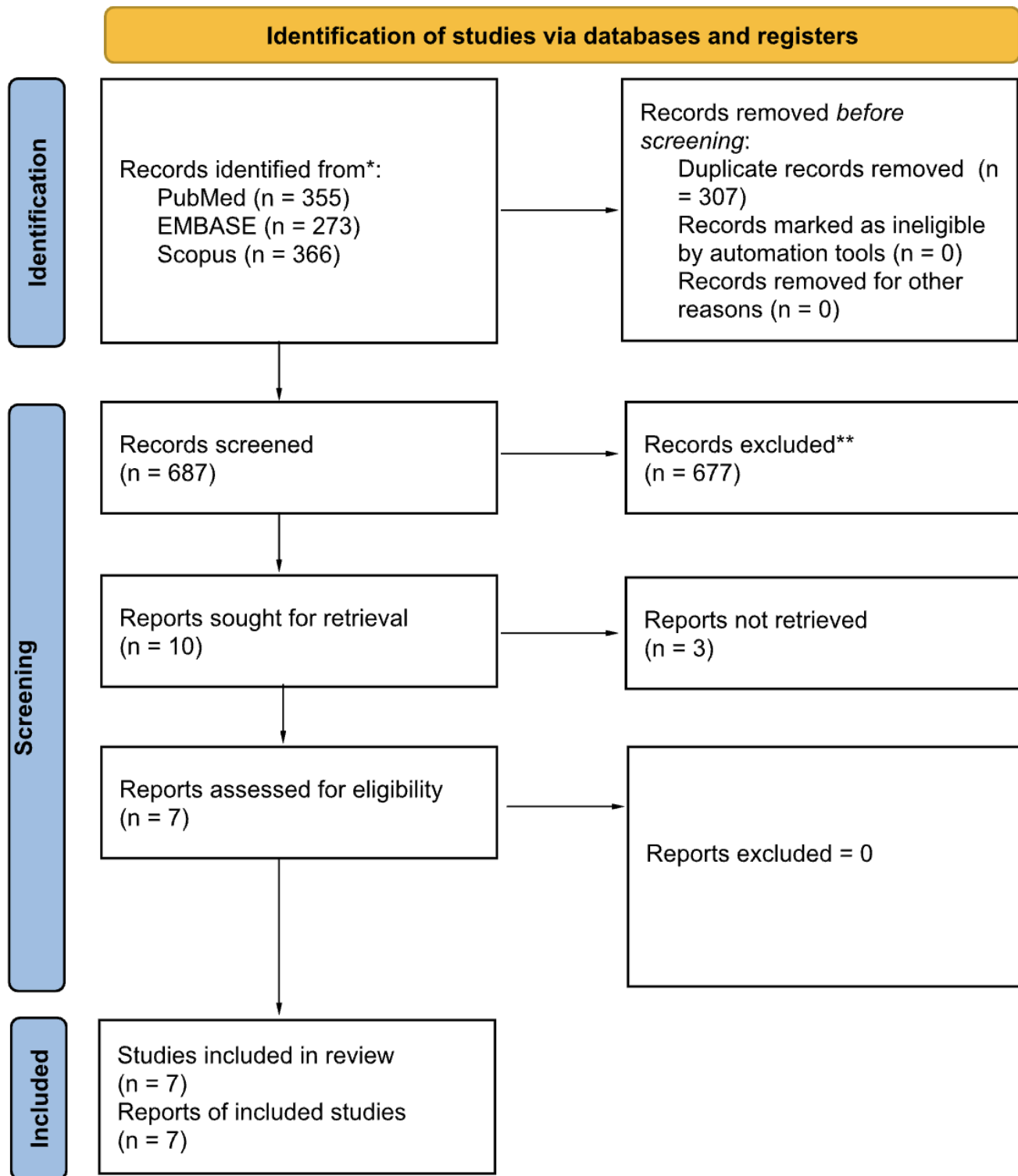


Figure 1

PRISMA flow diagram of search process

Supplementary Files

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