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SCHOOL OF MEDICINE, LABORATORY OF BIOMATHEMATICS

M.SC. "RESEARCH METHODOLOGY IN BIOMEDICINE, BIOSTATISTICS AND CLINICAL BIOINFORMATICS"

"ASSESSMENT OF REPORTING QUALITY OF META- ANALYSES OF RCTS IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION PUBLISHED FROM APRIL 2014 TO MAY 2018 USING PRISMA STATEMENT"

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" Αξιολόγηση της ποιότητας αναφοράς των Μετα-αναλύσεων Τυχαιοποιημένων Κλινικών μελετών για τη νεοαγγειακή μορφή Ηλικιακής Εκφύλισης Ωχράς Κηλίδας, που δημοσιεύτηκαν από τον Απρίλιο του 2014 έως τον Μάιο του 2018 χρησιμοποιώντας το PRISMA statement "

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ΠΕΡΙΛΗΨΗ

Εισαγωγή: Ο θεμέλιος λίθος της τρέχουσας θεραπευτικής αγωγής για τη νεοαγγειακή Εκφύλιση της Ωχράς Κηλίδας είναι η θεραπεία με φάρμακα αντι-Αγγειακού Ενδοθηλιακού Αυξητικού Παράγοντα. Συστηματικές Ανασκοπήσεις(ΣΑ) και Μετα-αναλύσεις(ΜΑ) στοχεύουν στην αποτελεσματικότητα και την ασφάλεια της εξιδρωματικής ΗΕΩ θεραπείας.

Στόχοι: Να αξιολογηθεί η ποιότητα αναφοράς Μετα-αναλύσεων στην θεραπευτική αντιμετώπιση και ασφάλεια για τη νεοαγγειακή ΗΕΩ με βάση το PRISMA Statement.

Μέθοδοι: Ηλεκτρονική αναζήτηση πραγματοποιήθηκε τον Αύγουστο του 2018 ώστε να βρεθούν οι δημοσιευμένες μετα-αναλύσεις από τον Απρίλιο 2014 έως το Μάιο του 2018. Η αξιολόγηση πραγματοποιήθηκε με βαθμολογήσεις του PRISMA checklist για καθεμία μετα-ανάλυση και για κάθε PRISMA θέμα. Η στατιστική ανάλυση των χαρακτηριστικών που επηρεάζουν την ποιότητα αναφοράς εμπεριέχει ανάλυση πολυμεταβλητότητας σε υπο-ομάδες και ανάλυση συσχέτισης.

Αποτελέσματα: Δώδεκα μετα-αναλύσεις συμπεριλήφθηκαν τελικά, τρεις ούσες Cochrane ΣΑ. Η μέση PRISMA βαθμολόγηση είναι 23,2/27(86,1%). Έντεκα PRISMA θέματα είχαν σημαντικά υψηλότερη εκατοστιαία βαθμολογία σε δώδεκα ΜΑ από εκείνη σε εννέα ΜΑ. Θετική ισχυρή συσχέτιση παρουσιάζεται ανάμεσα στην εκατοστιαία βαθμολόγηση και το συντελεστή απήχησης περιοδικού. Η ανάλυση πολυμεταβλητότητας μεταξύ υψηλόβαθμες και χαμηλόβαθμες Μετα-αναλύσεις ανέδειξε συσχέτιση με αρκετές παραμέτρους (π.χ. συντελεστή απήχησης, ημερομηνία δημοσίευσης).

Συμπέρασμα: Γενικά, η αξιολόγηση της ποιότητας αναφοράς ήταν ευνοϊκή. Όπως αναμενόταν, ο ρόλος-κλειδί των διαφόρων χαρακτηριστικών των μετα-αναλύσεων μπορεί να επηρεάσει την ποιότητα αναφοράς. Η έλλειψη αναφοράς συγκεκριμένων θεμάτων (πρωτόκολλο, στρατηγική αναζήτησης, αξιολόγηση σφαλμάτων) δηλώνει την επιτακτικότητα για συμμόρφωση στο PRISMA statement.

Λέξεις-κλειδιά: PRISMA, ΗΕΩ, ποιότητα αναφοράς, μετα-ανάλυση, συστηματική ανασκόπηση, αντι-Αγγειακού Ενδοθηλιακού Αυξητικού Παράγοντα,

ABSTRACT

Background: The cornerstone of current treatment strategy of Neovascular Age-related Macular Degeneration is anti-VEGF therapy. Systematic Reviews(SRs) and Meta-analyses(MAs) are targeted on the efficacy and safety of exudative-AMD treatment.

Objective: To evaluate the reporting quality of meta-analysis on neovascular AMD treatment and safety profile based on PRISMA statement.

Methods: Electronic search performed in August 2018 to retrieve meta-analyses published from April 2014 to May 2018. PRISMA evaluation was determined by total scores of individual MAs and items scores. Statistical analysis of parameters affecting the reporting evaluation included subgroup multivariate analysis and regression analysis.

Results: Twelve meta-analyses were finally included, three being Cochrane SRs. Mean PRISMA score is 23,2/27 (86,1%). Eleven PRISMA ITEMS had significantly higher %score in 12 MAs than in 9 non-Cochrane MAs measurements. Positive strong correlation identified between PRISMA %score and Journal Impact Factor(JIF) . Multivariate analysis between high-scored and low-scored MAs established difference in means of several parameters (JIF,Publication Year).

Conclusions: The evaluation of overall reporting quality was favorable. As expected, the key role of several characteristics of meta-analysis affects this quality. Under-reporting of specific items (protocol, search strategy and assessment of risk of bias) indicate the urgency for PRISMA compliance.

Keywords: PRISMA, AMD, anti-VEGF, reporting quality, meta-analysis, systematic reviews

Introduction

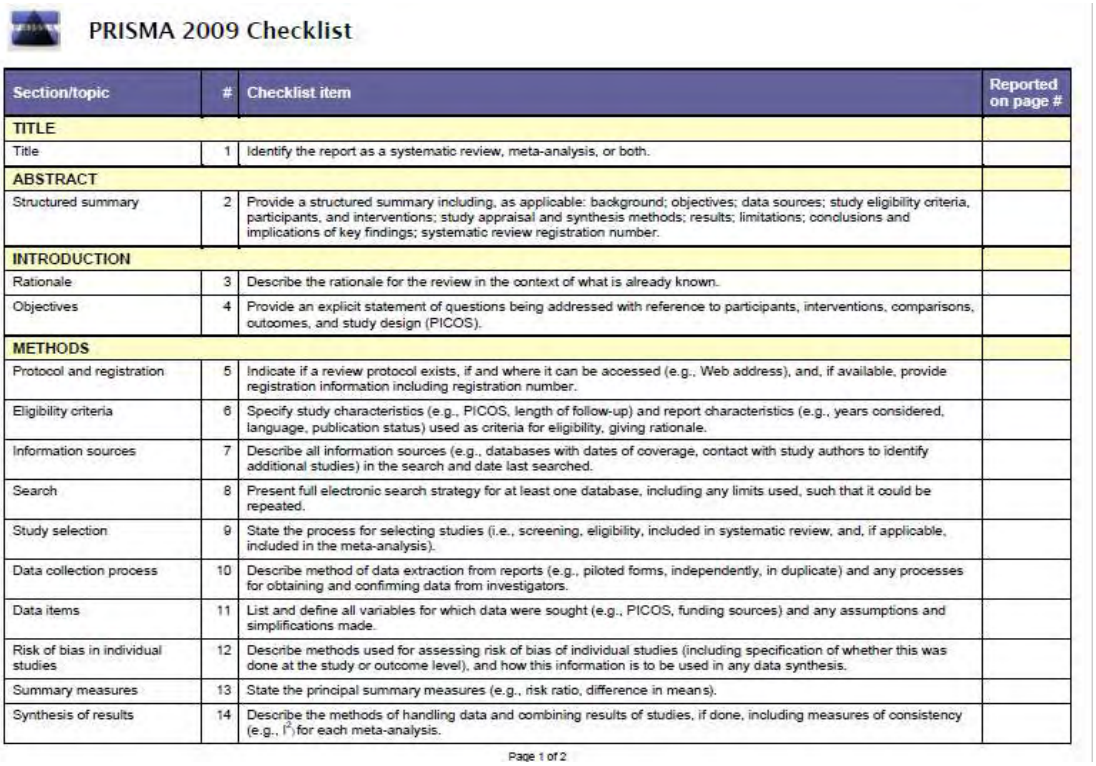
Age-related macular degeneration treatment trends: Age-related macular degeneration (AMD) is numbered among the leading causes of visual impairment in developed countries. After cataract and glaucoma, it is considered a major cause of visual loss and blindness globally (1-3). AMD is a chronic degenerative disease of the central part of the retina, including the macular area. Having an unfavorable progression, it can lead to visual impairment and in serious cases it is responsible for central blindness. In most cases, central vision lost by AMD is largely irreversible and has a tremendous impact on the patient's life. As a result of increasing aging of the population worldwide, this impact will continue to affect more elderly individuals. AMD affects more than 1.75 million individuals in the United States and the prediction estimates that this number will raise to 3 million by 2020 (3). Two different clinical types of the disease present with different clinical manifestations: the non-neovascular (dry) type and the neovascular (wet) type, which leads to approximately 90% of devastating visual losses due to both these types (4). The treatment strategies against neovascular AMD's pernicious progression changed by the introduction of Anti-Vascular Endothelial Growth

Factor (anti-VEGF) agents. Previous treatment strategies included mainly PhotoDynamic Therapy (PDT). VEGF-A is found to promote angiogenesis and choroidal neovascularization (CNV) (5). A new era has begun in the treating options for patients having exudative-AMD since the approval of ranibizumab by the Food and Drug Administration (FDA) in the US in 2006. The European Agency for the Evaluation of Medicinal Products (EMEA) also approved ranibizumab for AMD treatment in 2007. Many other countries across the world have later approved ranibizumab, for example Japan in 2009. Ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA, USA) was not the first anti-VEFG agent to be used in AMD therapy by intravitreal injections. Pegaptanib (Macugen Eyetech Inc., Palm Beach Gardens, FL, USA) was the initial anti-VEGF drug in use from 2004, although it was later abandoned due to visual deterioration (6-7). Pegaptanib's breakthrough is not forgotten, since it opened a new horizon in not only the understanding of pathophysiology but also a new therapeutic perspective in a previously regarded field with limited treatment future. An off-label used anti-VEGF agent is bevacizumab (Avastin, Genentech, Inc., South San Francisco, CA, USA/Hoffmann-La Roche Ltd., Basel, Switzerland first used off-label in 2005). Bevacizumab was approved by the FDA in 2004 for the treatment of metastatic cancer of the colon, but did not gain approval for intravitreal injections so far. Its low cost is a major advantage versus ranibizumab (8). Nevertheless, research has emerged considerations about bevacizumab's systemic safety profile. In 2011, US Food and Drug Administration approved another anti-VEGF agent, aflibercept (VEGF Trap-Eye, Eylea, Regeron, Tarrytown, New York, USA) for the treatment of neovascular AMD (9). Longer half-life of aflibercept and increased binding affinity has increased expectations in number retreatments needed in AMD therapeutic challenge. To our most recent knowledge, conbercept, an additional anti-VEGF Trap-Eye, was approved by the China Food and Drug Administration to be added to treatment options for neovascular AMD in China ((also named KH902, Chengdu Kanghong Biotech Co., Ltd., Sichuan, China) (10). Nowadays, three agents are the cornerstone of wet-AMD treatment: bevacizumab, ranibizumab and aflibercept.

Key purpose of Meta-analysis: Systematic reviews (SRs) and meta-analysis (MAs) are at the top of the pyramid describing the validity and importance of Evidence-Based Medicine. High-level information and evidence about the effects of interventions and healthcare decisions are presented in systematic reviews and meta-analysis. An extremely important effort is made to gather results from studies and through complex and detailed analysis to provide recommendations and guidelines on clinical practice. Reviewers can methodologically handle data from studies to summarized pooled effect estimates. By this procedure called meta-analysis, the review authors can demonstrate a pooled and overall effect of all clinical research performed on a certain field of interest. Meta-analysis major use is to draw conclusions on the topic under investigation by integrating certain numerical data from independent studies, according to their weighted measurement. Meta-analyses are the most popular citated forms of clinical research (11). They represent the quantitative form of systematic reviews aiming to determine a more precise effect of the treatment or any specific research theme. Glass was the first author to define meta-analysis as 'the statistical analysis of a large collection of analysis results from individual studies for the

purpose of integrating the findings in 1976 (12). The source of aggregated data is mostly derived from Randomized Controlled Trials (RCTs), although other study designs, such as observational studies, have been included in meta-analytic assessments. Nonrandomized studies have a tendency to result into large treatment effects, thus leading to contradictory meta-analytic pooled effects (13). When conducting a meta-analysis, authors should scrutinize their explicit methodological strategies step-by-step. Ideally, a protocol should be followed. Being more valuable than any study, meta-analysis can be susceptible to different kinds of biases, for example publication bias and selective reporting bias (14). Time lag bias and language bias have also been reported to affect the estimated results of a meta-analysis (15,16).

Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement: The foremost consulting paper for the proper conduct of meta-analysis was published by Cochrane Collaboration and consists of specific guidelines to be attended by reviewers performing SRs and MAs (17). In 2009, the same year the Cochrane Handbook was published, another guidance tool was available called the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. (18). The PRISMA statement is considered an indispensable tool to be used in order to facilitate the transparent demonstration of information in a systematic review or meta-analysis. Adequate information should be reported in an unambiguous way in aim of readers to understand the merits and the limitations of a research effort in a published paper. PRISMA statement is the updated guidance tool of the QUOROM (Quality Of Reporting Of Meta-analysis) (19). The QUOROM statement was published in 1999, but further need for improving reporting of collation of evidence and the expanding accumulation of knowledge on the proper methodological conduct of clinical trials resulted in the broader and more detailed PRISMA statement. It includes 27 items in a checklist and a four-phase flow diagram. Furthermore, PRISMA statement is accompanied by an Explanation and Elaboration document assisting authors, readers and editors in comprehending each reporting item independently by fully describing the meaning of each item and by presenting an example (20). The PRISMA checklist and additional document is available and downloadable to facilitate any researcher in order to endorse this valuable statement in clearly presenting a systematic review or meta-analysis. PRISMA statement's major scope is to provide all key characteristics that should be systematically and transparently presented and described in a meta-analysis to enlarge its potential utility in medicinal practice. Furthermore, the scrutinized specification of information included in a meta-analysis raises the possibility for expanded applicability of the results provided by the analysis.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additiona analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Objectives

In this task, we aim to assess the reporting quality of Meta-analysis of Randomized Controlled Trials using the PRISMA statement as a guidance and recommendation tool. Our goal is to investigate whether meta-analysis in this research area has supported the use of PRISMA checklist in presenting accurately what they did and how they did it. This task is restricted to meta-analysis and consequently, it does not include simply systematic reviews without quantitative analysis. Moreover, the only design type of studies included in each meta-analysis is Randomized Controlled Trials. The reporting quality of the meta-

analyses in this assessment is to be inspected by PRISMA scoring and statistical analysis.

Eligibility criteria

All included meta-analysis in this task had to fulfill clearly the below criteria:

- They should contain quantitative analysis (i.e. meta-analysis) and not only qualitative results.
- The studies analyzed should be only Randomized Controlled Trials (RCTs).
- The participants' cause of choroidal neovascularization should be neovascular Age-related Macular Degeneration, not other degenerative diseases of the retina, such as polypoidal choroidal vasculopathy.
- The meta-analysis included should investigate topics that refer to neovascular AMD therapeutic approaches and/or the safety profile of these approaches.
- The meta-analysis should be published from April, 1st in 2014 to May, 31ST in 2018.

Exclusion criteria

- Any other study design type, for example retrospective studies, preclinical studies, cohort studies, case cohort studies.
- Any other topic relevant to AMD, but not relevant to therapeutic effectiveness or ocular/systemic safety of exudative AMD treatment, such as prevalence and incidence of AMD, genetic polymorphisms, risk factors and biomarkers, pathogenetic issues, diagnostic methods.
- Any other cause of choroidal neovascularization, for example myopia, uveitis or other degenerative disease.
- Any systematic review that does not contain meta-analytic assessment.
- Any deviation from the dates of publication mentioned (April 2014 to May 2018.

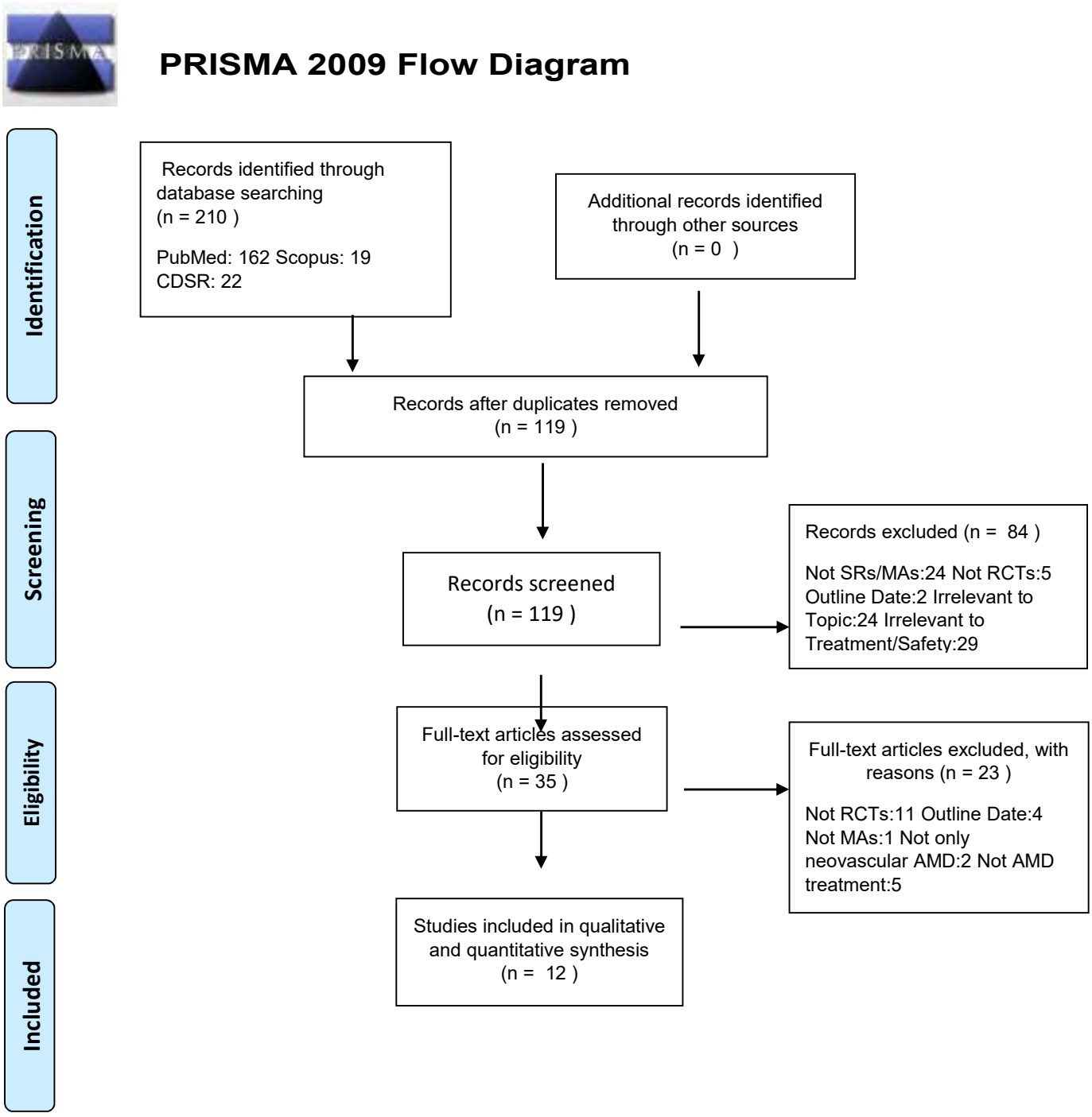
Literature search

We searched the Cochrane Database of Systematic Reviews (from inception to August 2018), PubMed (from January 2014 to September 2018), Scopus (from January 2014 to August 2018 limited to Open Access and Medicine applications) and EMBASE databases. We also searched other electronic sources, such as Open Science Directory and Directory of Open Access Journals in an effort to identify additional articles. Only articles in the English language were assessed for eligibility. May 31st, 2018 was the last date searched.

Data extraction Process and Search Results

A systematic literature search was performed in the above electronic data sources (PubMed, CDSR, Scopus, EMBASE) and data were screened by title and summary. Date filters were applied in both PubMed and Scopus databases. Overall, 210 articles were extracted and after duplicates removed, 119 articles were screened. Additionally, data extracted from Open Science Directory and Directory of Open Access Journals were also screened for eligibility (42 articles)

and all of them excluded, as they were either duplicates or irrelevant. The initial search terms involved: ‘AMD’, ‘ AMD treatment’, ‘macular degeneration’, ‘neovascular age-related macular degeneration’, ‘anti-VEGF’, ‘anti-vascular endothelial growth factor’, ‘Ranibizumab OR Lucentis’, ‘Bevacizumab OR Avastin’, ‘Pegaptanib OR Macugen’, ‘Aflibercept OR Eylea’, ‘anti-VEGF safety’, ‘meta-analysis’ and ‘systematic review’. The following information was extracted from each article: title, first author, year of publication, abstract. 84 records were excluded, predominantly due to irrelevant theme of interest, and 35 full text articles were evaluated thoroughly according to fulfillment of eligibility criteria. The majority of the excluded full-text articles contained other types of study design. Finally, twelve meta-analyses were assessed, three being Cochrane Systematic Reviews (21-32). Four-phase flow diagram is summarizing this process.



Methods

The 27-item checklist of PRISMA was determined for each meta-analysis. The score assigned to each item was either 0 or 1, with equal weight. Zero represents the lack of adequate reporting and 1 was assigned to papers that the reporting was sufficiently accurate. The total highest score is 27/27(100%) and the total minimum score is 0/27(0%). We decided on simplifications for clarified explanation on this assessment. For ITEM №4, if the authors did not report specific objectives according to the PICOS approach, but it was clarified through the information across the article, the evaluation was 1. For ITEM №5, if there was report of a registration number but no protocol, the item's evaluation was 0. For ITEMS concerning the risk of bias assessment, if the authors reported only quality assessment with a cumulative score, for example Jadad score, the items were scored 0. For ITEM №27, if support was mentioned in general rather than a specific funding source, the item's evaluation was 0. PRISMA ITEMS score was calculated as percentage of evaluations for individual items. Data were analyzed by statistical package SPSS (IBM SPSS statistics 23.0). Level of statistical significance threshold was a Pvalue of 0,05, except for linearity threshold set at 0,001. Pearson correlation 'r' was calculated for investigation of correlation between PRISMA evaluation and other variables, e.g. journal impact factor. Subgroup multivariate analysis was conducted to identify possible difference between meta-analyses assigned to high PRISMA score (≥24/27) and meta-analyses assigned to lower PRISMA score (≤23/27) in simultaneous evidence from dependent characteristics. Multivariate analysis was also performed between meta-analyses with and without claim of PRISMA adherence in accumulated evidence from characteristic measurements. Lastly, secondary outcomes analysis used multivariate analysis and chi-square test. Chi-square test was used in aim to detect difference in proportions of meta-analyses with high and low PRISMA score in the usage of different guidance tools for bias estimates.

Characteristics of the Meta-analyses included

The meta-analyses characteristics are displayed in Tables 1 and 2. Five meta-analyses were conducted according to PRISMA guidance. All papers included RCTs only, with the exception of Li S et al (22) including 4 RCTs and 2 quasi-RCTs in their analysis. The number of studies included in the MAs ranged from 2 (Sarwar S) to 15 (Nguyen CL). The mean number of studies was 8,2. Four out of twelve MAs included >10 RCTs (33,3%). Similarly, three out of 9 non-Cochrane MAs included >10 RCTs (33,3%) (Nguyen CL, Ba J, Ueta T). According to year of publication, 6 out of 12 papers were published in 2014 (50%). Also, three MAs were published in 2017 and 2018 (23%). Journal impact factors (JIFs) ranged from 0,705 (Si JK) to 6,135 (Ueta T). Mean JIF among meta-analyses was 3,471. The highest impact factors were possessed by Ophthalmology and Cochrane Collaboration. Mean number of authors was 7,2. Eight MAs used the Cochrane Handbook of Systematic Reviews of Interventions as a tool for quality and risk of bias evaluation and four MAs used Jadad score or author's opinion. All papers presented the four-phase flow diagram and 6 out of the 9 non-Cochrane reviews

presented the reasons of excluding studies on the flow diagram. However, in Ueta et al meta-analysis (28) the type of the flow diagram was not the typical four-phase.

Primary outcomes

1. Scoring: compliance to PRISMA statement measured by PRISMA score (proportion and percentage) for individual meta-analyses based on the evaluation of each meta-analysis. Also, PRISMA ITEMS percentage score for individual items based on the evaluation of the cumulative score of meta-analyses.
2. Comparison between all 12 MAs and 9 non-Cochrane MAs in mean difference of PRISMA ITEMS percentage score.
3. Correlation between PRISMA percentage score in individual meta-analysis and year of publication, number of authors, number of studies, number of patients and journal impact factor. If detected, investigation of the possible linear correlation.
4. Subgroup comparison between MAs with PRISMA score ≤23/27 and MAs with PRISMA score ≥24/27 in accumulated evidence from the mean values of: number of authors, number of studies, number of patients, year of publication and impact factor by multivariate analysis.

Secondary outcomes

1. Comparison between MAs with PRISMA endorsement and MAs without PRISMA endorsement in mean difference of PRISMA percentage score.
2. Subgroup comparison between MAs with PRISMA endorsement and MAs without PRISMA endorsement in accumulated evidence from the mean values of: PRISMA percentage score, number of authors, number of studies, number of patients, year of publication and impact factor by multivariate analysis.
3. Comparison between MAs using Cochrane Handbook of Systematic Reviews of Interventions as a guidance tool for risk of bias assessment and MAs using Jadad score or author's opinion in mean difference of PRISMA percentage score.
4. Subgroup comparison between the MAs using the Cochrane Handbook of Systematic Reviews of Interventions for risk of bias assessment and the MAs using Jadad score or author's opinion in the accumulated evidence from the mean values of: PRISMA percentage score, number of authors, number of studies, number of patients, year of publication and impact factor by multivariate analysis.
5. Comparison of the proportions of MAs with PRISMA score ≤23/27 and the MAs with PRISMA score ≥24/27 in the usage of different guidance tools for risk of bias assessment (either Cochrane Handbook of Systematic Reviews of Interventions or Jadad score/author's opinion)

Results

Primary results

Results of PRISMA ITEMS scoring: PRISMA ITEMS percentage score in all 12 meta-analyses and in 9 non-Cochrane meta-analyses are presented in Table 3 and they are demonstrated visually in Simple Bar Charts (Figures 1 and 2). Sixteen PRISMA ITEMS were 100% reported. In 12 MAs, ITEM №5:Protocol and Registration (41,6%), ITEM №8:Electronic Search Strategy (41,6%), ITEM №27:Funding (41,6%) and ITEM №12:Methods of Risk of Bias in individual studies (58,3%) were the least reported items, to be followed by ITEM №15:Risk of Bias across studies (66,6%) and ITEM №22:Results of Risk of Bias across studies (66.6%). These results are prominently lower in the nine non-Cochrane subgroup.

	META-ANALYSIS	№ of AUTHORS	№ of STUDIES	STUDY DESIGN	№ of PATIENTS	Tool for Quality and Risk of bias Assessment	Quality
1	Nguyen CL	5	15	RCT	8320	Cochrane Handbook of Systematic Reviews of Interventions	High
2	Li S	5	6	RCT and quasi-RCT	278	Cochrane Handbook of Systematic Reviews of Interventions	Moderate
3	Tong Y	7	8	RCT	800	Author's Opinion	Judgment Missing
4	Ba J	7	12	RCT	5225	Jadad score	Moderate
5	Wang W	2	4	RCT	2613	Jadad score	High
6	Kodjikian L	7	5	RCT	2686	Cochrane Handbook of Systematic Reviews of Interventions	Low
7	Si JK	10	7	RCT	742	Jadad score	High
8	Ueta T	5	11	RCT	6596	Cochrane Handbook of Systematic Reviews of Interventions +MedRA classification of adverse events	Moderate
9	Su Y	3	8	RCT	817	Cochrane Handbook of Systematic Reviews of Interventions	Moderate
10	Sarwar S	10	2	RCT	2457	Cochrane Handbook of Systematic Reviews of Interventions + GRADE	High
11	Moja L	21	9	RCT	3665	Cochrane Handbook of Systematic Reviews of Interventions + MedRA classification of adverse events	Moderate
12	Solomon SD	5	12	RCT	5496	Cochrane Handbook of Systematic Reviews of Interventions	High

Table 1: Meta-Analyses Characteristics

№	META-ANALYSIS	Year of publication	Journal	Impact Factor for the year	Primary Outcome	Other Outcomes
1	Nguyen CL	2018	BMC Ophthalmology	1,770	Anti-VEGF agents: mean change in BCVA	Anti-VEGF agents: mean change in CRT, Safety RRs
2	Li S	2017	PLoS One	2,776	Topical NSAIDS and anti-VEGF vs anti-VEGF: mean change in BCVA	Topical NSAIDS and anti-VEGF vs anti-VEGF: mean change in CRT and injection number, ORs for 4 adverse events
3	Tong Y	2016	International Journal of Ophthalmology	1,177	PDT and anti-VEGF vs anti-VEGF: mean change in BCVA	PDT and anti-VEGF vs anti-VEGF: mean change in CRT and BCVA more than 15,10,5 or 0 letters and injection number
4	Ba J	2015	Drug Design Development and Therapy	2,881	Anti-VEGF agents: mean change in BCVA	Anti-VEGF agents: mean change in CRT, lesion size, BCVA change in different regimens
5	Wang W	2014	PLoS One	3,234	Anti-VEGF agents (ranibizumab vs bevacizumab): safety RRs for death from all causes	Anti-VEGF agents (ranibizumab vs bevacizumab): safety RRs for arteriothrombotic events, stroke, MI, venous thrombosis and hypertension
6	Kodjikian L	2014	Graefes Archive for Clinical and Experimental Ophthalmology	1,908	Anti-VEGF agents (ranibizumab vs bevacizumab): mean change in BCVA	Anti-VEGF agents (ranibizumab vs bevacizumab): mean change in CRT and ORs for systemic adverse events
7	Si JK	2014	International Journal of Ophthalmology	0,705	PDT and ranibizumab vs ranibizumab: mean change in BCVA	PDT and ranibizumab vs ranibizumab: mean change in CRT and BCVA gaining more than 3 and 0 lines, injection number, safety for four adverse events
8	Ueta T	2014	Ophthalmology	6,135	Ranibizumab regimen monthly vs PRN, 0,5mg vs 0,3mg, 0,3mg vs 0,0mg: mean change in cerebrovascular accidents, MI, non-ocular hemorrhage	Ranibizumab regimen o,5/0,3mg vs 0,0, 0,5mg vs 0,3/0,0mg, monthly vs PRN/control: mean change in cerebrovascular accidents, MI, non-ocular hemorrhage
9	Su Y	2018	Photodiagnosis and Photodynamic Therapy	2,895	PDT and ranibizumab vs ranibizumab: mean change in BCVA	PDT and ranibizumab vs ranibizumab:): mean change in CRT, LS, injection number, proportion of patients gaining >15 letters, proportion of patients losing >15 letters, RR of adverse events
10	Sarwar S	2016	Cochrane Database of Systematic Reviews	6,124	Aflibercept vs ranibizumab, bevacizumab, or sham: mean change in BCVA outcomes	Aflibercept vs ranibizumab, bevacizumab, or sham: mean change in morphological outcomes, safety outcomes, quality-of life outcomes, mean number of injections
11	Moja L	2014	Cochrane Database of Systematic Reviews	6,032	Bevacizumab versus ranibizumab : safety RRs for death and all SSAEs	Bevacizumab versus ranibizumab : safety RRs for different SSAEs in MedRA SOC classification
12	Solomon SD	2014	Cochrane Database of Systematic Reviews	6,032	Anti-VEGF agents: mean change in BCVA outcomes	Anti-VEGF agents: mean change in morphological outcomes, BCVA outcomes, quality-of-life, ocular or systemic adverse events, economic data outcomes

Table 2: Meta-Analyses Characteristics (continue)

SECTION	№	PRISMA Item (definition)	% Percentage of Total score in 12 MAs	% Percentage of Total score in 9 MAs (Cochrane excluded)
TITLE	1	Title	100	100
ABSTRACT	2	Structured Summary	91,6	88,8
INTRODUCTION	3	Rationale	100	100
	4	Objectives	100	100
METHODS	5	Protocol & Registration	41,6	22,2
	6	Eligibility Criteria	91,6	88,8
	7	Information Sources	100	100
	8	Search Strategy	41,6	22,2
	9	Study Selection	100	100
	10	Data collection progress	75,0	66,6
	11	Data Items	100	100
	12	Methods for Risk of Bias in individual studies	58,3	44,4
	13	Summary Measures	100	100
	14	Synthesis of Results	100	100
	15	Risk of Bias across studies	66,6	55,5
	16	Additional Analysis	100	100
RESULTS	17	Study Selection	100	100
	18	Study Characteristics	100	100
	19	Results on Risk of Bias in individual studies	75,0	44,4
	20	Results of Individuals studies	100	100
	21	Synthesis of Results	100	100
	22	Results of Risk of Bias across studies	66,6	55,5
	23	Additional Analysis Results	100	100
DISCUSSION	24	Summary Evidence	100	100
	25	Limitations	100	100
	26	Conclusions	91,6	88,8
FUNDING	27	Funding	41,6	22,2

Table 3: PRISMA ITEMS percentage score in 12 MAs and 9 MAs

Results of PRISMA scoring in individual meta-analyses: All 3 Cochrane MAs (Sarwar CL et al, Moja L et al, Solomon SD et al) were assessed with the highest PRISMA score 27/27 (100%). The remaining meta-analyses score ranged from 19/27 (70,3%) to 26/27 reported items (96,2%). The mean PRISMA score is 23,2/27 (86,1%) for all 12 MAs. Excluding Cochrane MAs, the mean PRISMA score for 9 MAs changes to 22/27 (81,4%). PRISMA statement was claimed to be endorsed by 5 out of 12 papers and by 5 out of 9 non-Cochrane MAs. The mean PRISMA score in the above five MAs was 22,2/27. The results of scoring are displayed in Table 4.

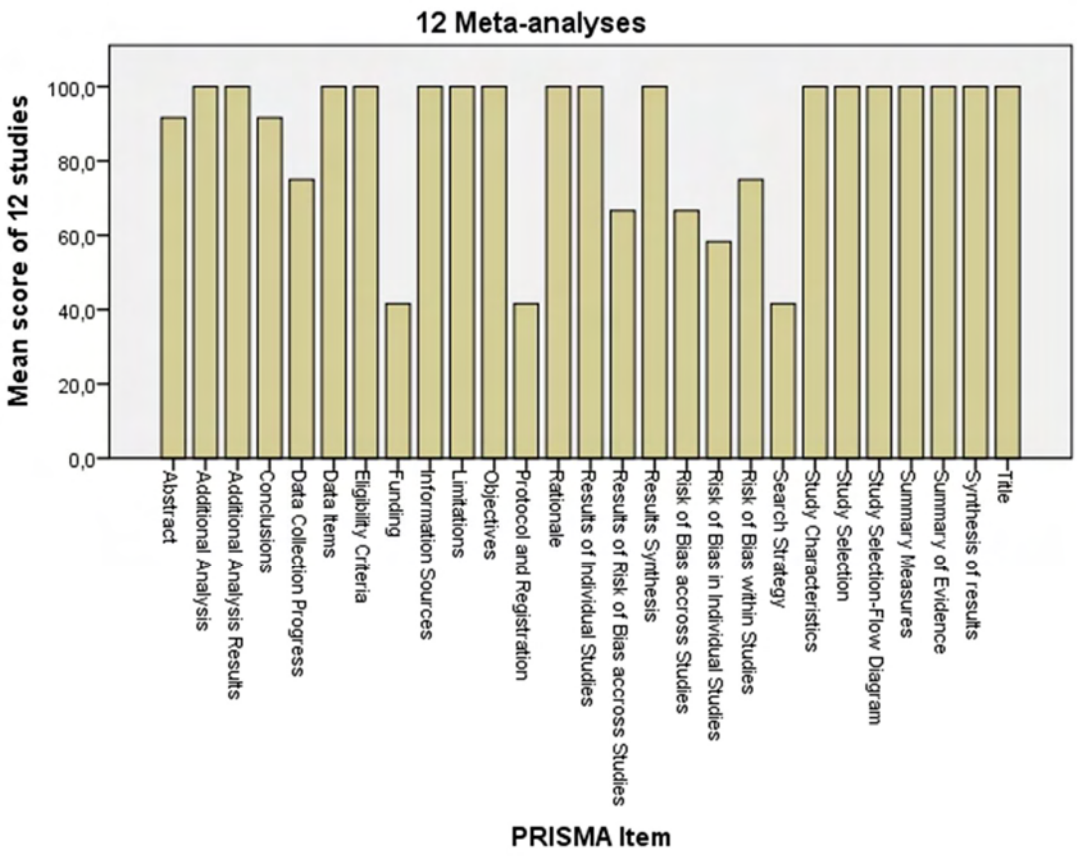


Figure 1: Simple Bar Chart of PRISMA items score in 12 meta-analyses

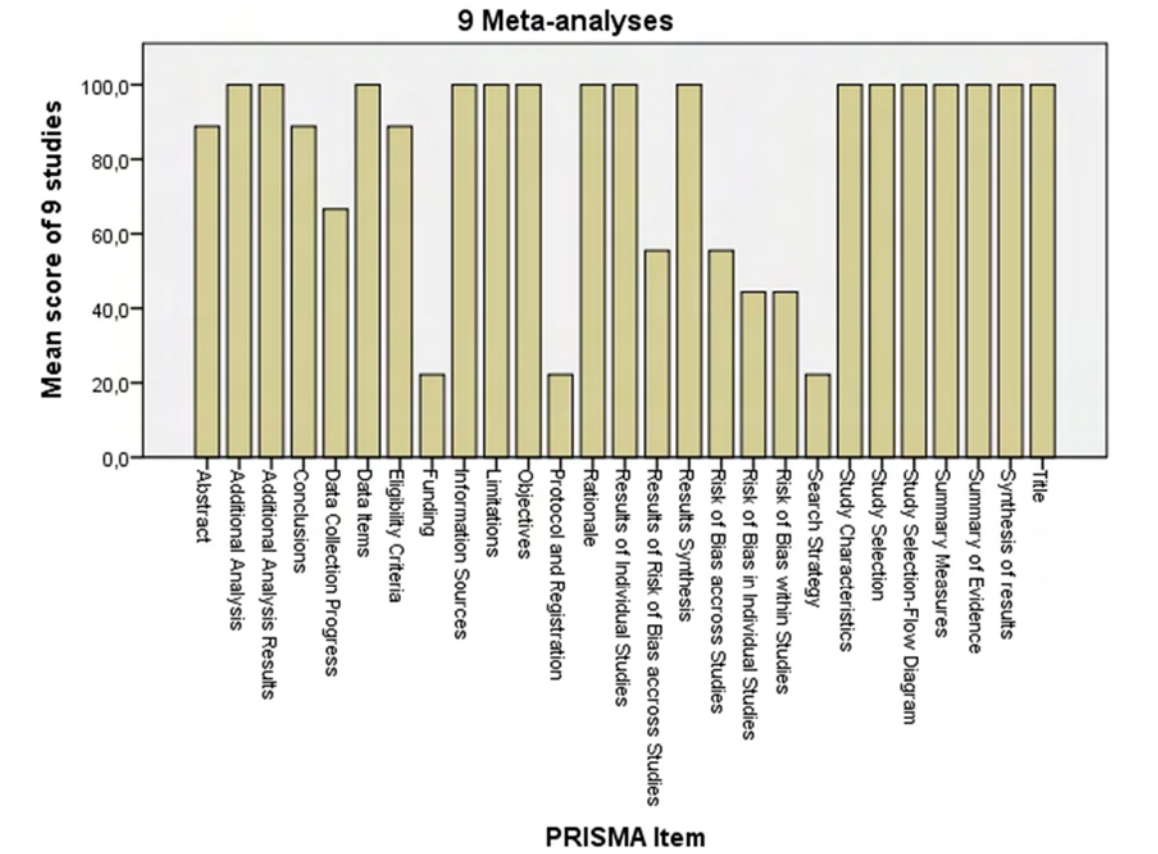


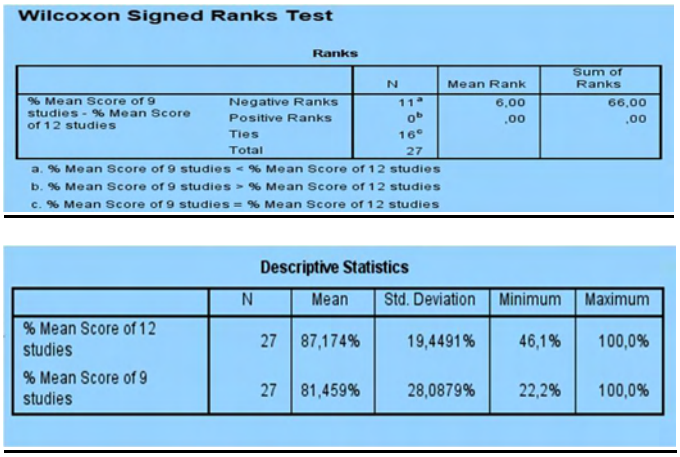
Figure 2: Simple Bar Chart of PRISMA items score in 9 non-Cochrane meta-analyses

Results of difference in means of PRISMA ITEMS percentage score between all 12 MAs and 9 non-Cochrane MAs:

In order to detect the possible difference in means of PRISMA ITEMS %score, we decided to distinguish between the score of items from all 12 MAs and the score of items after the exclusion of Cochrane Systematic Reviews (Sarwar S, Moja L, Solomon SD). Normality distribution test demonstrated negative results (Pvalue=0,000<0,05 in Shapiro-Wilk and Kolmogorov-Smirnoff), stating the need for performing non-parametric Wilcoxon test. Wilcoxon test was statistically significant (Pvalue=0,003<0,05), as shown in SPSS Figures 1,2 and 3. We concluded that there is evidence of difference in mean percentage score of PRISMA ITEMS. In fact, in 11 PRISMA ITEMS the %score was higher in 12 MA measurements than in 9 non-Cochrane measurements. In 0 ITEMS, no difference was detected. The results of the descriptives are also presented below. The mean % score of PRISMA ITEMS in 12 meta-analyses is 87,1% and in 9 meta-analyses is 81,4%. The inclusion of 3 Cochrane Systematic Reviews in this assessment raised significantly the results of 11 PRISMA ITEMS percentage score.

	META-ANALYSIS	PRISMA SCORE	%	PRISMA ENDORSEMENT
1	Nguyen CL	25/27	92,5	NO
2	Li S	24/27	88,8	YES
3	Tong Y	19/27	70,3	NO
4	Ba J	19/27	70,3	NO
5	Wang W	20/27	74,0	YES
6	Kodjikian L	22/27	81,4	YES
7	Si JK	19/27	70,3	YES
8	Ueta T	26/27	96,2	YES
9	Su Y	24/27	88,8	NO
10	Sarwar S	27/27	100	NO
11	Moja L	27/27	100	NO
12	Solomon SD	27/27	100	NO

Table 4: PRISMA score in individual meta-analyses included



Wilcoxon Signed Ranks Test

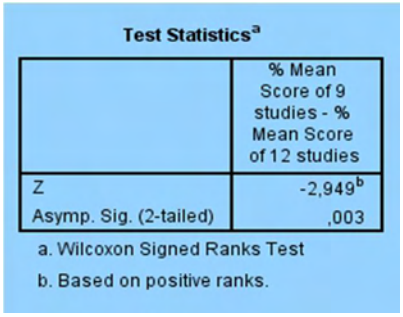
Ranks

		N	Mean Rank	Sum of Ranks
% Mean Score of 9 studies - % Mean Score of 12 studies	Negative Ranks	11[a]	6,00	66,00
	Positive Ranks	0[b]	,00	,00
	Ties	16[c]		
	Total	27		

a. % Mean Score of 9 studies < % Mean Score of 12 studies
b. % Mean Score of 9 studies > % Mean Score of 12 studies
c. % Mean Score of 9 studies = % Mean Score of 12 studies

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
% Mean Score of 12 studies	27	87,174%	19,4491%	46,1%	100,0%
% Mean Score of 9 studies	27	81,459%	28,0879%	22,2%	100,0%



Test Statistics[a]

	% Mean Score of 9 studies - % Mean Score of 12 studies
Z	-2,949[b]
Asymp. Sig. (2-tailed)	,003

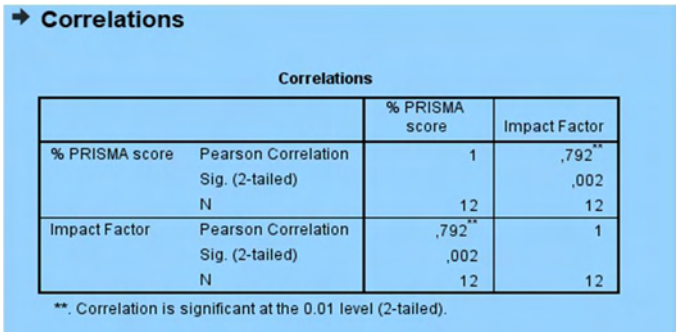
a. Wilcoxon Signed Ranks Test
b. Based on positive ranks.

SPSS Figures 1, 2 and 3: Primary Results

Results of correlation between PRISMA percentage score in individual meta-analysis and year of publication, number of authors, number of studies, number of patients and journal impact factor: For investigating the possible correlation between PRISMA %score in individual studies and other characteristics measured (year of publication, number of authors, number studies, number of patients, impact factor), we performed bivariate correlation in SPSS statistical package. The variables used were PRISMA percentage score and each one of: number of authors, number of studies, number of patients, year of publication and impact factor. The results are listed in Chart 1.

Correlations between PRISMA %score and:	Correlation coefficient (r)	Pvalue	Significance (Pvalue<0,05)
Year of Publication	0,118	0,715	NO
Number of Authors	0,258	0,418	NO
Number of Studies	0,140	0,665	NO
Number of Patients	0,385	0,216	NO
Journal Impact Factor	0,792	0,002	YES

Chart 1: Correlations Results


Correlations

Correlations

		% PRISMA score	Impact Factor
% PRISMA score	Pearson Correlation	1	,792**
	Sig. (2-tailed)		,002
	N	12	12
Impact Factor	Pearson Correlation	,792**	1
	Sig. (2-tailed)	,002	
	N	12	12

**. Correlation is significant at the 0.01 level (2-tailed).

SPSS Figure 4: Primary Correlation Results

Because of Pvalue (=0,002) being beyond the limit of statistical significance and the correlation coefficient r (=0,792) being larger than 0,7 , we concluded that there is statistically significant positive strong correlation between PRISMA percentage score in individual meta-analyses and journal impact factor. The scatter dot diagram in Figure 3 presents visually the correlation. Linear regression was performed on this result, but the linearity was not established, as shown in SPSS Figure 5 (Pvalue=0,002 >0,001).

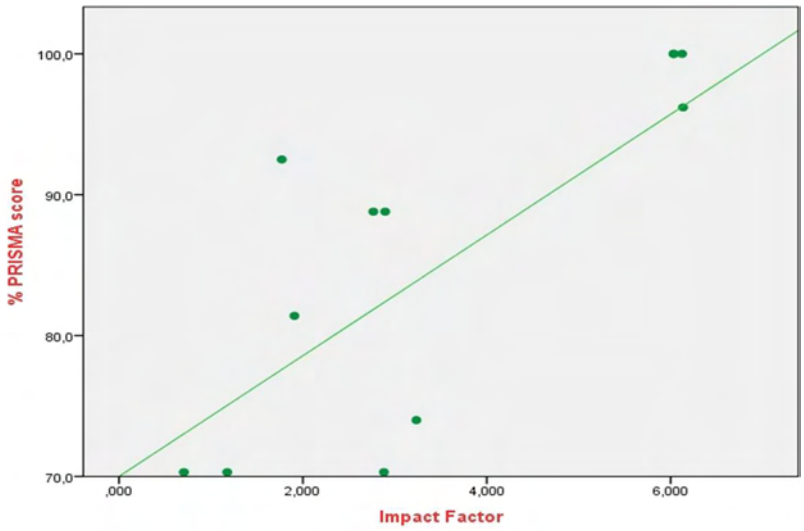


Figure 3: Scatter Dot Diagram JIF/%score

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1036,729	1	1036,729	16,780	,002[b]
	Residual	617,841	10	61,784		
	Total	1654,570	11			

a. Dependent Variable: % PRISMA score

b. Predictors: (Constant), Impact Factor

SPSS Figure 5: Primary Linearity Results

Results of multivariate analysis between High PRISMA score (≥24/27) MAs VS low PRISMA score MAs (≤23/27) in the mean values of: number of authors, number of studies, number of patients, year of publication and impact factor. We distinguished studies that possessed PRISMA score ≤23/27 and studies that possessed PRISMA score ≥24/27. We performed multivariate analysis by SPSS statistical package for comparing the MAs with PRISMA score ≤23/27 and the MAs with PRISMA score ≥24/27, as two separate values, and the mean values of: number of authors, number of studies, number of patients, year of publication and impact factor. These continuous variables are assumed to be dependent and thus, we tested the accumulated correlation between variables simultaneously on PRISMA score evaluation. For multivariate analysis, we performed a large amount of combinations between these continuous variables, and we display in Chart 2 the statistically significant results (Hotelling's T2 Pvalue<0,05) of this analysis.

Multivariate analysis of continuous variables between MAs with PRISMA score ≥24/27and MAs with PRISMA score ≤23/27	***Hotelling's Trace Pvalue***	**Significance**
Impact Factor and Number of studies	0,059	Borderline

Number of authors, Number of patients, Number of Studies, Year of Publication and Impact factor	**0,026**	YES
Number of authors, Number of Studies, Year of Publication and Impact Factor	0,009	YES
Number of studies, Number of Patients, Year of Publication and Impact Factor	0,009	YES
Year of Publication, Impact Factor and Number of studies	0,002	YES
Year of Publication and Impact Factor	0,001	YES

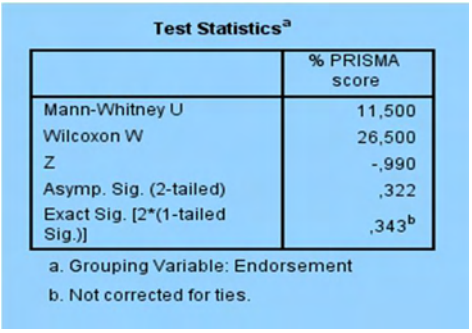
Chart 2: Multivariate Analysis

We concluded that there is evidence of a significant difference in means for MAs with high PRISMA score ≥24/27 and MAs with lower PRISMA score ≤23/27 taking account for variables as Number of authors, Number of patients, Number of Studies, Year of Publication and Impact factor of publication journal (Pvalue=0,026) simultaneously. The evidence is stronger when Year of Publication, Impact Factor and Number of studies are accumulated (Pvalue=0,002) and when Impact Factor and Publication Year are accumulated (Pvalue=0,001), as expected.

Secondary outcomes

Results of statistical difference of MAs with and without PRISMA endorsement in means of PRISMA percentage score: Five meta-analyses were conducted according to PRISMA guidance (Li S et al, Wang W et al, Kodjikian L et al, Si JK et al and Ueta T et al). So, PRISMA statement was claimed to be endorsed by 5 out of 11 papers (45,4%) and by 5 out of 9 non-Cochrane MAs (55,5%). The mean PRISMA score in the above five MAs was 22,2/27.

We tested the possible difference of MAs with PRISMA adherence and without PRISMA adherence in means of PRISMA percentage score. The normality test resulted in Pvalue=0,031 <0,05 and thus, we assume that our measurements do not follow normal distribution and the hypothesis for conducting a parametric test is not fulfilled. Non-parametric Mann-Whitney U test was performed. Statistical significance is not established in this outcome, as shown in SPSS Figure 6 (Pvalue=0,322 >0,05).



Test Statistics[a]

	% PRISMA score
Mann-Whitney U	11,500
Wilcoxon W	26,500
Z	-,990
Asymp. Sig. (2-tailed)	,322
Exact Sig. [2*(1-tailed Sig.)]	,343[b]

a. Grouping Variable: Endorsement

b. Not corrected for ties.

SPSS Figure 6: Secondary Results

Results of multivariate analysis between PRISMA Endorsement and no PRISMA endorsement MAs in the mean values of: PRISMA percentage score, number of authors, number of studies, number of patients, year of publication and impact

factor: We performed multivariate analysis by SPSS statistical package for comparing the MAs with PRISMA endorsement and MAs without PRISMA endorsement, as two separate values, and the mean values of: PRISMA %score in individual studies, number of authors, number of studies, number of patients, year of publication and impact factor. These variables are assumed to be dependent and thus, we tested the accumulated correlation between variables simultaneously on PRISMA endorsement. For multivariate analysis, we performed a large amount of combinations between these continuous variables, however, no results were statistically significant. As an implication for future evaluation, we present results of most promising combinations in Chart 3.

Multivariate analysis of continuous variables between MAs with and without PRISMA Endorsement	***Hotelling's Trace Pvalue***
Number of authors and Year of Publication	0,169
Number of authors, Number of Studies and Year of Publication	0,181
Number of authors, Number of Patients and Year of Publication	0,198
Year of Publication, Impact Factor and %PRISMA score	0,211
Year of Publication and Impact Factor	0,211
Year of Publication, Impact Factor and Number of authors	0,223
Year of Publication, Impact Factor, Number of authors and Number of Studies	0,235
Year of Publication and Number of Studies	0,243
Year of Publication, Number of Studies and Impact Factor	0,244

Chart 3: Multivariate Analysis

Results of difference between MAs using Cochrane Handbook of Systematic Reviews of Interventions as a guidance tool for risk of bias assessment and MAs using Jadad score or author's opinion in means of PRISMA percentage score: We tested the possible difference of MAs using the Cochrane Handbook of Systematic Reviews of Interventions VS MAs using Jadad score or author's opinion in means of %PRISMA score measurements. The normality test resulted in Pvalue=0,001 <0,05 and thus, we assume that our measurements do not follow normal distribution and the hypothesis for conducting a parametric test is not fulfilled. Non-parametric Mann-Whitney U test was performed to detect a possible difference of these parameters. Statistical evidence was high (Pvalue=0,006), as presented in SPSS Figure 7. We concluded that there is statistical difference in PRISMA percentage score between MAs using the Cochrane Handbook of Systematic Reviews of Interventions for risk of bias assessment and MAs using only Jadad score or just author's opinion on this topic.

Test Statistics[a]

	% PRISMA score
Mann-Whitney U	,000
Wilcoxon W	10,000
Z	-2,761
Asymp. Sig. (2-tailed)	,006
Exact Sig. [2*(1-tailed Sig.)]	,004[b]

a. Grouping Variable: TOOL_QUALITY

b. Not corrected for ties.

SPSS Figure 7: Secondary Results

Results of multivariate analysis between MAs using the Cochrane Handbook of Systematic Reviews of Interventions for risk of bias assessment and the MAs using Jadad score or author's opinion in the mean values of: PRISMA percentage score, number of authors, number of studies, number of patients, year of publication and impact factor: We performed multivariate analysis by SPSS statistical package for comparing the MAs using the Cochrane Handbook of Systematic Reviews of Interventions for risk of bias assessment and the MAs using Jadad score or author's opinion, as two separate values, in the mean values of: PRISMA percentage score, number of authors, number of studies, number of patients, year of publication and impact factor. For multivariate analysis, we performed a large amount of combinations between these continuous variables, and the statistically significant results (Hotelling's T2 Pvalue<0,05) of this analysis are presented in Chart 4.

Multivariate analysis of continuous variables between MAs using Cochrane Handbook of Systematic Reviews of Interventions for risk of bias assessment and the MAs using Jadad score or author's opinion	***Hotelling's Trace Pvalue***	**Significance**
%PRISMA score, Number of authors, Number of Studies and Number of Patients, Impact Factor and Year of publication	**0,021**	YES
%PRISMA score, Number of authors, Number of Studies and Number of Patients	0,009	YES
%PRISMA score, Number of Studies and Number of authors	0,003	YES
Number of authors, Number of Studies	0,001	YES
Impact Factor, Number of Studies and %PRISMA score	0,000	YES
Impact Factor and %PRISMA score	0,000	YES
Year of Publication, Impact Factor and %PRISMA score	0,000	YES

Chart 4: Multivariate Analysis

The results came up to our expectations. We concluded that there is evidence of a significant difference in means for MAs using the Cochrane Handbook of Systematic Reviews of Interventions and MAs using Jadad score or author's opinion on risk of bias assessment taking account for variables as PRISMA %score, number of authors, number of patients, number of Studies, year of

Publication and impact factor of publication journal (Pvalue=0,021). The evidence is stronger when Year of Publication, Impact Factor and PRISMA percentage score are accumulated (Pvalue=0,000) and when Impact Factor and PRISMA percentage score are accumulated (Pvalue=0,000), as expected.

Results of chi-square test: In order to compare the proportions of MAs with PRISMA score ≤23/27and the MAs with PRISMA score ≥24/27 that used either Cochrane Handbook of Systematic Reviews of Interventions or Jadad score/author's opinion, we performed chi-square test. The odds ratio of this difference (OR=0,2) was not statistically significant {95%CI (0,035, 1,154)}, as displayed in SPSS Figure 8. Therefore and least expected, there is not a statistically significant correlation between the proportion of high score MAs and the usage of guidance tool.

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
For cohort TOOL_QUALITY = Cochrane Handbook of SRs of interventions	,200	,035	1,154
N of Valid Cases	12		

SPSS Figure 8: Chi-square test

Discussion

The median compliance in this assessment was 16/27 items (59,2%), which is relatively consistent in comparison with previous studies that investigate the reporting quality of reviews in ophthalmology (33). Nevertheless, this consistency is considered to be poorer than previous studies on reporting quality in other fields (34-36). Cochrane Systematic Reviews met all criteria of impeccable reporting and more than half of 9 remaining Meta-analyses achieved more than 80% in total scoring (Nguyen CL, Li S, Kodjikian L, Ueta T, Su Y). This achievement may reflect the fact that widespread compliance with the PRISMA checklist by authors has improved over the years. Furthermore, this achievement may indicate that widespread compliance by journal editors and reviewers, making PRISMA adherence mandatory for acceptance, has benefited the reporting quality of articles. Regardless of Cochrane SRs, since they significantly raise the compliance rates in our study, three items with approximate compliance of 20% determine the poor reporting of protocol and registration description, electronic search strategy clarification and funding source clarification. The lack of adequate reporting of protocol and registration in our estimations is highlighted in previous investigational work on ophthalmology (33) and other fields of interest (34,36-39). Moreover, four PRISMA items with approximate compliance of 50% obviously identify the problematic reporting of risk of bias methodology and findings description, evidence in accord with previous findings (33,36-39). Scrutinized reporting of risk of bias methods and outcome-level assessment is weighted of crucial value and plays a pivotal role in overall reporting quality of a meta-analysis. Detailed risk of bias estimates are the most valued arrows in healthcare professionals' quiver when clinical decisions are based on Evidence-Based Medicine. We believe that the most prominent strength in this task lies in the strict inclusion of meta-analysis of RCTs. Moreover, our task strength lies in

the statistical handling of data investigating several parameters. Because PRISMA statement appeals to all medical specialties, specific details added in reporting of each medical specialty should also be concerned. In ophthalmology, specific methodological issues include presentation of data from each eye as a challenge for sufficient reporting quality (33). Anticorruption of unawareness of PRISMA reporting principles and aliveness aiming for widespread explanation of PRISMA items will undeniably result in compliance improvement (40).

The main limitation of this study is that the compliance results in sixteen PRISMA items achieved the highest score (100%) indicating a scoring generosity aspect. However, our scoring was strict consistently with previous studies for risk of bias assessment related items. To our judgment, if scoring is generous on behalf of authors for specific items (e.g. objectives) and strict for methodology and outcomes of risk of bias evaluations, the weighted importance of these evaluations is more obviously revealed in scoring results. Another limitation is that search results included only published meta-analyses, an indication that publication bias may affect this assessment's outcomes. The inclusion of three Cochrane SRs may eliminate this effect due to unpublished RCTs entry.

To summarize, our assessment proved the significance of incorporating Cochrane Systematic Reviews by raising PRISMA ITEMS percentage score. Another primary finding is the strong positive association of PRISMA percentage score of individual meta-analysis with Journal Impact Factor (Pearson correlation=0,792, P=0,002). The last of primary outcomes is the association of high PRISMA score (≥24/27) MAs VS low PRISMA score (≤23/27) MAs with the combination of simultaneous evidence from certain characteristics of meta-analysis (Number of authors, Number of patients, Number of Studies, Year of Publication and Impact factor) (P=0,026). The highest evidence was produced of the combination of Journal Impact Factor and Year of publication (P=0,001) implicating their accumulated strong correlation to high reporting quality. Secondary findings in this work were also important. Multivariate analysis showed that the usage of a standardized guidance tool, as the Cochrane Handbook of Systematic Reviews of Interventions compared to other methodology used (Jadad score/author's opinion), is associated to the combination of evidence from PRISMA percentage score, Number of authors, Number of patients, Number of Studies, Year of Publication and Impact factor (P=0,021). Finally, our assessment identified the difference in mean PRISMA percentage score between MAs using the Cochrane Handbook of Systematic Reviews of Interventions for risk of bias assessment in their analysis and MAs using only Jadad score or just author's opinion on this topic (P=0,006).

Conclusions

The reporting quality of ophthalmological Meta-analyses in exudative AMD treatment and safety profile was generally optimal. Further improvement is required, especially in describing the review protocol and registration, electronic search strategy, funding sources, and risk of bias methodology and evaluation. Universal endorsement of PRISMA statement by journals is recommended at the time of journal submission of articles. The key role of several characteristics of meta-analyses (e.g. journal impact factor) substantially affects their reporting

quality. We strongly suggest that adherence to PRISMA is mandatory to fulfill all criteria as vital elements of reporting quality, although we suggest that much weight should be given to risk of bias procedure and outcomes.

Funding: No funding was received for this work.

Ethics approval and consent to participate: Not applicable. This study did not involve human participants, human data or human tissue.

Abbreviations: AMD=Age-related macular degeneration, CNV=Choroidal Neovascularization, QUOROM=Quality Of Reporting Of Meta-analysis, PRISMA=Preferred Reporting Items for Systematic reviews and Meta-Analyses, PICOS=Patient/Population/Problem, Interventions, Comparisons, Outcomes, Study design, anti-VEGF=anti-Vascular Endothelial Growth Factor, JIF=Journal Impact Factor, SR=Systematic Review, MA=Meta-Analysis.

Competing Interests: No competing interests are declared by the authors committee.

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