Reporting quality in systematic reviews of *in vitro* studies: a systematic review.

Short title: *SR of reporting quality of SR of in vitro studies*

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Abstract

Background: Systematic reviews (SRs) and/or meta-analyses of *in vitro* research play an important role in establishing the foundation for clinical studies. In this study, we aimed to evaluate the reporting quality of SRs of *in vitro* studies using PRISMA checklist.

Method: Four databases were searched including PubMed, Virtual Health Library (VHL), Web of Science (ISI), and Scopus. The search was limited from 2006 to 2016 to include all SR and/or MA of pure *in vitro* studies. The evaluation of reporting quality was done using the PRISMA checklist.

Results: Out of 7702 search results, 65 SRs were included and evaluated with PRISMA checklist. Overall, the mean overall quality score of reported items of PRISMA checklist was 68%. We have noticed an increasing pattern of the numbers of the published SR of *in vitro* studies over the last ten years. In contrast, *the reporting quality was not significantly improved over the same period* ($p = 0.363$). There was positive but not significant correlation between the overall quality score and the journal`s impact factor of the included studies.

Conclusions: *The adherence of SRs of in vitro studies to the PRISMA guideline was poor; Therefore, we believe that using reporting guidelines and paying attention of journals to this fact will improve more the quality of SRs of in vitro studies.*

Keywords: Reporting quality; Systematic review; Meta-analysis; PRISMA; *in vitro*.

Introduction

In 1979, the Canadian Task Force on the Periodic Health Examination published recommendations about health examination based on medical research with the classification of the level of evidence [1]. Furthermore, in an article of Sackett et al about antithrombotic medications, the levels of evidence have become the cornerstone to building guidelines and clinical recommendations [2]. In the widely accepted hierarchy of evidence-based medicine described by Oxford Centre for Evidence-based Medicine, systematic reviews (SRs) and meta-analyses (MAs) were placed at the highest level in agreement with other grading systems [1, 2, 3]. SRs and MAs provide high-quality information to clinicians and scientists since they meticulously evaluate and analyze the whole body of evidence to answer a specific research question. These studies, however, can have detrimental flaws which might mislead physicians and scientists in their clinical practice or research. The two major factors considered in evaluating the thoroughness of the conduct of SRs are reporting quality and risk of bias assessment. Transparency in reporting design, conduct, and analysis of the studies will allow the scientific community to adequately identify limitations, increase the reproducibility of data, and judge the reliability of the findings. Therefore, reporting quality has called attention in different types of studies.

Although several reporting guidelines are available according to the study design, and are also enforced by some journals, the quality of reporting still has room for improvement [4, 5, 6, 7, 8, 9, 10, 11, 12]. [6, 12]. [7] [11]. [8, 9, 10]. The applicability of results from the poorly reported studies should be questioned. Overall, the transparency in the documentation of clinical studies has increased due to implementation of the reporting guidelines, a common agreement among authors and editors is still needed to improve the quality of reporting furthermore. In 1996, a scientific group developed a guidance called the QUOROM Statement (QUality Of *R*eporting Of Meta-analyses) for reporting meta-analysis [17]. After that a meeting in June 2005, was held to update QUOROM yielded in an international survey for review authors, consumers and groups use systematic review and meta-analysis. Survey's results were used to update QUOROM, which was renamed as PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) [18]. The PRISMA checklist consists of a 27-item and a four-phase flow diagram, which aims at improving the reporting of systematic reviews and meta-analyses.

Regarding *in vitro* studies, reporting quality is vital as well. Data from *in vitro* research establish the foundation on which clinical studies advance. Owning several high-tier journals, Nature Publishing Group set an example of good practice in maintaining reporting quality. The potential authors are requested to follow their checklist on reporting experimental design, statistics, describing agents, methods, data deposition policy, presenting electrophoresis, gel data, and other factors before submitting their papers [19]. Nature editors suggested additional guidelines for each type of study: Animals in Research: Reporting In Vivo Experiments (ARRIVE) for animal preclinical research, Reporting recommendations for tumor MARKer prognostic studies (REMARK) in studies on the biomarker, Biospecimen reporting for improved study quality (BRISQ) to describe biospecimen [20, 21, 22]. For SRs/MAs, although there are no specific reporting guidelines dedicated for SRs of *in vitro* studies, Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) became highly recommended for both clinical and preclinical fields [18, 23, 24]. Hence, we aimed to evaluate the reporting quality of *in vitro* SRs using the PRISMA tool, which includes critical reporting items for SRs.

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Methods

Search strategy

Based on the recommendations of preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [18], this systematic review was conducted by searching four databases including Pubmed, Virtual Health Library (VHL), Web of Science, and Scopus. Search terms were "*in vitro*"[All Fields] AND ("systematic review"[All fields] OR "meta-analysis"[All fields] OR "meta-analysis"[Publication Type] OR ("Cochrane Database Syst Rev"[Journal] OR ("cochrane"[All Fields] AND "database"[All Fields] AND "syst"[All Fields] AND "rev"[All Fields]) OR "cochrane database syst rev"[All Fields])). The search was done on October 2016 and there were no restrictions but the publication date that was limited from 2006 to 2016.

Selection criteria and data extraction

We included all SRs and/or MAs of pure *in vitro* studies in which only *in vitro* studies were included. *In vitro* study was defined as the technique that is performed in controlled environment outside of a living organism. Excluding combined or *ex vivo* studies.

Independently, three reviewers assessed title and abstract of studies for commitment to eligibility criteria after duplicate removal using Endnote X7 program (Thompson Reuter, USA). One round of full-text screening was conducted by two or three independent reviewers to make sure that included studies meet the eligibility criteria. Data extraction from included papers was conducted in multiple rounds. At each round, three reviewers independently extracted data into an Excel sheet containing the items of PRISMA checklist. We also recoded the publication year, 2016 journal`s impact factor (IF) where the included papers were published and It was extracted from the Web of Science database, country of the first authors, and a number of countries of all co-authors where applicable for each included study. Then, reviewers underwent discussion to resolve any conflict. The decision of screening and extraction was always taken by consensus of all reviewers and when a disagreement occurred, a consensus decision was reached after consulting with the supervisor (NTH).

Assessment of the reporting quality

Eligible studies were evualted with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [25]. The PRISMA statement is a list of twenty-seven items that are recommended to ensure the reporting quality of systematic reviews. Each item is judged to be one of three reposponses we have developed to evaluate the adherence of each paper to the PRISMA guideline. These responsese are “applicable and reported”, “applicable and not reported”, or “not applicable nor reported” response scored with (1), (0), and (NA) respectively. Applicable means that this item could be evaluated in the study. The overall quality score was calculated by dividing the total score of the applicable and reported items upon the number of applicable items. In the present study, each review was evaluated independently by three reviewers and the consensus was reached out after discussion. The supervisors (NTH, KH) were consulted when disagreement occurs.

Statistical analysis

The evaluation of each item of PRISMA checklist was based on three responses; “applicable and reported”, “applicable and not reported”, or “not applicable nor reported” scored with (1), (0), and (NA) respectively. Statistical analyses were performed using the Statistical Package for the Social Sciences (version 22.0, SPSS Inc, Chicago, IL, USA). Regarding the responses, data were presented as median and interquartile range (IQR). Data were first analyzed for normality and decision were based on Shapiro-Wilk test result. Spearman`s correlation test was used to test the correlation between the overall score and IF.

Univariable and multivariable logistic regression analyses were used to determine the association between PRISMA score and some important predictors, which included year of publication, presence of meta-analysis, and journal's impact factor. Linear regression was used to test the trend of overall score over the search period. The trend of the overall score and SR of *in vitro* studies over the publication year were presented in form of scatter plots. Two-tailed significance levels of < 0.05 were considered to indicate statistical significance.

Results

Study selection

The search strategy identified 7702 potentially relevant records on 10th of October 2016. After removal of duplicates, we had 7624 papers. After screening titles and abstracts, we retrieved 111 full-text papers for more detailed information. Finally, 65 papers met the eligibility criteria and were included in the review. Flow diagram summarizes the process of studies selection and the reasons for exclusions (Fig. 1).

Study characteristics

The publication period of the 65 eligible studies ranged from 2007 to 2016. All included studies were systematic reviews of *in vitro* studies published in the English language. The country of the first author was Brazil in 13 articles (21.5%), Netherlands in eight (12.3%), five articles (7.6%) for each of Iran and Canada, USA in four articles (6.1%), three articles (3%) for Italy, two articles for Switzerland, New Zealand, and China, and one article for each of Australia, Austria, Belgium, Brunei, Ghana, Germany, Greece, Indonesia, India, Israel, Jordan, Korea, Liechtenstein, Mexico, Norway, Saudi Arabia, Sweden, Slovenia, Portugal, Turkey, and UK. Study characteristics and result summary of the overall frequency of reporting items are in Table 1 and Table 2, respectively.

168 **Table 1. Study characteristics of the included studies**

Geographic distribution	Author/publication year	Country of the first author	Journal	IF (2016)	Score*
Europe	**Boersema/2016** [26]	Netherlands	BioResearch Open Access	No IF	0.6
	van Heumen/2008 [27]	Netherlands	Dental Materials	3.93	0.68
	Snijder/2015 [28]	Netherlands	Biomedizinische Technik	No IF	0.65
	Louropoulou/2015 [29]	Netherlands	Clinical Oral Implants Research	3.46	0.95
	Montano/2010 [30]	Netherlands	Toxicological Sciences	1.22	0.5
	Dobbenga/2016 [31]	Netherlands	Acta Biomaterialia	6	0.5
	Behring/2008 [32]	Netherlands	Odontology	1.53	0.5
	Golbach/2016[33]	Netherlands	Environment International	5.92	0.7
	Gizzo/2015 [34]	Italy	European Journal of Cancer Prevention	2.415	0.6
	Rotelli/2015 [35]	Italy	Surgical Oncology	3.65	0.43
	Salamanna/2016 [36]	Italy	Oncotarget	5	0.96
	Coray/2016 [37]	Switzerland	Journal of the Mechanical Behavior of Biomedical Materials	2.87	0.66
	Finnema/2010 [38]	Switzerland	American Journal of Orthodontics and Dentofacial Orthopedics	1.6	0.72
	Moreira/2015 [39]	Portugal	Clinical implant dentistry and related research	4.152	0.59
	Papia/2014 [40]	Sweden	Journal of Biomedical Materials Research Part B: Applied Biomaterials	2.881	0.56
	Bleuel/2015 [41]	Germany	PLoS ONE	4.41	0.63
	Napotnik/2016 [42]	Slovenia	Bioelectrochemistry	3.55	0.88
	Baumeister/2016 [43]	UK	Psychopharmacology (Berl)	3.54	0.78
	Tzanakakis/2016 [44]	Greece	Journal of Prosthetic Dentistry	NA	0.45
	Nilsen/2016 [45]	Norway	European Journal of Oral Sciences	1.6	0.59
	Schmid-Schwap/2011 [46]	Austria	Dental Materials	3.93	0.62
	Bonczkowski/2016 [47]	Belgium	AIDS Reviews	2.06	0.54
	Heintze/2008 [48]	Liechtenstein	Dental Materials	3.93	0.64
Asia	**Shahravan/2007** [49]	Iran	Journal of Endodontics	2.904	0.81
	Khalesi/2015 [50]	Iran	Journal of Pediatric Gastroenterology and Nutrition	2.4	0.62
	Samiei/2016 [51]	Iran	*Materials Science and Engineering C: Materials for Biological Applications*	3.42	0.6
	Motamedian/2015 [52]	Iran	World Journal of Stem Cells	No IF	0.52
	Tabatabaei-Malazy/2012 [53]	Iran	Journal of Pharmacy & Pharmaceutical Sciences	2.33	0.54
	Ni/2015 [54]	China	International Journal of Antimicrobial Agents	4.09	0.74
	Xiao/2011 [55]	China	American Journal of Nephrology	2.6	0.68

	Ilango/2015 [56]	India	International Journal of Current Pharmaceutical Review and Research	No IF	0.22
	Rahman/2016 [57]	Brunei	Brain Research	2.56	0.68
	AlShwaimi/2016 [58]	Saudi Arabia	Journal of Endodontics	2.9	0.7
	Ahn/2016 [59]	Korea	Journal of Endodontics	2.9	0.63
	Masarwa/2016 [60]	Jordan	Journal of Evidence-Based Dental Practice	No IF	0.69
	Jayanegara/2014 [61]	Indonesia	Asian-Australasian Journal of Animal Sciences	0.75	0.59
	Zusman/2013 [62]	Israel	Antimicrobial Agents and Chemotherapy	4.41	0.74
	Yaylali/2015 [63]	Turkey	Journal of Endodontics	2.9	0.83
South America	**Lenzi/2016** [64]	Brazil	International Journal of Paediatric Dentistry	1.303	0.96
	Altmann/2016 [65]	Brazil	Orthodontics & Craniofacial Research	1.64	0.92
	Pereiraa/2015 [66]	Brazil	Journal of the Mechanical Behavior of Biomedical Materials	2.876	0.81
	de Rosa/2015 [67]	Brazil	Journal of Dentistry	3.109	0.81
	Moraes/2015 [68]	Brazil	Operative Dentistry	2.819	0.85
	Chaves/2012 [69]	Brazil	Journal of Prosthetic Dentistry	NA	0.73
	Kaizer/2014 [70]	Brazil	Dental Materials	3.931	0.68
	Aurelio/2016 [71]	Brazil	Dental Materials	3.931	0.81
	Pavan/2015 [72]	Brazil	PLoS One	4.41	0.89
	Bernades/2014 [73]	Brazil	The Journal of the American Dental Association	1.76	0.72
	da Costa/2013 [74]	Brazil	The Journal of Adhesive Dentistry	1.59	0.62
	Sarkis-Onofre/2014 [75]	Brazil	Operative Dentistry	2.81	0.92
	Skupien/2015 [76]	Brazil	Brazilian Oral Research	0.85	0.73
North America	**Lee/2008** [77]	USA	Journal of Prosthetic Dentistry	NA	0.54
	Bates/2015 [78]	USA	Clinical Biomechanics (Bristol, Avon)	1.636	0.59
	Pasipanodya/2015 [79]	USA	Clinical Infectious Diseases	8.736	0.75
	Arilla/2015 [80]	USA	Arthroscopy	3.7	0.92
	Ting/2016 [81]	USA	European Journal of Oral Sciences	1.6	0.59
	Nassar/2011 [82]	Canada	Journal of Prosthetic Dentistry	NA	0.63
	Ehsani/2009 [83]	Canada	The Angle Orthodontist	1.5	0.72
	Passos/2014 [84]	Canada	Journal of Prosthodontics	1.133	0.77
	Archambault/2010 [85]	Canada	The Angle Orthodontist	1.2	0.72
	Contreras-Ochoa/2012 [86]	Mexico	Parasitology Research	1.538	0.68
Oceania	**Tong/2015** [87]	New Zealand	Human Reproduction Update	11.194	0.77
	Peplow/2013 [88]	New Zealand	Cytokine	2.94	0.63
	Nawafleh/2016 [89]	Australia	Journal of Prosthodontics	1.133	0.6
Africa	**Fokou/2015** [90]	Ghana	Journal of Ethnopharmacology	3.05	0.5

*Overall score was calculated as (total score of applicable and reported items/total score of applicable and reported & applicable and not reported items) to PRISMA statement

IF 2016 was extracted from the Web of Science database.

IF: impact factor; NA: no 2016 IF in the database for this journal.

173 **Table 2. Result summary of reported items of PRISMA checklist among the included 65 studies.**

Items	Total number of applicable papers of each item, n (%)	Number of papers reporting that item, n (%)
Title	65 [100]	58 [89.2]
Abstract	65 [100]	42 [64.6]
Introduction		
Rationale	65 [100]	65 [100]
Objectives	65 [100]	62 [95.4]
Methodology		
Protocol registration	65 [100]	4 [6.1]
Eligibility criteria	65 [100]	64 [98.5]
Information sources	65 [100]	64 [98.5]
Search	65 [100]	62 [95.4]
Study selection	65 [100]	59 [90.8]
Data collection	65 [100]	47 [72.3]
Data items	65 [100]	29 [44.6]
Risk of bias in individual studies	65 [100]	17 [26.2]
Summary measures	36 [55.3]	28 [77.7]
Synthesis of results	32 [49.2]	27 [84.3]
Risk of bias across Studies	65 [100]	13 [20]
Additional analysis	24 [36.9]	15 [62.5]
Result		
Study selection	65 [100]	58 [89.3]
Study characteristic	65 [100]	58 [89.3]
Risk of bias in individual studies	65 [100]	19 [29.2]
Results of individual studies	65 [100]	61 [93.8]
Synthesis of result	26 [40]	20 [76.9]
Risk of bias across studies	65 [100]	12 [18.5]
Additional analysis	20 [30.7]	12 [60]
Discussion		
Summary of evidence	65 [100]	63 [96.9]
Limitations	65 [100]	28 [43.1]
Conclusion	65 [100]	64 [98.5]
Funding	65 [100]	31 [47.7]

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Synthesis of the results

Title and abstract

Titles in 89.2% (58/65) of articles contained the terms "SR or MA". Structured abstract was reported in 64.6% (42/65) of applicable articles.

Introduction (objectives and rationale)

All articles' introductions were found to be properly addressing the rationale item. The objectives item was reported in the majority of articles 95.4% (62/65). Three articles did not fulfill the PRISMA statement in reporting the objective items. One of them was found stating the objectives as reviewing new developments of the certain topic instead of providing an explicit statement of questions need to be addressed according to PRISMA statement requirements, as this article was published in world journal of stem cells which has no IF [52].

Methods items

Contrary to PRISMA statement requirements of reporting the existence, web address and the registration number of articles' protocols, only four articles reported protocol and registration item representing 6.1% of included articles. Two papers were registered in Prospero database [64, 91] while the third papers provided the protocol as an appendix of their paper at the journal website [92]. In contrast, one paper reported having protocol but with no information about if it registered or not [33]. Most of the articles specified criteria for eligibility as study characteristics and report characteristics but only one article did not fulfill this item [56]. All authors reported the searched databases of peer-reviewed literature with addressing dates of coverage besides reporting using reference lists if done except one article.[56] For search and study selection items, most of the articles addressed it with 95.4% (62/65) and 90.8% (59/65), respectively. However, there was no standard statement for reporting the study selection item. We considered it fulfilled if authors used a flow diagram or explained this process as paragraph identifying how they retrieved or excluded papers in their reviews and if any disagreements were found and how they were resolved.

Data collection item was reported in 72.3% (47/65) of articles. However, less than half reported specific data items with 44.6% (29/65). The only fifth of papers has reported the risk of bias across studies item while about quarter of included articles have reported the risk of bias in the individual studies item. The summary measures and synthesis of results items

were reported widely with 77.7% (28/36) and 84.3% (27/32) of the applicable articles, respectively. Additional analysis of data deals with the further analysis of subgroups or meta-regression [25], it was found applicable and reported only in 62.5% (15/24) of the applicable articles.

Result items

Concerning study selection item, most of the articles 89.3% (58/65) reported it in a paragraph or explained it with a flow diagram. They described clearly all screening process, the number of all screened studies, gave the reasons for exclusion of each. Then, they gave the number of the included studies that met the eligibility criteria and noted if there was a duplication. Meanwhile, most of the articles 89.3% (58/65) fully addressed study characteristics items in a table which included the study size, follow-up period and other specified characteristics. Reporting it provides a narrative summary of studies which allow the comparison between the main characteristic of the studies included in the review.

Only 29.2% (19/65) reported data on the risk of bias in each study and quality assessment for each of them while 18.5% (12/65) of the applicable articles reported the risk of bias across studies item. Reporting only summary data was inadequate because it failed to inform readers which studies had the particular methodological shortcoming. It was difficult for some of the included studies to assess the risk of bias because assessing the internal validity of a study requires adequate reporting of the study which was mostly poor and may require additional information from investigators as well. The synthesis of results and additional analysis items were reported in 76.9% (20/24) and 60% (12/20) of the applicable articles, respectively.

Discussion items

Almost all articles 96.9% (63/65) reported the “summary of evidence” item. They summarized the main finding for each main outcome. Only two articles (3.1%) did not fulfill this item due to the poor quality of reporting. Less than half of the articles 43.1% (28/65) discussed the limitations at study and outcome level. This discussion addressed the validity of reporting of the included studies, the limitations of the review process and the generalizability of the review. The conclusion item was reported in almost all articles with 98.5% (64/65). While funding item was reported in only 47.7% (31/65) of applicable articles.

Correlation and regression between the overall quality score and important factors

Journal`s IF of the fifty-six papers were reported (*Median*= 2.89, *IQR*= 2.29) and average overall quality score was (*M*= 0.68, *SD*= 0.14). Spearman`s rho test indicated positive correlation but not significantly between the overall quality score and the IF, r = 0.209 (p = 0.12) (Figure 2). The uni- and multivariable analyses between PRISMA score and some important predictors, which included year of publication, presence of meta-analysis, and journal's impact factor, showed that only the presence of meta-analysis within the systematic review statistically affected to the PRISMA score. If a systematic review included meta-analysis, its PRISMA score would increase 0.08 points (95% CI: 0,011; 0.15) after adjusting for year of publication and journal's impact factor (Table 3).

Table 3. *Association between PRISMA score and some important predictors through univariable and multivariable linear regression*

Factor	Univariable linear analysis			Multivariable linear analysis		
	Coef.	95%CI	P value	Coef.	95%CI	P value
Year of publication	0.006	-0.008; 0.020	0.375	0.008	-0.006; 0.021	0.273
Presence of meta-analysis	**0.099**	**0.031; 0.167**	**0.005**	**0.080**	**0.011; 0.150**	**0.024**
Journal's impact factor	0.011	-0.009; 0.030	0.283	0.011	-0.008; 0.031	0.240

Trend of SR of in vitro studies over the search period

The trend of published SR of *in vitro* studies was markedly increased over the period as shown in Figure 3A. Regression analysis revealed the trend of overall quality score was not significantly increasing over years (coefficient of correlation beta = 0.11, p = 0.363) (Figure 3B).

Agreement between three reviewers by each PRISMA's item

Among 27 items of PRISMA checklist, 12 items had the agreement of three reviewers which was 'almost perfect', i.e., the Kappa's index was above 0.90; 11 items had 'strong' agreement of three reviewers, i.e., the Kappa's index was in between 0.80 and 0.90. There were 4 items with 'moderate' agreement of three reviewers, i.e., the Kappa's index was in between 0.60 and 0.79 (Table 4).

Table 4. *Agreement between three reviewers by each PRISMA's item*

Items	Kappa's index	Level of Agreement
Title	1.000	Almost perfect
Abstract	0.908	Almost perfect
Introduction		
Rationale	1.000	Almost perfect
Objectives	0.870	Strong
Methodology		
Protocol registration	0.944	Almost perfect
Eligibility criteria	0.745	Moderate
Information sources	0.745	Moderate
Search	0.895	Strong
Study selection	0.942	Almost perfect
Data collection	0.901	Almost perfect
Data items	0.937	Almost perfect
Risk of bias in individual studies	0.900	Strong
Summary measures	0.900	Strong
Synthesis of results	0.982	Almost perfect
Risk of bias across Studies	0.746	Moderate
Additional analysis	0.887	Strong
Result		
Study selection	0.893	Strong
Study characteristic	1.000	Almost perfect
Risk of bias in individual studies	0.854	Strong
Results of individual studies	0.918	Almost perfect
Synthesis of result	0.891	Strong
Risk of bias across studies	0.843	Strong
Additional analysis	0.917	Almost perfect
Discussion		
Summary of evidence	0.651	Moderate
Limitations	0.895	Strong
Conclusion	1.000	Almost perfect
Funding	0.846	Strong

Discussion

In this systematic review, we used the PRISMA checklist to evaluate the reporting quality of SRs of *in vitro* studies. Generally, the mean overall score of reported PRISMA

items was 68% which indicate a moderate adherence of SR of *in vitro* studies to PRISMA checklist. It was noticed also that the trend of published SR of *in vitro* studies was increased recently. There were eight items reported in less than 50% of the applicable studies, they included four items in the methodology section, two items in the results section and two items in discussion sections. Items of methodology section included 1) protocol registration with 6.1%, 2) data items with 44.6%, 3) risk of bias in individual studies with 26.2%, and 4) risk of bias across studies with 20% of applicable articles. In the results section, the risk of bias in individual and across studies items were associated with 29.2% and 18.5% of applicable articles, respectively. Finally, limitations and funding items in discussion section were associated with low reporting of 43.1% and 47.7%, respectively. Our result was quite similar to other reviews of reporting quality of SR of urology [93], orthopedic [94], acupuncture [95], diagnostic research [96], and other medical fields [97, 98, 99, 100]. The highest reporting quality was in SR of urology [93], while the lowest was in SR of burn care management [100].

Protocol registration is the most unfulfilled item of PRISMA checklist although registration becomes more common. In an SR on reporting quality of SRs in vascular surgery, Tan et al reported only one out of 74 articles mentioning this item [101]. Registration can help eliminate the waste of conducting several SRs which address the same research question and reduce post hoc bias associated with selective outcome reporting [18]. Therefore, data has shown a positive association between protocol registration and quality of that SR/MA of studies in pediatric surgery [97].

The risk of bias of individual studies and across studies, data items, limitations, funding, and additional analysis are other under-reported items in this SR, as in other SRs of clinical studies [100, 102]. The accuracy of findings from SRs depends on the reliability of included studies, which can include research with poor methodological quality in meta-analysis and mislead the results. Listing and defining all variables, describing methods of additional analyses, as well as discussing limitations are also important to improve the transparency of SR. Last but not least, financial disclosure should be mandatory for every kind of research, including SR. Several authors observed that the results of studies are more likely to favor the sponsor’s products, exaggerate effects, and conceal harms [18].

Reviewers have found only five items from PRISMA statement that are "not applicable and not reported". They included Summary Measures, Synthesis of Results and

Additional Analysis from methodology section and Risk of Bias Across studies and Additional Analysis from results section. In sum, it appears that there are more SRs being published in basic sciences and preclinical research, yet their reporting quality remains a concern. PRISMA guideline was found to have potential limitations and be more generic in use instead of being standardized to various review types and it is not sufficient to evaluate the reporting quality if it used alone[103]. Therefore, Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guideline was found to be more detailed and reach the depth of evaluating the reporting quality and it was recommended to use both in the epidemiological reviews[103]. In this systematic review, we have faced several limitations. First, the limitation of our study to a certain range of publication year and study design might lead to missing some valuable data either before the limited years or in combined *in vitro* and *in vivo* studies. Second, we could not able to register our protocol in PROSPERO databases as they did not accept of *in vitro* studies. Third, the analysis revealed no significant increase of the trend of overall quality score over the year and that may be because of small sample size which is not enough to detect a significant increase. Thus, more *in vitro* studies are warranted to achieve that. Finally, more attention and evaluation should be done for the various *in vitro* techniques in order to know the reporting quality of each subset which we could not able to evaluate that in our paper.

Conclusion

The adherence of SRs of in vitro studies to the PRISMA guideline was less than optimal; Therefore, we believe that using reporting guidelines and paying attention of journals to this fact will improve more the quality of SRs of in vitro studies. Although, there are several items of PRISMA guideline that do not fit the designing and reporting of SRs of in vitro studies, it can be used until it gets improved. In addition, more attention should be paid to develop specific guideline to SRs of in vitro studies.

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Conflict of interest

None.

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Figure legend

Figure 1. Flowchart of the search strategy of this systematic review of *in vitro* studies - Summary of how the systematic search was conducted and eligible studies were identified (PRISMA flow diagram). PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Figure 2. Scatter plot showing the relationship between the overall score and journal`s impact factor (IF) - Spearman`s rho test indicated positive correlation but not significantly between the overall quality score and IF, r = 0.209.

Figure 3. Trend of SR of *in vitro* studies and overall quality score over the year- A- The number of SRs of *in vitro* studies published per year. B- Regression analysis revealed the trend of overall quality score was not significantly increasing over years (coefficient of correlation beta = 0.11, p = 0.363).