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«Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική και Κλινική Βιοπληροφορική»

ΤΙΤΛΟΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ

«Assess the reporting quality of RCTs for Platelet-Rich Plasma in the treatment of knee osteoarthritis published from 2011 to 2021 using the CONSORT statement»

«Αξιολόγηση της ποιότητας τυχαιοποιημένων κλινικών μελετών της θεραπευτικής ικανότητας του πλάσματος πλούσιου σε αιμοπετάλια στη θεραπεία της οστεοαρθρίτιδας του γόνατος οι οποίες δημοσιεύθηκαν μεταξύ 2011 και 2021 χρησιμοποιώντας το εργαλείο CONSORT»

Τριμελής Επιτροπή

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A. ABSTRACT

Background Platelet-Rich Plasma (PRP) injection is an encouraging treatment alternative of knee osteoarthritis (OA). The aim of this study is to assess the reporting quality of RCT studies using CONSORT statement.

Methods PubMed were systematically searched for RCT evaluating the therapeutic accuracy of PRP in knee OA published from inception through 2011-2021. Quality of reporting was assessed using CONSORT statement, an evidence-based tool consisting of 37 items. For each item and each study included an overall score was calculated. The correlation between the adherence and the variables: year of publication, H-index of first author, journal's impact factor, number of participants and references; was also investigated.

Results The search yielded 13 eligible studies. The mean study CONSORT score was 62.16% (range 51.51%-72.81%, SD 31.9%). Three studies reported less than the 50% of the items whereas 3 out of 13 included studies scored ≥70% but 2 of them scored ≥ 75%.CONSORT had no significant impact on the score of subsequent studies.

Conclusions Careful assessment is required to guarantee the critical appraisal and the credibility of a study

Abbreviations

PRP, Platelet-Rich Plasma
OA, osteoarthritis
RCT, Randomized controlled trials
CONSORT, Consolidated Standards of Reporting Trials

Keywords

Consort, statement, Platelet-Rich Plasma, PRP, osteoarthritis, OA, knee, Randomized controlled trials, RCT
Οστεοαρθρίτιδα, Πλάσμα Πλούσιο σε Αιμοπετάλια, Γόνατο, Ενοποιημένα Πρότυπα Δοκιμών Αναφοράς

B. INTRODUCTION

Osteoarthritis and the role of PRP

Osteoarthritis (OA) is the most common joint disease, which is characterized by progressive loss of joint cartilage, subchondral bone sclerosis, changes in the synovial membrane and reduced viscosity of the synovial fluid [1]. The most commonly affected joint is the knee, and the rate of knee OA has been reported as 30 % in subjects over 50 years of age examined by radiographic imaging [2]. There is no definitive treatment method to stop progression of OA. However, sort of treatment methods, such as modification of daily activities, some medical treatment, or physiotherapy, intra-articular injections and joint replacement, have the primary goal of relieving the scale pain and enhancing joint functions [3]. The most appropriate treatment choice for the patient depends on the clinical history, contraindications to specific treatments and the way well the patient would be ready to tolerate the treatment being considered. Especially in cases where the target patient group is of advanced age and straightforward treatment methods haven't been successful, physicians have increasingly preferred injections due to the potential side effects of non-steroidal anti-inflammatory drugs (NSAIDs) [3]. Topical medications are often used for short-term relief, but are not effective in cases of severe OA [4]. The knee joint cartilage is non-vascular. Given that nourishment is predicated on diffusion, as intra-articular injections are given at high concentrations, they need become the well-liked method in cartilage regeneration. Various intra-articular agents have been developed for this purpose [5, 6, 7].

Among these developments, intra-articular mucopolysaccharide (HA) injection, which is widely utilized in knee OA, is a crucial component of synovia. HA plays a key role in lubrication of the articular surface, reduces the stress on weight-bearing surfaces and transports chondronutriive substances coming from the synovium. HA concentrations in the synovial fluid of osteoarthritic knees have been shown to be reduced [8]. HA injections have a task within the treatment of OA thanks to its viscoinduction properties, which stimulate endogenous HA expression from the synovium, and viscosupplementation increases the viscoelasticity [9].

PRP is an autologous biologic treatment made from the patient's own plasma, which is obtained at a higher concentration than full blood, is an encouraging treatment option. Biologically active proteins expressed by active platelets cause organic phenomenon by binding to the trans-membrane receptors within the target cells. As a result, cellular recruitment, growth and morphogenesis are triggered and, at the same time, inflammation is reduced [10]. Thus, as a minimally invasive treatment option, it has been widely used in clinical studies [11]. PRP injection has been presented as an encouraging treatment alternative for cartilage damage associated with arthrosis or sporting injuries [12, 3. Long term clinical effectiveness has been shown by the treatment of knees with OA [12]. There is a plethora of studies examining the therapeutic accuracy of PRP in the treatment of knee OA. Aim of our study is to assess the reporting quality of these studies using the CONSORT statement.

The Consort statement

Randomized controlled trials (RCTs) are generally accepted as the gold standard for assessing the effects of health care interventions [13]. However, should they lack methodological rigors; RCTs may submit to misleading results [14]. Adequate reporting of RCTs is one among critical methodological issues, since the knowledge reported has profound impact on the choices by healthcare professionals and policy makers. Previous studies showed that RCTs with poor reporting, in comparison to those with good reporting, grant larger effect estimates across a spread of healthcare conditions [15]. In order to enhance the reporting of RCTs, scientific communities have made great efforts to develop recommendations, like the Consolidated Standards of Reporting Trials (CONSORT) statement which aims to improve the general reporting of RCTs [16, 17]; in this way, one should appraise the quality of RCTs before any clinical decision making. This assessment depends on an honest reporting/writing of the methods and results sections of the RCTs. In an attempt to standardize the reporting, a group of experts joined together in 1996 and produced the CONSORT statement,[18] which is a checklist with recommendations for reporting of clinical trials in biomedical literature. This CONSORT statement was revised in 2001, [19] and the most recent one was published in 2010 [20, 21]

C. METHODS

Search strategy

A search was performed PubMed with results included from inception. The search strategy for Pubmed was “osteoarthritis disease” OR “OA” AND “Plasma-Rich Plasma” OR “PRP” AND “treatment” and including only RCT. Eligible studies from auto-alerts were included from 2011 up to 2021. Reference lists of included studies were checked for additional sources.

Inclusion and exclusion criteria

Exclusion criteria were: (1) studies concerning pediatric population, (2) previous knee operations,(3) rheumatoid or autoimmune abnormalities, (4) systematic or metabolic disease, (5) non-English language publications, (6) unpublished studies, (7) animal studies, (8) conference publications and abstracts, (9) duplicated studies

Study selection and assessment of quality

After removing the duplicates of title and abstracts of initial search results were screened for relevance. The full texts of the remaining results were assessed for eligibility based on predetermined criteria. For all included studies the following data were collected: year of publication, journal’s impact factor, citations, first author h-index, references, and number of participants. The reporting quality of the studies was assessed using the CONSORT statement. Every element of the checklist was answered “YES”, “NO”, with each “YES” scoring 1 point. Each one of 37 items was weighted equally. An overall reporting quality score percentage was calculated for each item and for each study by dividing the number of gathered points by the total available

Statistical Analysis

Statistical analysis was carried out using IBM SPSS Statistics V.25 and Microsoft Excel 2011. Pearson’s and Spearman correlation was used to estimate the correlation between CONSORT and pre-specified variables (year of publication, journal impact factor, citations, first author h-index, references, and number of participants). The normality check and the equality of variances check was performed using the Shapiro-

Wilk and the Levene's test, respectively. A p-value<0.05 was considered as statistical significant.

D. RESULTS

Study search results

Initial search identified 80 potential. After the removal of duplicates and non-relevant articles, 25 articles were full text assessed in accordance to predetermined criteria. After the eligibility evaluation 13 studies were included to the study.

Figure 1 Flow chart of study search, selection, inclusion and exclusion of articles

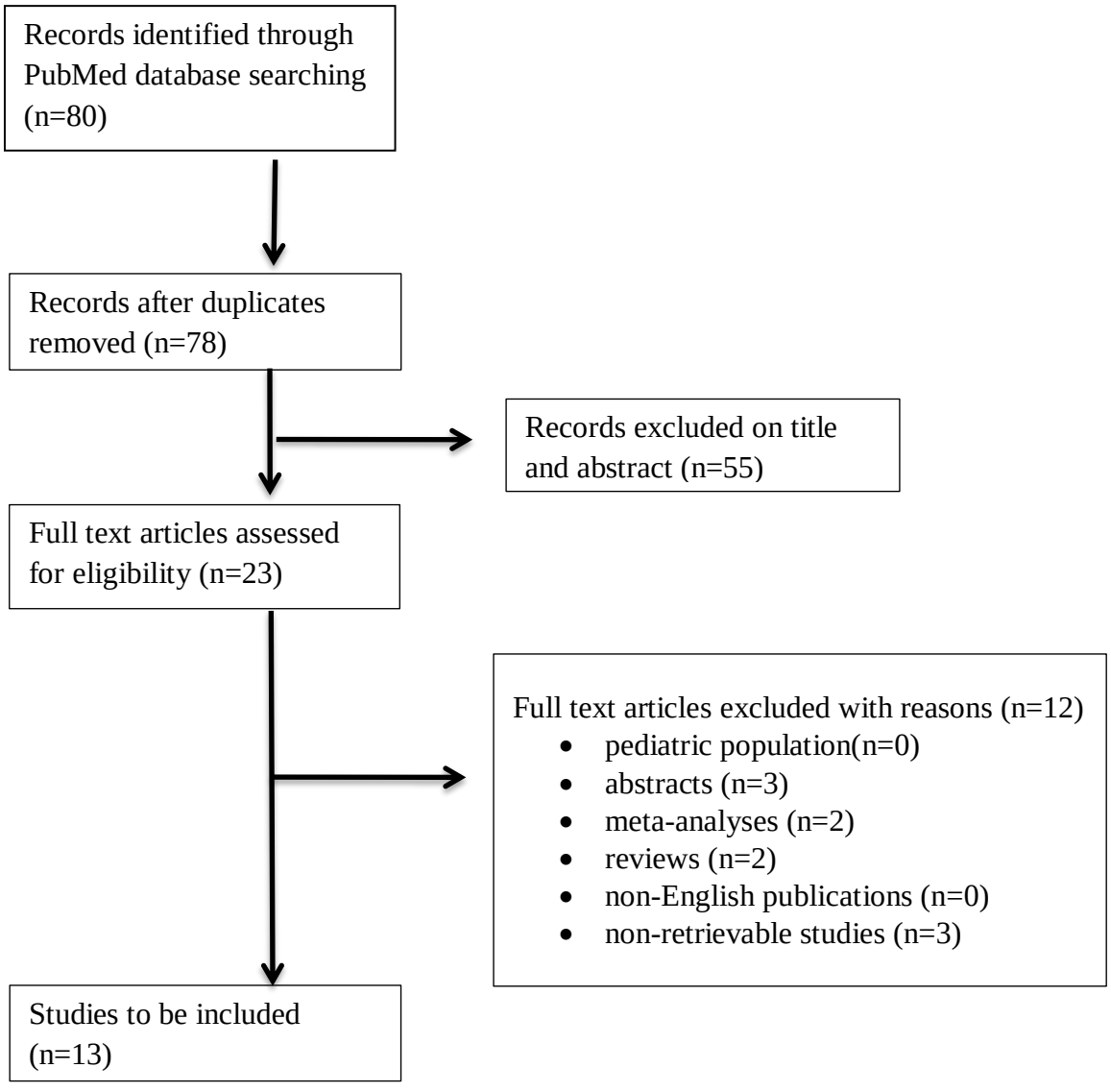


Table 1 **The Consort statement checklist and the score of each item**

Section & Topic
Title and abstract
Introduction
Background and objectives
Methods
Trial design
Participants

Interventions
Outcomes
Sample size
Randomisation: Sequence generation
Allocation concealment mechanism
Allocation concealment mechanism

Implementation
Blinding
Statistical methods

Results
Participant flow (a diagram is strongly recommended)
Recruitment
Baseline data
Numbers analysed
Outcomes and estimation

Ancillary analyses
Harms
Discussion
Limitations
Generalisability

Interpretation
Other information
Registration
Protocol
Funding

The best reported elements were:

- Item 2a, 2b: All the studies had a scientific background and eχplanation of rationale as well as specific objectives or hypotheses(13/13)
- Item 4a: For the aid of the readers, a comprehensive description of the appropriateness criteria are used for the selection of the trial's participants (13/13)
- Item 5: The outline should allow a clinician eager to use the intervention to understand exactly the way to administer the intervention that was evaluated within the trial.[22](13/13)
- Item 6a: Primary and secondary is recommended to be identified and totally explained. Also, equivalent

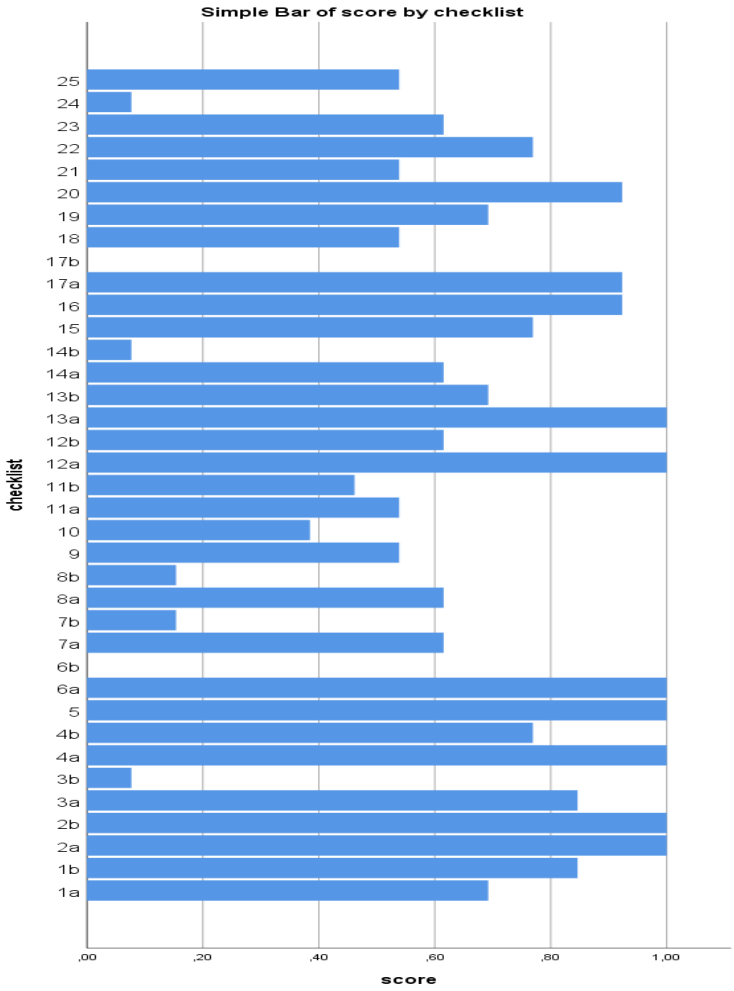


Figure 2 Percentage of studies adequately reporting each CONSORT item

- Item 16: Numbers of participants (denominator) that are comprised in each analysis and if the analysis was by original assigned groups(12/13)
- Item 17a: For each and every outcome, study results should be reported as a synopsis of the result in each group, together with the contrast between the groups, known as the effect size. (12/13)
- Item 20: Trial restrictions, grapple with sources of potential bias, imprecision, and, if relevant, multiplicity of analyses (12/13)

On the contrary, the worst reported elements were:

- Item 3b: Important alters to methods after trial commencement (such as eligibility criteria) and with reasons (1/13)
- Item 6b: Any changes to trial aftermaths posterior to the trial commenced, with reasons (0/13)
- Item 7b: When applicable, explanation of any meantime analyses and stopping guidelines (2/13)
- Item 8b Type of randomization; details of any limitation (such as blocking and block size) (2/13)
- Item 14b: Why the trial ended or was stopped (0/13)
- Item 17b: For binary results, presentation of each absolute and relative effect sizes is suggested (8/13)
- Item 24: Where the full trial protocol can be accessed (1/13)

The variability of the adherence between the different sections of list is notable. The title, the abstract and the introduction parts were reported in an almost excellent level while the "other information" section and "secondary questions" on method's section were disappointing.

The mean study CONSORT compliance was 62.16% (range 51.51%-72.81%, SD 31.9%). No article scored 100%. Kade L. Paterson et al, *2016* [23] was the article of our analysis that attained the highest reporting score 30/37 (88.2%), whereas Fabio Cerza *et al, 2012* [24] marked 15/37 (40.5%)(Figure 2). 3 out of 13 included studies scored ≥70% but 2 of them scored ≥ 75% and 3 study reported < 50% of the items.

Figure 2 CONSORT statement of studies included in the analysis (maximum achievable score: 30/37)

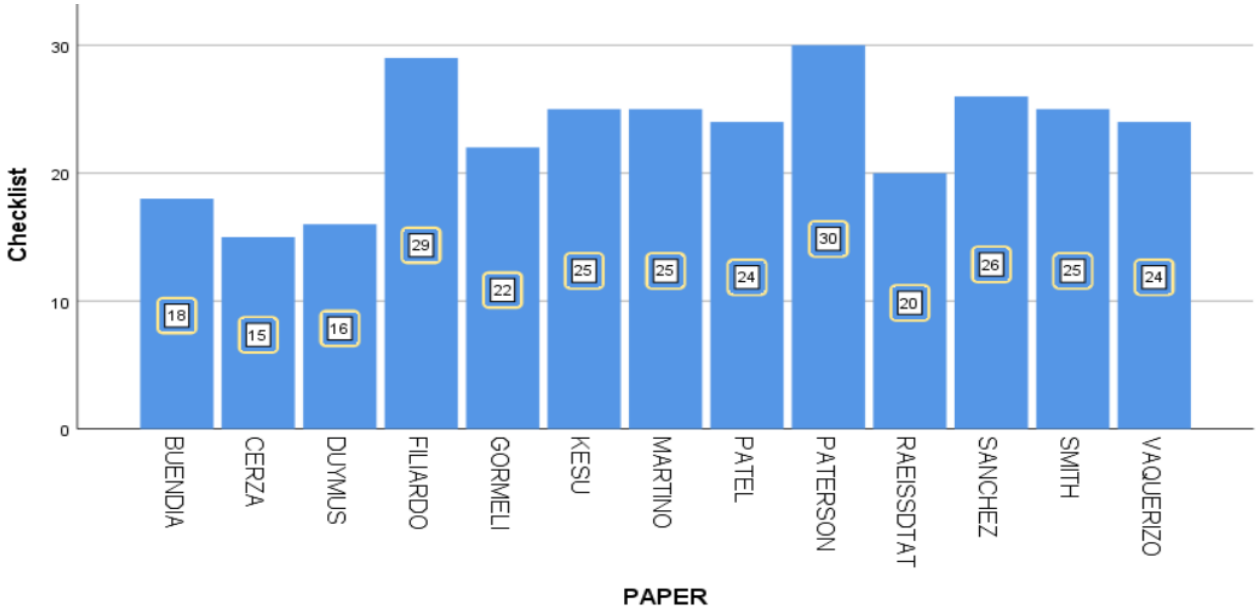


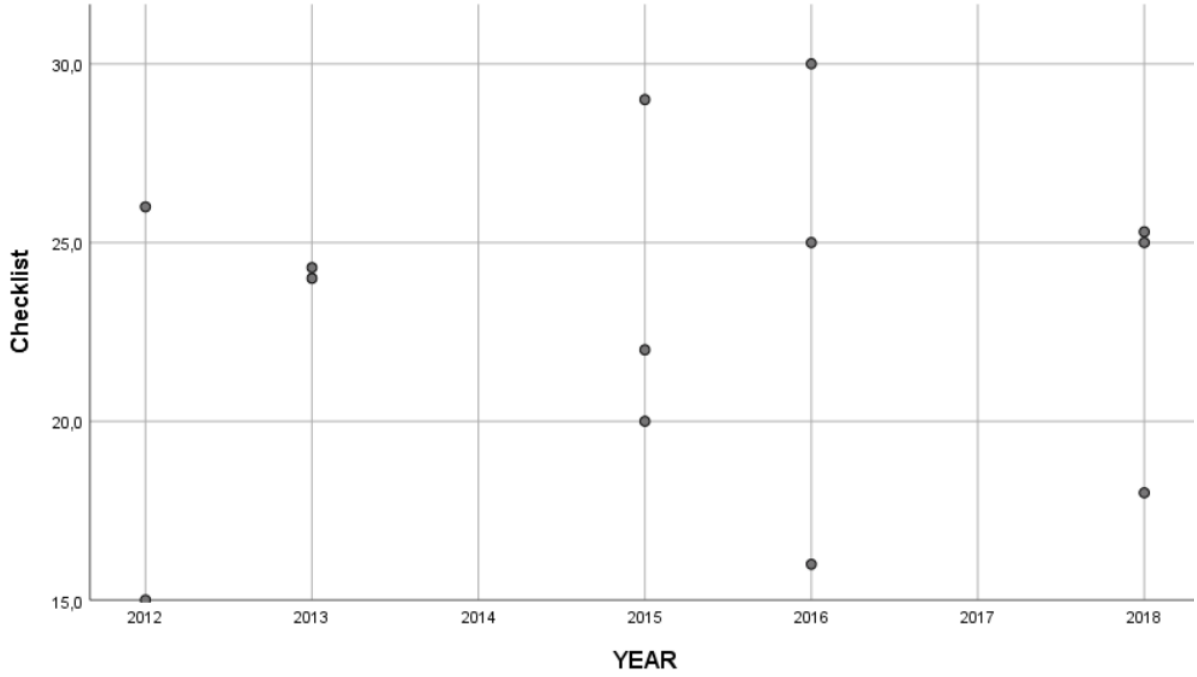
Figure 3 CONSORT score and pre-specified variables

PAPER	SCORE	YEAR	Impact Facor	CITATIONS	H-IDNEX	REFERENCES	PARTICIPANTS
CERZA	15	2012	5,81	105	10	33	120
DUYMUS	16	2016	4,46	52	16	34	102
FILIARDO	29	2015	5,81	83	21	37	443
RAEISSDTAT	20	2015	1,14	84	34	30	87
GORMELI	22	2015	3,17	78	25	33	162
PATEL	24	2013	5,81	178	44	20	78
PATERSON	30	2016	2,05	31	31	42	23
SANCHEZ	26	2012	4,92	97	36	30	176
SMITH	25	2016	5,81	52	56	50	114
VAQUERIZO	24	2013	4,29	62	23	30	96
BUENDIA	18	2018	2,89	33	36	26	106
KESU	25	2018	2,98	46	39	32	99
MARTINO	25	2018	5,81	26	41	39	197

Time trend and CONSORT statement

The CONSORT score had a little increase with time although without statistical significant correlation with the year of publication (r=0.084, p=0.78; figure 3)

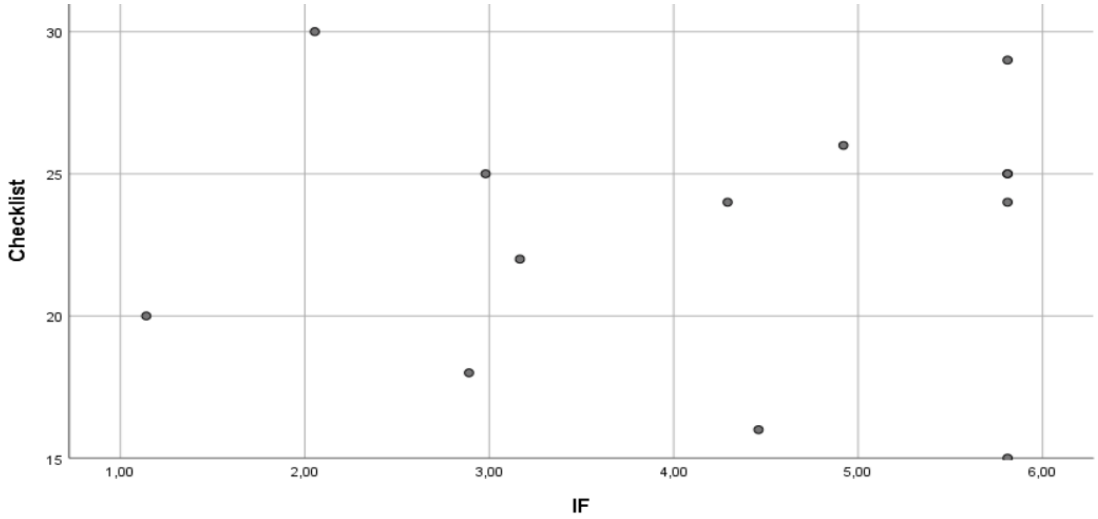
Figure 4 Studies score and year of publication



CONSORT score and other variables

The CONSORT score had no statistically significant correlation neither with journal's impact factor (r=0.046, p=0.88) nor with number of citations (r=0.04, p=0.898). Moreover there is no statistically significant correlation between CONSORT score and first author's h-index (r=0.418, p=0.156) neither with number of references of each paper (r=0.366, p=0.219).

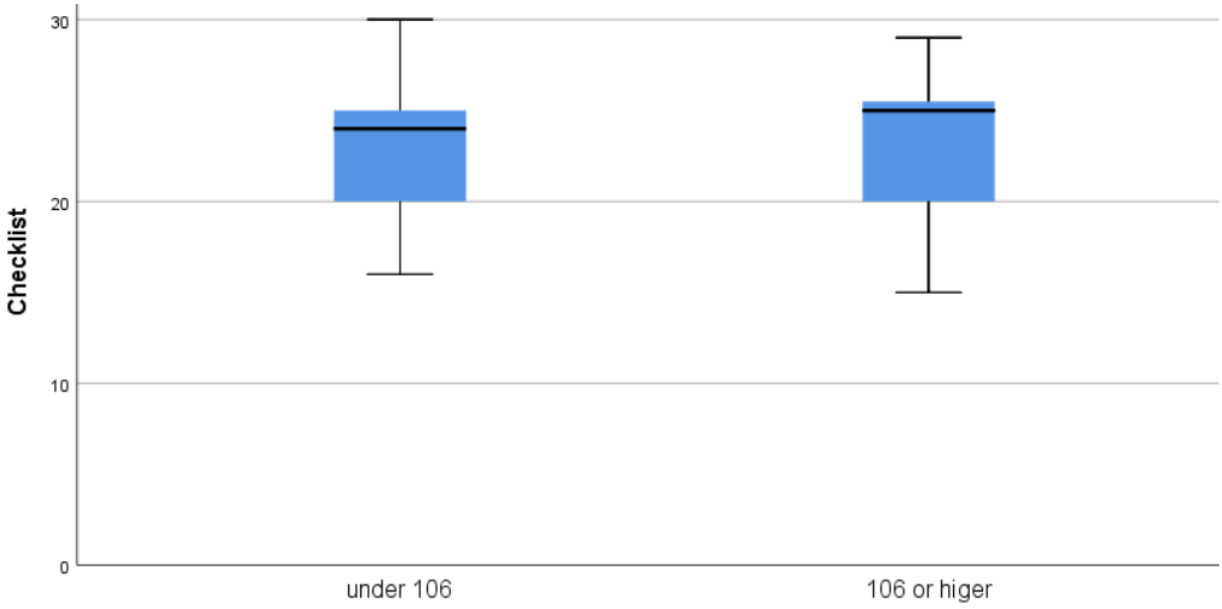
Figure 5: The impact factor and CONSORT score



In addition the numbers of participants and CONSORT score had no statistically significant correlation (r=0.094, p=0.761). Comparison of adherence was conducted between studies with greater and shorter number of participants. As a cut-off n=106 was selected, since it represented the 50th quartile of the number of participants of all the included studies.

However, trials that included 106 or more patients had also no statistical significant higher score (mean score 22.8, SD=4.75) than trials with less than 106 subjects (mean score 23.17, SD=4.88) p=0.77

Figure 6: The number of subject's impact on trials' CONSORT score



E. DISCUSSION

In this survey, diagnostic accuracy studies examining the role of PRP injection for the treatment of AO of knee, indexed in the PubMed during a period of 10 years, have been assessed using the CONSORT statement.

Our evidence reveals a moderate to satisfactory reporting quality (51.51%-72.81% with 10/13 (76.9%) trials reporting ≥ 50% and 2/13 (15.3%) trials reporting ≥75% of the CONSORT items. The mean adherence score (62.16) is comparable to that of previous publications in other fields of medicine [37]. The variance of the reporting between different sections of the checklist is remarkable. The title, the abstract and the introduction parts approximate 100% adherence but, notwithstanding this, the section "other information" display discouraging results. Explicitly, only one study gives access to the full protocol. The methods section is generally adequately reported (Trial design, Participants, Interventions, Outcomes) but randomization, allocation concealment mechanism, implementation, blinding were not as good as we should expected.

Existing studies assessing the reporting of randomized trials are deficient. Studies were specialty specific,[39,40] were not conducted systematically,[41] or assessed trials of noninvasive interventions.[38,42] The extent to which recently published surgical trials comply with CONSORT, which may be regarded as the current standard of trial reporting, is therefore unknown. We completed a systematic review to identify randomized trials assessing PRP intervention, to assess the extent of compliance with the CONSORT statement. We found that just more than 50% of CONSORT items were reported sufficiently, with a concerning gap within the reporting of several items. The variables most strongly associated with CONSORT score were the title, the abstract and the introduction. We also found that issues related to the other information" section and "secondary questions" on method's section of the trials were underreported. Our findings are consistent with studies in other subspecialties that have used the CONSORT checklist as a measure of reporting quality, [44]. The extent to which recently published surgical trials comply with CONSORT, which may be regarded as the current standard of trial reporting, is therefore unknown.

To begin with a study should involve a sample size large enough to have a high probability (power) of detecting as statistically significant a clinically important difference of a given size, if such a difference exists. For such a purpose and in superiority trials, authors should describe 1) the estimated outcomes in each group for the primary outcome(s) (the clinically important difference between groups) 2) type I error 3) power 4) standard deviation for continuous outcomes, of the measurements. In the present study, approximately 62% of the RCTs report sample size calculation.

The reporting of the randomization process should include details about the methods about generating the random sequence. In this review, it was observed that this item was reported inadequately, with 61.5% included the method used to generate the random allocation sequence and poorly 15.3% the type of randomization (such as blocking and block size). In the fields of surgery, these figures were 44% and 43% respectively [36]. Usually, authors refer to terms such as ‘‘random allocation’’ or ‘‘the groups were randomized,’’ without further elaboration. Authors should specify the method used to generate the sequence (such as a random number table or a computerized random number generator, coin toss, and dice throwing), restrictions to the procedure like stratification and block randomization. Trials that have been characterized as "randomized" should have adopted truly random allocation methods.

Allocation concealment seeks to stop foreknowledge of the sequence generation before implementation, and it’s as important as sequence generation to avert selection bias. Allocation concealment can always be successfully implemented. It should not be confused with blinding, as blinding prevents performance and detection bias.[43] Despite the importance of allocation concealment, one can observe in 46.2% of the cases that there was no description of this item at all.

Blinding is additionally a key element in RCT reporting. In the present review, 46.8% of the RCTs performed poor or no reporting of blinding, putting the study at high risk of bias. Patient blinding is especially important when patient-centered subjective outcomes such as pain scores are collected, as they are more prone to bias.

We did not identify any significant improvement in the reporting quality over time. In addition in our study, h-index of first author and the impact factor of journal had inconsequential association with the CONSORT score. These findings are in consistency with previous survey which noted a small increase between low- (IF<2), medium- (IF 2-7), and high-ranked (IF>7) journals with 52.63, 56.57, and 59.21%, consort's compliance [45]. In addition with no significant improvement in the reporting quality has been identified it terms of journal's references not journal's participants.

RCT are the one of the best method to compare treatments and invasive procedures with each other. Even if recent research methods, such as meta-analyses and umbrella meta-analyses, provide more accurate data, the quality of RCTs remains central, as they represent the structural element of the aforementioned research methodologies. Scarcity in reporting afflicts the quality of RCT and therefore downgrades the significance of the outcomes. Therefore reporting can be substantially improved by disseminating the utilization of the CONSORT statement; proper orientation of authors, training researchers, reviewers, funders and journal editors has a key role to prevent against incomplete adherence, one of the largest sources of avoidable waste in biomedical research [46].

Study limitations

Several limitations of the study merit consideration. Firstly, the search strategy was restricted only in PubMed. Subsequently, articles indexed in other databases were omitted. Secondly, non-English literature was excluded increasing the potential risk of selection bias. Thirdly, the outcome measure, CONSORT score, is a subjective evaluation. Especially in our study the presence of one sole assessor inhibits the measurement of intra-observer agreement as an index of systematic bias. However we should not misapprehend that do not necessarily mean that the quality of the science of an article and its CONSORT score concur.

Conclusion

To summarize, it is of high priority to spread the role of CONSORT statement in order to ensure a comprehensive reporting status of RCT. Some vital sections of the checklist such as sample size, randomization, 'other information' performed below

the satisfactory level. Hence, careful assessment is required to guarantee the critical appraisal and the credibility of a study.

Conflict of interests: The authors of this manuscript certify that they have no proprietary, financial, or other personal interest of any nature or kind in any product, service, and/or company that is presented in this article.

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