

The Promising Effect of Automatic Positive Airway Pressure in Heart Failure Patients Suffering from Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis

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ABSTRACT

Purpose: There is a link between Heart Failure (HF) and Sleep Disordered Breathing (SDB). Obstructive Sleep Apnea (OSA) patterns affect the Left Ventricular Ejection Fraction (LVEF) in HF. The current study aimed to evaluate the effect of Automated Positive Airway Pressure (APAP) in HF patients with OSA.

Methods: A systematic search in databases PubMed, Medline, Cochrane Library, Scopus, and Web of Science from January 1980 to January 2023 was performed to find the related articles. Then, the Cochrane risk of bias tool was used to assess the risk of bias. Finally, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) were employed to judge the robustness of the evidence. In order to combine the results, Random Effect (RE) or Fixed Effect (FE) models were used.

Results: Three studies were eligible based on the inclusion criteria. The patients in the intervention and control groups were 47 and 55, respectively. The mean age of patients in the intervention and control groups was 66.33 and 66.2 years, respectively. The meta-analysis results showed that the mean of integrated changes for LVEF, 6-MWT, and peak VO_2 was (MD=2.48, 95% CI: 0.10 to 4.85, p-value=0.04), (MD=13.82, 95% CI: -77.98 to 35.63, p-value=0.214 and (MD=1.03, 95% CI: to 2.18, p-value=0.081), respectively.

Conclusion: In patients with HF and OSA, Automatic PAP (APAP) can improve the amount of LVEF. In addition, APAP therapy also increases 6-MWT and peak VO_2 .

Keywords: Obstructive sleep apnea; Sleep-disordered breathing; Heart failure with reduced ejection fraction; Positive airway pressure therapy; Airway

Abbreviations: HF: Heart Failure; SDB: Sleep Disordered Breathing; OSA: Obstructive Sleep Apnea; LVEF: Left Ventricular Ejection Fraction; APAP: Automated Positive Airway Pressure; CPAP: Continuous Positive Airway Pressure; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; RE: Random Effect; RCT: Randomized Clinical Trial; FE: Fixed Effect; 6-MWT: The Six-Minute Walk Test

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INTRODUCTION

Heart Failure (HF), a syndrome with insufficient cardiac output, contributes to high morbidity and mortality rates [1]. Left Ventricular Ejection Fraction (LVEF) is an accepted criterion for classifying HF patients based on which the best treatments are chosen for these patients [2]. The six-Minute Walk Test (6-MWT) is a standard tool for predicting Heart Failure (HF) in cardiovascular diseases linked to maximum oxygen consumption [3]. One of the most common comorbidities in HF patients is Obstructive Sleep Apnea (OSA), a sleep-related breathing disorder associated with heart failure with reduced LVEF [4,5].

Despite considerable advances in treatments, there is still an upward trend in the prevalence of HF. The coexistence of OSA exacerbates morbidity and mortality; therefore, the importance of finding suitable treatment to improve factors like LVEF and exercise capacity for these patients is undeniable. Continuous Positive Airway Pressure (CPAP) is the gold standard in patients suffering from OSA with or without HF. Constant positive pressure is applied during sleep [6-10]. Different studies have shown that LVEF improvement results from utilizing CPAP for patients with HF who are complicated with OSA. However, the time-consuming task of identifying the effective pressure is a major challenge in CPAP which can be solved by Automatic PAP (APAP) devices utilizing algorithms to adjust the pressure based on factors including sleep stage, posture, and the degree of nasal congestion. In this regard, we included studies with Randomized Controlled Trials (RCT) design in a systematic review and meta-analysis to evaluate the effect of APAP in HF patients with OSA.

LITERATURE REVIEW

Data sources

This study follows the popular Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline 13. Different databases, including PubMed, Medline, The Cochrane Library, Scopus, and Web of Science, were searched systematically from January 1980 to January 2022 to retrieve English language RCTs. In addition, reference lists of the chosen studies were checked. In the present study, to find changes in LVEF which were the result of using Auto-titrating Positive Airway Pressure (APAP), articles including the keywords "Obstructive sleep apnea", "OSA", "Heart Failure", "HF", "Continuous Positive Airway Pressure", "CPAP", "sleep-disordered breathing", "auto-titrating", "APAP" and their combinations were searched [11].

Study selection

Inclusion criteria consisted of:

- Studies including patients with HFrEF (Heart Failure reduced Ejection Fraction) and OSA comorbidity which used the APAP method.
- LVEF changes in baseline and after the intervention, 6-MWT, and maximum oxygen consumption (peak VO_2).

- English language articles. As to the exclusion criteria, we followed these criteria: Papers presented at conferences, studies on animal specimens, and studies with incomplete reported data on outcomes.

Data extraction and quality assessment

Three steps were followed to decide on the articles. First, review the titles of all articles to exclude the ones that were not in line with the aim of the study. Afterward, the abstract and full texts of the articles were examined according to the inclusion and exclusion criteria. Then, by screening the full text of the articles, those with a weak relationship with the study's objectives were identified and removed. Finally, the required information from the full text of the articles was extracted in the extraction form. These data included: The lead author, publication date, country, sample size, the mean age of participants in the study, changes of LVEF, 6-MWT, and peak VO_2 at baseline as well as after the intervention. To organize study titles and abstracts and identify duplicates, the software Endnote X5 was used. Each step was performed by independent authors and was subsequently cross-checked. Finally, the third reviewer solved ambiguities and disagreements through discussion until reaching a consensus [12].

Quality assessment

To perform the quality assessment of included studies, the Cochrane collaboration risk of bias tool in review manager 5.4.1 was used, covering six domains: Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. In addition, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess the quality of evidence for included outcomes. The results of the GRADE approach were represented as very low, low, moderate, and high [13].

Statistical analysis

The mean difference and standard deviation for LVEF, 6-MWT, and peak VO_2 between the intervention and control groups were extracted from the articles. In addition, heterogeneity between studies was examined by Cochrane (Q) and I^2 statistics which express the percentage of differences between studies. If the values of the I^2 statistic were less than 50%, the fixed effects model was used by the Mantel-Haenszel method, and if it was more than 50% or p-value <0.05 , the random effects model was used to calculate the pooled changes in the studied outcomes. Statistical analyses were performed using CMA v.2.0 software. Also, a bilateral statistical significance was set at $\alpha=0.05$.

RESULTS

Search results and study characteristics

A systematic search of sources identified 741 articles, of which 192 were duplicates. After examining the title and abstracts, 530 articles were excluded. In addition, sixteen research articles were excluded from our analysis after their full texts were reviewed.

Finally, three articles were eligible to be included in the current meta-analysis study. The eligibility of studies was checked based on the inclusion criteria. The flow chart for the identified and included articles is shown in Figure 1 [14].

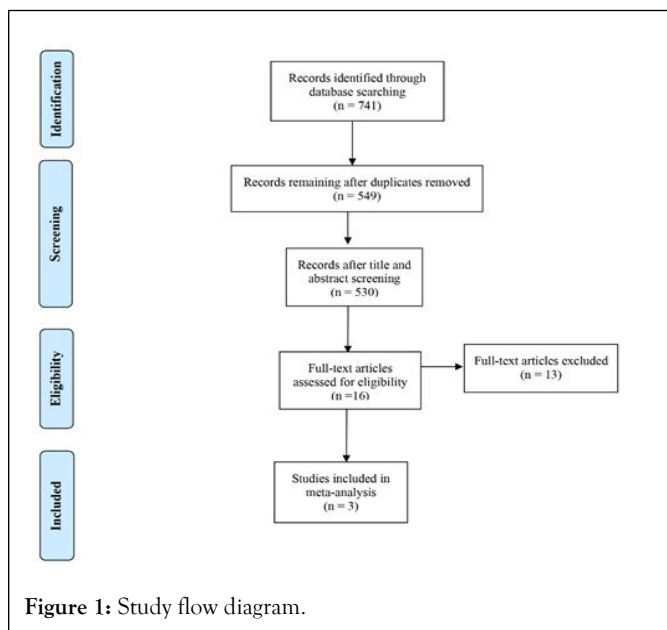


Figure 1: Study flow diagram.

Participant characteristics

Three studies that were published from 2007 to 2023 were included in this meta-analysis. The selected studies had a total of 6 months of follow-up. The mean age of the participants was over 65.32 years. In one study, Angiotensin-Converting Enzyme inhibitors (ACE), Angiotensin Receptor Blockers (ARB), beta blocker, and diuretics were used. In another study, beta blockers, ACE inhibitors, and statins were mentioned. However, in a study by Smith, et al., cardiovascular drugs were not mentioned. The characteristics of the studies are listed in Table 1 [15].

Table 1: Baseline characteristics of included studies in the meta-analysis.

Study (year)	Type of study	Treatment		Number of patients		Age	
		Intervention	Control	Intervention	Control	Intervention	Control
Fox, et al.	Randomized, controlled pilot study	APAP device (AutoSet™ S8, S8II, S9 or AirCurve™; ResMed, Sydney, Australia)	Nasal strips	25	33	67.4 ± 9.8	64.9 ± 10.1
Sharma, et al.	Randomized control trial	APAP, The ApneaLink Air (ResMed, San Diego, CA)	Standard therapy	10	11	70.6 ± 11.5	66.7 ± 11.2
Smith, et al.	Double-blind randomized placebo-controlled	APAP (Autoset Spirit: ResMed, Sydney, Australia)	Sham CPAP	12	11	61	61

Quality assessment

In the quality assessment of the full text articles, we found that the articles had high quality. However, there was an unclear risk of bias in the blinding section. The high quality of the articles can be related to the design of the studies. The result of the quality assessment is shown in Figures 2 and 3.

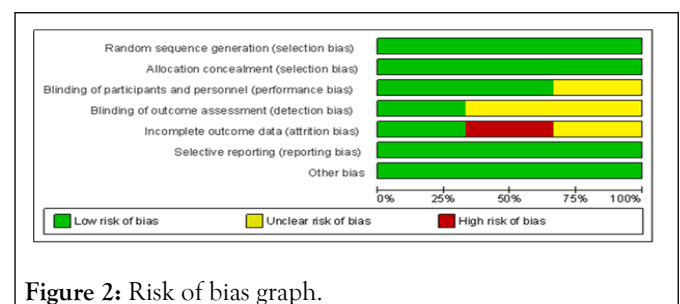


Figure 2: Risk of bias graph.

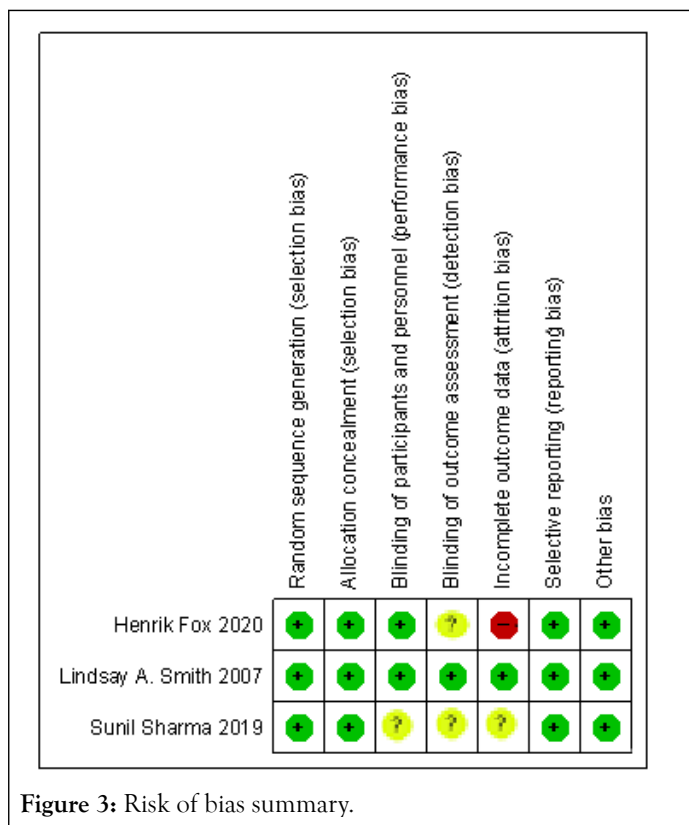


Figure 3: Risk of bias summary.

Meta-analysis results

Results of LVEF changes: LVEF changes were reported based on the three research studies which had been investigated. The total number of patients who were in the intervention and control groups was 47 and 55, respectively. Moreover, the mean age of the patients in the intervention group was 66.33, and the mean age in the control group was 66.2, respectively. It must also be noted that we found significant heterogeneity between the studies (Q-value=6.46, df=2, p-value=0.04, I²=69.08) [16].

Based on the results of the meta-analysis and the random effects model, we found that compared to the control group, the pooled mean LVEF changes in the intervention group was 2.48%, which was statistically significant. (pooled mean change=2.48, 95% CI: 0.10 to 4.85, z-value=2.05, p-value=0.04). Figure 4 indicates the forest plot from the meta-analysis.

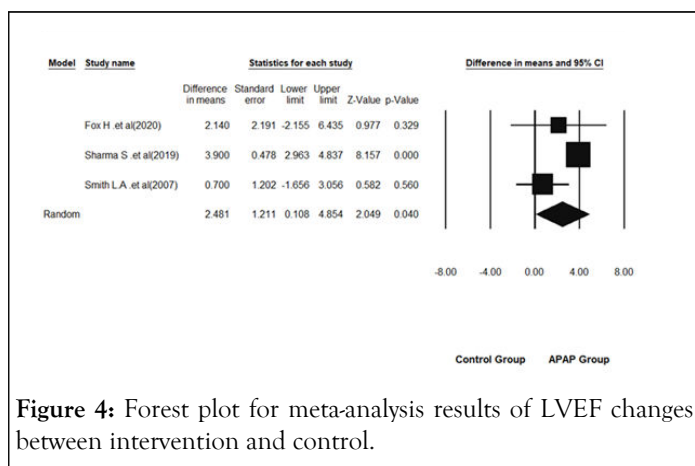


Figure 4: Forest plot for meta-analysis results of LVEF changes between intervention and control.

Results of the 6-MWT: 6-MWT changes were reported in the three studies investigated. Also, the total number of patients in the intervention group was 47 and 55 in the intervention and control groups, respectively. Moreover, the mean age of patients was 66.33 years in the intervention group and 64.2 years in the control group. Furthermore, we found that the heterogeneity between studies was not significant (Q-value=0.389, df=2, p-value=0.82, I²=0.00). As the results of the meta-analysis and the fixed effects model indicated, the mean change of 6-MWT in the intervention group, compared with the control group, was 13.82 units, which was not statistically significant. (Pooled mean change=13.82, 95% CI: -77.98 to 35.63, z-value=1.24, p-value=0.214). Figure 5 indicates the forest plot from the meta-analysis [17].

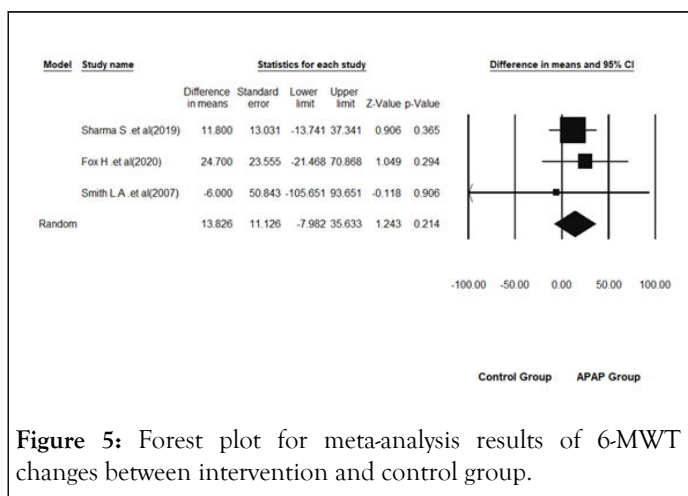


Figure 5: Forest plot for meta-analysis results of 6-MWT changes between intervention and control group.

Results of peak VO₂: The peak VO₂ changes were reported in two of the studies. Overall the total number of patients was 37 and 44 in the intervention and control groups, respectively. Moreover, the mean age of patients in the intervention and control groups was 64.2 and 69.95 years, respectively. Furthermore, we found that the heterogeneity between the studies was not significant (Q-value= 0.527, df=1, p-value=0.46, I²=0.00). Based on the meta-analysis and the fixed effects model results, the mean peak VO₂ changes in the intervention group compared with the control group were 1.03 units, indicating that it was not statistically significant. (Pooled mean change=1.03, 95% CI: -0.125 to 2.18, z-value=1.74, p-value=0.081). Figure 6 presents the forest plot from the meta-analysis [18].

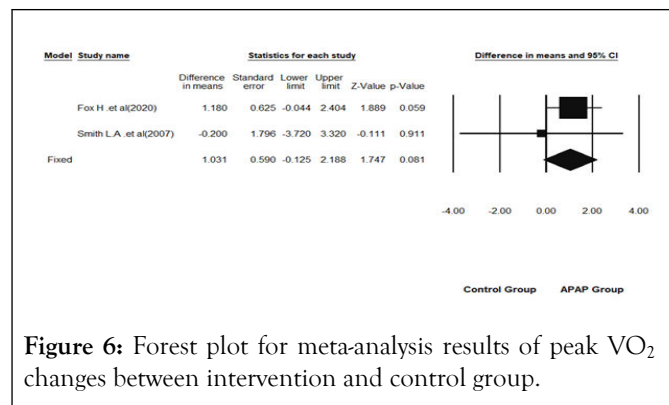


Figure 6: Forest plot for meta-analysis results of peak VO₂ changes between intervention and control group.

This study evaluated the quality of finally drawn evidence from the GRADE approach's meta-analysis. Our findings indicated

that the strength of evidence in the three studies was high. The result of the grade is shown in Table 2.

Table 2: The strength of the evidence obtained from meta-analysis for study outcomes.

Outcome	No. of studies	Study design	Risk of bias	Certainty assessment				No. of patients		Effect	Certainty
				Inconsistency	Indirectness	Imprecision	Other considerations	APAP	Control		
LVEF	3	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	47	55	2.48 (0.108 to 4.854)	⊕⊕⊕⊕ High
6 MW	3	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	47	55	13.826 (7.982 to 35.63)	⊕⊕⊕⊕ High
Peak VO ₂	2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	37	44	1.03 (0.125 to 2.188)	⊕⊕⊕⊕ High

DISCUSSION

Our findings indicated that the quality of life of patients with HFrEF would reduce due to shortness of breath during physical activity. 6-MWT guidelines are provided by the American chest association. 6-MWT and LVEF show reliable information for the physical activity of the HFrEF patient 16. To the best of the author’s knowledge, this investigation is the first systematic review and meta-analysis of RCTs conducted to determine the impact of APAP on OSA patients with HF. The current meta-analysis assessed the influence of APAP on LVEF of patients who suffer from HFrEF and OSA. This study indicated a 2.48% improvement in LVEF by utilizing the APAP strategy compared with other control conditions. Moreover, APAP was successful in increasing 6-MWT and peak VO₂; however, they were not statistically significant. These results are discussed in detail below [19].

Several studies have assessed how the use of different types of PAP treatments, including CPAP and APAP, influences cardiac function. The efficacy of CPAP in OSA patients with or without HF was examined in different meta-analysis studies, which confirmed that LVEF could be improved. Subsequently, a decrease in cardiovascular-related mortality was observed. LVEF changes by utilizing APAP in patients with comorbid HF and OSA were examined in the RCTs included in our meta-analysis. While all three studies showed an increase in LVEF rates, the amount of change was different. Also, the sample size of the mentioned articles was generally small; thus, making robust conclusions was not possible. Therefore, in light of the data above, the present meta-analysis pooled the results and showed a statistically significant improvement in LVEF (2.48%). This is in line with the result of the Sun, et al., study, which demonstrated a great improvement in LVEF after CPAP.

The 6-MWT is a simple measurement tool to assess the functional status of patients, and it is used to predict the morbidity and mortality in Left Ventricular (LV) dysfunction.

The correlation between this exercise capacity test and mortality has been shown in previous research [20]. Moreover, a clearly recognizable relationship exists between maximum oxygen consumption and the distance patient walks in a 6-minute period. In the present meta-analysis, the pooled estimate of 6-MWT (pooled mean change=13.82) showed an improvement as a result of APAP treatment which was not statistically significant. A meta-analysis done by Fletcher, et al. proved the positive impact of CPAP on the peak rate of oxygen uptake. HF patients with preserved left ventricular Ejection Fraction (HFpEF) suffering from Sleep-Disordered Breathing (SDB) who were included in another meta-analysis indicated that exercise capacity could be improved by CPAP significantly. It is to be noted that exercise capacity is influenced by several factors such as age, sex, height, and weight; therefore, future investigations are advised to take these actors into account.

Maximum oxygen consumption (peak VO₂) can be measured immediately after an exercise test. Two of the included studies in the current meta-analysis reported this outcome, and the results showed an improvement by APAP. However, the statistically significant level still needs to be reached, which can be explained by the limited number of patients. In a previous meta-analysis of examining CPAP on the exercise capacity of OSA patients, an increase was shown in peak VO₂. The CPAP’s success in reducing cardiovascular mortality events of the OSA population has been proved [21-25].

The American Academy of Sleep Medicine (AASM) recommended using APAP for patients suffering from OSA without significant comorbidities, which has considerable benefits, including reduced cost, faster treatment initiation, and improved accessibility of care. According to the information mentioned above, the lack of RCTs that examined the APAP treatment in OSA patients with HF comorbidity is obvious. It is to be noted that future studies must consider various confounding factors that can affect the results. For example, the functional capacity of patients is not only impaired by OSA but

by other factors, such as obesity which may negatively affect the results. However, the included studies in the present systematic review were of high quality. According to the inclusion criteria, all studies had an RCT design, which is ideal for being included in meta-analysis studies. However, the results of GRADE are based on four factors so that the quality of the evidence can be determined: Study design, study quality, consistency, and high directness.

This study had some limitations. First, the control groups among included studies were different. Secondly, most of the included patients in the studies were men, and future studies are advised to evaluate the impact of treatments on both genders. In some studies, the effect of cardiovascular drugs on improving the clinical condition of patients, especially improving LVEF, has been evaluated; however, in this study, their effects could not be examined

CONCLUSION

This study showed the effectiveness of APAP in reducing the consequences of OSA in patients with HFrEF. In addition, an improvement in the amount of LVEF was observed. Although APAP successfully increased 6-MWT and peak VO₂, the results were not statistically significant. Therefore, further clinical trial studies are encouraged to establish the strength of the evidence.

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CONFLICT OF INTEREST

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

CONSENT FOR PUBLICATION

Not applicable.

ETHICAL APPROVAL

For this type of study, formal consent is not required.

INFORMED CONSENT

This article does not contain any studies with human participants performed by any of the authors.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Not applicable.

AUTHOR CONTRIBUTORSHIP

Mohammad Nourabi: Design, running search strategy, result interpretation, senior author, drafting, revision, and final approval of the manuscript. Mehdi Geravandi: Study selection, data extraction, running search strategy, result interpretation, drafting, revision, and final approval of the manuscript. Sara Zand: Data extraction, revision, and final approval of the manuscript. Sina Dolatshahi: Study selection, revision, and final approval of the manuscript. Hossein Hosseini-fard: Data analysis, result interpretation, revision, and final approval of the manuscript. Moein Geravandi: Study selection, data extraction, drafting, revision, and final approval of the manuscript. Zahra Hooshanginezhad: Study selection, result interpretation, senior author, drafting, revision, and final approval of the manuscript

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