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Efficacy of medium cut-off dialyzers and comparison with high-flux dialyzers in patients on maintenance hemodialysis: A systematic review and meta-analysis

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Abstract

Medium cut-off (MCO) dialyzers were designed to provide better clearance of uremic toxins. We conducted a meta-analysis comparing MCO with high-flux (HF) dialyzers for the effect on uremic toxins in maintenance hemodialysis (HD) patients. Five databases were systematically searched for relevant studies and nine studies were identified finally. Reduction ratio (RR) of urea, urea, creatinine, β2-macroglobulin (β2-MG), kappa free light chain (κFLC), and lambda FLC (λFLC) levels were not significantly different between MCO and HF dialyzers. But RR of β2-MG, κFLC, and λFLC were greater for MCO than HF dialyzers. MCO dialyzers could better reduce tumor necrosis factor-α (TNF-α) levels. Subgroup analysis stratified by study design indicated that in randomized controlled trial (RCT) studies, albumin levels was lower in MCO than HF dialyzers group, but the two dialyzers treatments were equivalent in non-RCT subgroup. Compared with HF dialyzers, MCO dialyzers provided higher middle-molecules uremic toxins clearance and obviously reduced TNF-α levels.

KEYWORDS

albumin, hemodialysis, high-flux dialyzers, medium cut-off dialyzers, uremic toxins

1 | INTRODUCTION

End-stage renal disease (ESRD) leads to the progressive accumulation of uremic toxins which have negative effect on patient's health. According to their size and protein-binding properties, uremic toxins are classified into three main groups: small molecules (<0.5 kDa), middle molecules (0.5–60 kDa), and protein-bound toxins [1]. HD is the main method for ESRD patients to remove uremic toxins. Low-flux (LF) dialysis was the traditional HD modality used in the past decade, providing effective clearance of small solutes, but have negligible removal of middle molecules and protein-bound uremic toxins [2].

The spectrum of uremic toxins removed enlarged ones by using HF dialyzers. HF dialyzers can clear some middle molecules like β2-MG (11.8 kDa), but these dialyzers cannot effectively remove molecular weight above 15–20 kDa for their molecular radii being larger than HF membrane pores [3, 4]. The retention of larger middle molecules are associated with inflammation, cardiovascular events, and other uremia complications in patients, such as amyloidosis, mineral and bone disorders, protein-energy wasting, and anemia [1, 5, 6]. Therefore, HF dialysis might not significantly reduce mortality compared with LF dialysis [7, 8]. Larger middle molecules uremic toxins can be removed either by convection or through the use of highly permeable

membranes. Another dialytic modality, hemodiafiltration (HDF) can improve patient survival, since it has a higher efficiency for clearing middle molecules uremic toxins than HF dialysis for increased convection by HDF [9–11]. But the use of this technique is limited for the flowing reasons, including economic problems, vascular access dysfunction, or water treatment systems unable to provide ultrapure water [12].

MCO dialyzers have a novel class of membrane with a more distribution of larger sizes pore and a higher number of pores, so MCO dialyzers have a higher permeability and have increased convective transport. MCO dialyzers have been introduced to the dialysis practice as they can perform HD as efficient as online HDF [13–15]. However, global major blood purification modality is HF dialysis, and HDF is still not widely used. In previous years, new trials have been carried out testing the clinical effects of MCO dialyzers over HF dialyzers on uremic toxins in maintenance HD patients. We felt it necessary to perform a comprehensive systematic review and meta-analysis with the aim of summarizing the entire currently available evidence to evaluate the effects of MCO dialyzers on uremic toxins as compared with HF dialyzers.

2 | MATERIALS AND METHODS

2.1 | Data sources and search strategy

PubMed, Embase, Cochrane Central Register of Controlled Trials, Ovid-MEDLINE, and VIP information database were searched for English-language articles without time restriction up to June 2021 through focused, high sensitive search strategies (Figure 1). The reference list of each publication was also scanned in order to identify additional literature about this topic.

2.2 | Study selection and data extraction

We included any randomized controlled studies or non-randomized controlled studies that tested the effects of MCO dialyzers on uremic toxins in ESRD patients on maintenance HD treatment as compared with HF dialyzers.

The inclusion criteria were as follows: (i) patients aged >18 years receiving maintenance HD, (ii) clinical parameters: the studies involved should report at least one clinical parameter of interest; (iii) intervention: the intervention group using MCO dialyzers, while the comparison group received HF dialyzers.

Exclusion criteria: Duplicate publications, reviews, case reports, letter, conference abstract, the deals were examined during a single HD secession, studies without the HF dialyzer group, studies with statistical mistakes, or studies with incomplete data. In the case of multiple publications from the same population, we included the most recent publication.

Data were extracted independently by two investigators and exported to an Excel database. The following items recorded for each study were extracted: first author, year of publication, region, study design, sample size, treatment duration, and the clinical parameters of interest, including the levels of urea, creatinine (Cre), β2-MG, κFLC, λFLC, IL-6, TNF-α, albumin, and RR of urea, β2-MG, κFLC, λFLC.

2.3 | Data analysis

To evaluate a possible effect of dialyzer on continuous variables with the same scale, we used the mean difference (MD); for variables expressed in different scales should convert to the same scale. Data that were available as median and range were converted to mean and SD by applying the Hozo formula [16]. Heterogeneity was measured by the Chi^2 test on $N - 1$ degrees of freedom, with an alpha of 0.05 considered for statistical significance and the Cochrane-I^2 [17]. I^2 values of 0%–30%, 30%–60%, and >60% were considered low, medium, and high levels of heterogeneity, respectively. We used fixed effects or random effects model because it takes into account the heterogeneity across studies. Pre-stratified subgroup analysis was performed to investigate possible sources of heterogeneity, including study design. The presence of publication bias was also evaluated using

Pubmed database (*n* = 42)
Embase database (*n* = 95)
Cochrane central (*n* = 43)
Ovid medline (*n* = 58)
VIP information database (*n* = 38)

276 citations retrieved by Literature searching

215 Excluded:
- Search overlap
- Intervention not pertinent
- Review articles/letter/case report /conference abstract

61 articles selected for full Text evaluation

52 Excluded:
- 15 Outcome not of interest
- 8 Just single dialysis session
- 12 without the HF dialyzer group
- 17 Without complete data
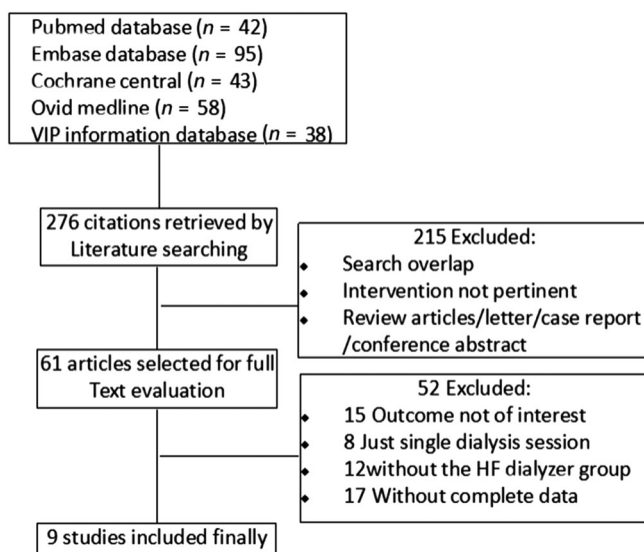
9 studies included finally

FIGURE 1 Study selection flow

Egger's tests and funnel plots. All analyses were performed using RevMan 5.3. We considered statistical significance as $p < 0.05$.

2.4 | Quality and risk of bias assessment

The quality of RCTs was assessed by using the checklist developed by the Cochrane Renal Group which evaluates the presence of potential selection bias (random sequence generation and allocation concealment), performance bias (blinding of investigators and participants), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective reporting), and possible other sources of bias. In addition,

possible selection bias or confounding by indication was evaluated for non-randomized studies.

3 | RESULT

3.1 | Search results

Two hundred and seventy-six potentially relevant references were initially retrieved. By screening titles and abstracts, a total of 215 citations were excluded because of search overlap, intervention not pertinent, review articles, letter, case report, and conference abstract. Among the 61 studies selected for full text examination, 52 studies were excluded because of the following reasons: outcome

TABLE 1 Characteristics of included studies

Study	Region	Type of study	Number of participants	Mean age, years	Male ratio, %	Measurement time	Clinical parameters
Zickler et al. [18]	Germany	RCT	MCO: 23 HF: 25	58.9	72.9%	4 weeks of each dialysis modality + 8 weeks of extension phase	The levels of Cre, β2-MG, κFLC, λFLC, IL-6, TNF-α, albumin
Belmouaz et al. [19]	France	RCT	MCO: 20 HF: 20	75.5	70%	3 months of each dialysis modality + 3 months weeks of extension phase	The levels of urea, Cre, β2-MG, κFLC, λFLC, IL-6, TNF-α, albumin Reduction rate of urea, β2-MG, κFLC, λFLC
Sevinc et al. [20]	Turkey	RCT	MCO: 26 HF: 24	56.4	58%	12 weeks of each dialysis modality + 12 weeks of extension phase	The levels of urea, Cre, β2-MG, κFLC, λFLC, IL-6, albumin Reduction rate of urea, β2-MG, κFLC, λFLC
Lim et al. [21]	South Korea	RCT	MCO: 24 HF: 25	62.2	75%	12 weeks	The levels of BUN, Cre, β2-MG, κFLC, λFLC Reduction rate of β2-MG, κFLC, λFLC
Weiner et al. [22]	American	RCT	MCO: 86 HF: 86	59	61%	4 and 12 weeks	The levels of albumin Reduction rate of β2-MG, κFLC, λFLC
Lim et al. [23]	South Korea	RCT	MCO: 24 HF: 25	62.2	75%	12 weeks	The levels of TNF-α, albumin
Yeter et al. [24]	Turkey	Non-RCT	MCO: 15 HF: 15	52.9	66%	6 months	The levels of β2-MG, Cre, BUN, albumin Reduction rate of urea
Ahn et al. [25]	South Korea	Non-RCT	MCO: 16 HF: 18	51.6	64.7%	12 months	The levels of β2-MG, albumin Reduction rate of β2-MG
Cho et al. [26]	South Korea	Non-RCT	MCO: 38 HF: 19	54.6	57.8%	12 months	The levels of BUN, Cre, β2-MG, κFLC, λFLC, albumin Reduction rate of BUN, β2-MG, κFLC, λFLC

were not pertinent to the topic [15], the dealt were examined just a single HD session with MCO dialyzer or HF dialyzer [8], the studies only include the MCO dialyzer group [12], or complete data cannot be provided [19]. A total of nine articles were reviewed in detail. The selection process used to identify the studies is shown in Figure 1.

3.2 | Study characteristics

The main characteristics of the nine studies included are shown in Table 1. Among the nine [18–27] selected studies, six [18–23] were RCTs of which three [18–20] had a cross-over and three [21–23] had a parallel design, one was non-randomized controlled prospective study [24], and two were observational studies [25, 26]. Eight were single-center and two [18, 22] were multicenter studies. The final population analyzed included 500 patients, but the range was variable across studies, spanning from 15 [24] to 86 [22]. The mean age of participants spanned from 51.6 years [25] to 75.5 [19]. Male gender spanned from 57.8% [26] to 75% [21]. The study duration varied from 4 weeks [22] to 12 months [25, 26].

Eight of the included studies compared MCO dialyzers to HF dialyzers while the other one trial [24] compared the effect of three types of HD modalities (LF, MCO, and HF membranes) on the uremic toxins. The blood flow rate ranged around 300 mL/min, the dialysate flow rate was around 500 mL/min, and dialysis time per session was about 4 h. Just four [21, 22] of the included studies assessed the urine volume, spanning from 0 [20] to 513.5 mL/day [21]. Dialysis vintage was specified in 90% of the studies, spanning from 12 [25] to 192.5 months [26].

3.3 | Study quality and risk of bias

Risk of bias in RCTs is summarized in Table 2. Random sequence generation was detailed in all of the included trials and allocation concealment in four [19, 21–23]. All of the RCTs were open label studies. None of the trials was blinding of participants, and investigators and outcome assessors was not specified in three studies [19, 21, 23]. Attrition bias was not assessable in four studies as the drop-out rate was not specified [18, 21–23]. Reporting bias was low in three trials [20, 21, 23] and unclear in the remainder [21, 23]. Risk of confounding by indication was apparently high in all observational studies as the method for grouping of patients could lead to selection bias.

3.4 | RR of urea and the levels of small solutes after a period of HD using MCO dialyzers vs. HF dialyzers

In a meta-analysis of four studies (177 patients) [19, 20, 24, 26], there is no significant difference of RR of serum urea between MCO group and HF group (MD = 0.03; 95% CI: −2.68, 2.74; $P = 0.98$; Figure 2a). Subgroup analysis also showed that the results of two RCTs and two non-RCTs were consistent. However, high heterogeneity was detected between studies ($Chi^2 = 8.07$, $p = 0.04$; $I^2 = 63\%$; Figure 2a).

In a meta-analysis of six studies (274 patients) [18–20, 23, 24, 26], there is no significant difference of the levels of serum urea between MCO group and HF group (MD = −2.17; 95% CI: −9.75, 5.41; $p = 0.57$; Figure 2b). Subgroup analysis showed that the results of four RCTs and two non-RCTs were consistent. Low heterogeneity was detected between studies ($Chi^2 = 6.78$, $p = 0.24$; $I^2 = 26\%$; Figure 2b).

In a meta-analysis of five studies (226 patients) [19, 20, 23, 24, 26], there is no obvious difference of the levels of serum creatinine between MCO group and HF group (MD = −0.33; 95% CI: −0.37, 1.03; $p = 0.35$; Figure 2c). Subgroup analysis showed that the results of three RCTs were consistent with that of two non-RCTs. No heterogeneity was detected between studies ($Chi^2 = 2.95$, $p = 0.57$; $I^2 = 0\%$; Figure 2c).

TABLE 2 Risk of bias assessment for the RCTS

| Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting avoided	Free of other bias
Zickler et al. [18]	Yes	No	No	Yes	No	Yes	Yes
Sevinc et al. [20]	Yes	No	No	Yes	Yes	No	Yes
Lim et al. [21]	Yes	Yes	No	Unclear	No	Unclear	Yes
Belmouaz et al. [19]	Yes	Yes	No	Unclear	Yes	Yes	Yes
Lim et al. [23]	Yes	Yes	No	Unclear	No	Unclear	Yes
Weiner et al. [22]	Yes	Yes	No	Yes	No	Yes	Yes
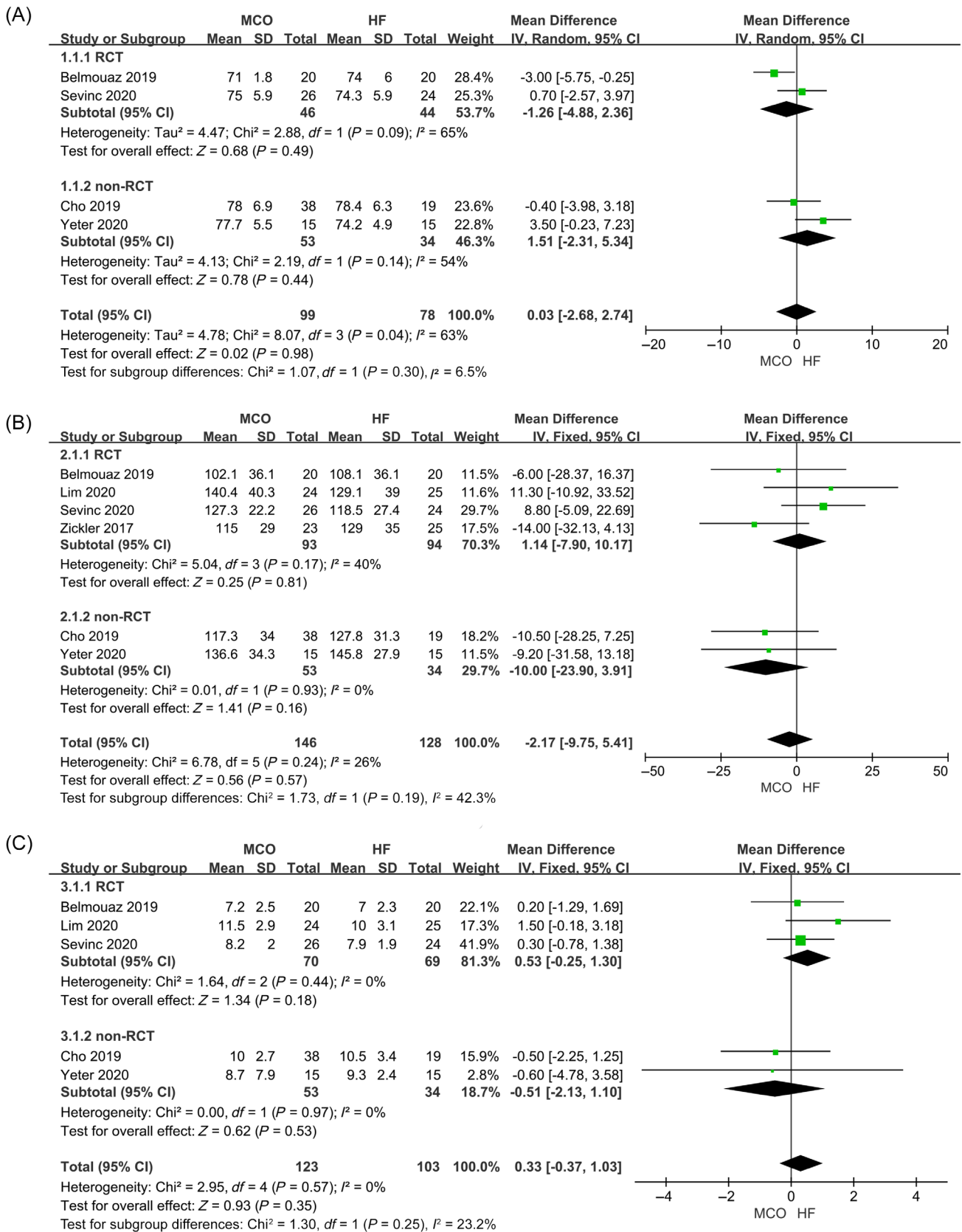
FIGURE 2 Forest plot of comparisons in MCO dialyzers vs. HF dialyzers. Outcomes included (A) RR of urea, (B) the levels of urea, and (C) the levels of creatinine
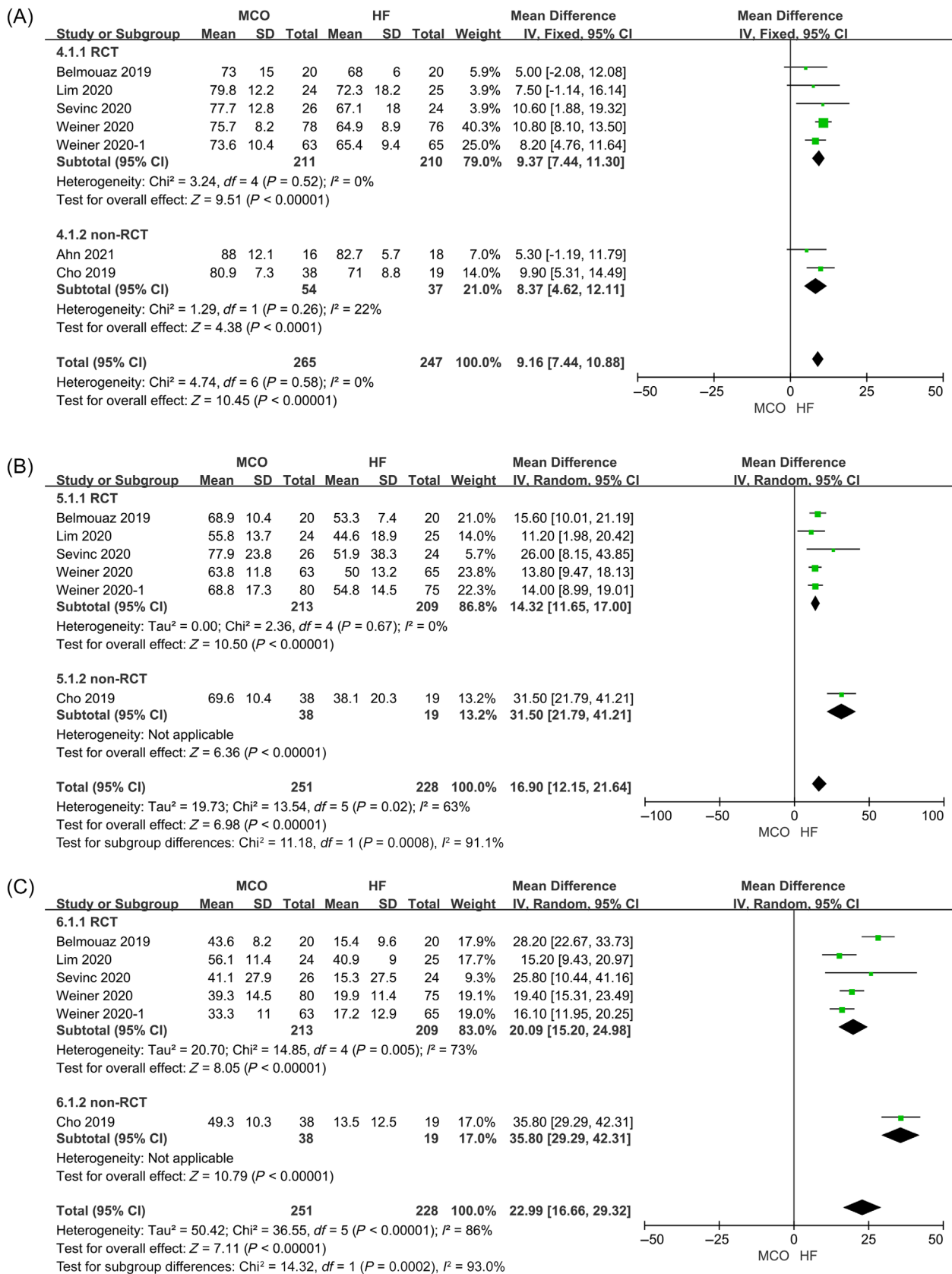
(A)

Study or Subgroup	MCO Mean	SD	Total	HF Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.1.1 RCT								
Belmouaz 2019	73	15	20	68	6	20	5.9%	5.00 [-2.08, 12.08]
Lim 2020	79.8	12.2	24	72.3	18.2	25	3.9%	7.50 [-1.14, 16.14]
Sevinc 2020	77.7	12.8	26	67.1	18	24	3.9%	10.60 [1.88, 19.32]
Weiner 2020	75.7	8.2	78	64.9	8.9	76	40.3%	10.80 [8.10, 13.50]
Weiner 2020-1	73.6	10.4	63	65.4	9.4	65	25.0%	8.20 [4.76, 11.64]
Subtotal (95% CI)			211			210	79.0%	9.37 [7.44, 11.30]

Heterogeneity: Chi² = 3.24, df = 4 (P = 0.52); I² = 0%
Test for overall effect: Z = 9.51 (P < 0.00001)

4.1.2 non-RCT								
Ahn 2021	88	12.1	16	82.7	5.7	18	7.0%	5.30 [-1.19, 11.79]
Cho 2019	80.9	7.3	38	71	8.8	19	14.0%	9.90 [5.31, 14.49]
Subtotal (95% CI)			54			37	21.0%	8.37 [4.62, 12.11]

Heterogeneity: Chi² = 1.29, df = 1 (P = 0.26); I² = 22%
Test for overall effect: Z = 4.38 (P < 0.0001)

| **Total (95% CI)** | | | 265 | | | 247 | 100.0% | 9.16 [7.44, 10.88] |

Heterogeneity: Chi² = 4.74, df = 6 (P = 0.58); I² = 0%
Test for overall effect: Z = 10.45 (P < 0.00001)

−50 −25 0 25 50
MCO HF

(B)

Study or Subgroup	MCO Mean	SD	Total	HF Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
5.1.1 RCT								
Belmouaz 2019	68.9	10.4	20	53.3	7.4	20	21.0%	15.60 [10.01, 21.19]
Lim 2020	55.8	13.7	24	44.6	18.9	25	14.0%	11.20 [1.98, 20.42]
Sevinc 2020	77.9	23.8	26	51.9	38.3	24	5.7%	26.00 [8.15, 43.85]
Weiner 2020	63.8	11.8	63	50	13.2	65	23.8%	13.80 [9.47, 18.13]
Weiner 2020-1	68.8	17.3	80	54.8	14.5	75	22.3%	14.00 [8.99, 19.01]
Subtotal (95% CI)			213			209	86.8%	14.32 [11.65, 17.00]

Heterogeneity: Tau² = 0.00; Chi² = 2.36, df = 4 (P = 0.67); I² = 0%
Test for overall effect: Z = 10.50 (P < 0.00001)

5.1.2 non-RCT								
Cho 2019	69.6	10.4	38	38.1	20.3	19	13.2%	31.50 [21.79, 41.21]
Subtotal (95% CI)			38			19	13.2%	31.50 [21.79, 41.21]

Heterogeneity: Not applicable
Test for overall effect: Z = 6.36 (P < 0.00001)

| **Total (95% CI)** | | | 251 | | | 228 | 100.0% | 16.90 [12.15, 21.64] |

Heterogeneity: Tau² = 19.73; Chi² = 13.54, df = 5 (P = 0.02); I² = 63%
Test for overall effect: Z = 6.98 (P < 0.00001)
Test for subgroup differences: Chi² = 11.18, df = 1 (P = 0.0008), I² = 91.1%

−100 −50 0 50 100
MCO HF

(C)

Study or Subgroup	MCO Mean	SD	Total	HF Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
6.1.1 RCT								
Belmouaz 2019	43.6	8.2	20	15.4	9.6	20	17.9%	28.20 [22.67, 33.73]
Lim 2020	56.1	11.4	24	40.9	9	25	17.7%	15.20 [9.43, 20.97]
Sevinc 2020	41.1	27.9	26	15.3	27.5	24	9.3%	25.80 [10.44, 41.16]
Weiner 2020	39.3	14.5	80	19.9	11.4	75	19.1%	19.40 [15.31, 23.49]
Weiner 2020-1	33.3	11	63	17.2	12.9	63	19.0%	16.10 [11.95, 20.25]
Subtotal (95% CI)			213			209	83.0%	20.09 [15.20, 24.98]

Heterogeneity: Tau² = 20.70; Chi² = 14.85, df = 4 (P = 0.005); I² = 73%
Test for overall effect: Z = 8.05 (P < 0.00001)

6.1.2 non-RCT								
Cho 2019	49.3	10.3	38	13.5	12.5	19	17.0%	35.80 [29.29, 42.31]
Subtotal (95% CI)			38			19	17.0%	35.80 [29.29, 42.31]

Heterogeneity: Not applicable
Test for overall effect: Z = 10.79 (P < 0.00001)

| **Total (95% CI)** | | | 251 | | | 228 | 100.0% | 22.99 [16.66, 29.32] |

Heterogeneity: Tau² = 50.42; Chi² = 36.55, df = 5 (P < 0.00001); I² = 86%
Test for overall effect: Z = 7.11 (P < 0.00001)
Test for subgroup differences: Chi² = 14.32, df = 1 (P = 0.0002), I² = 93.0%

−50 −25 0 25 50
MCO HF

FIGURE 3 Forest plot of comparisons in MCO dialyzers vs. HF dialyzers. Outcomes included (A) RR of β2-MG, (B) RR of κFLC, and (C) RR of λFLC
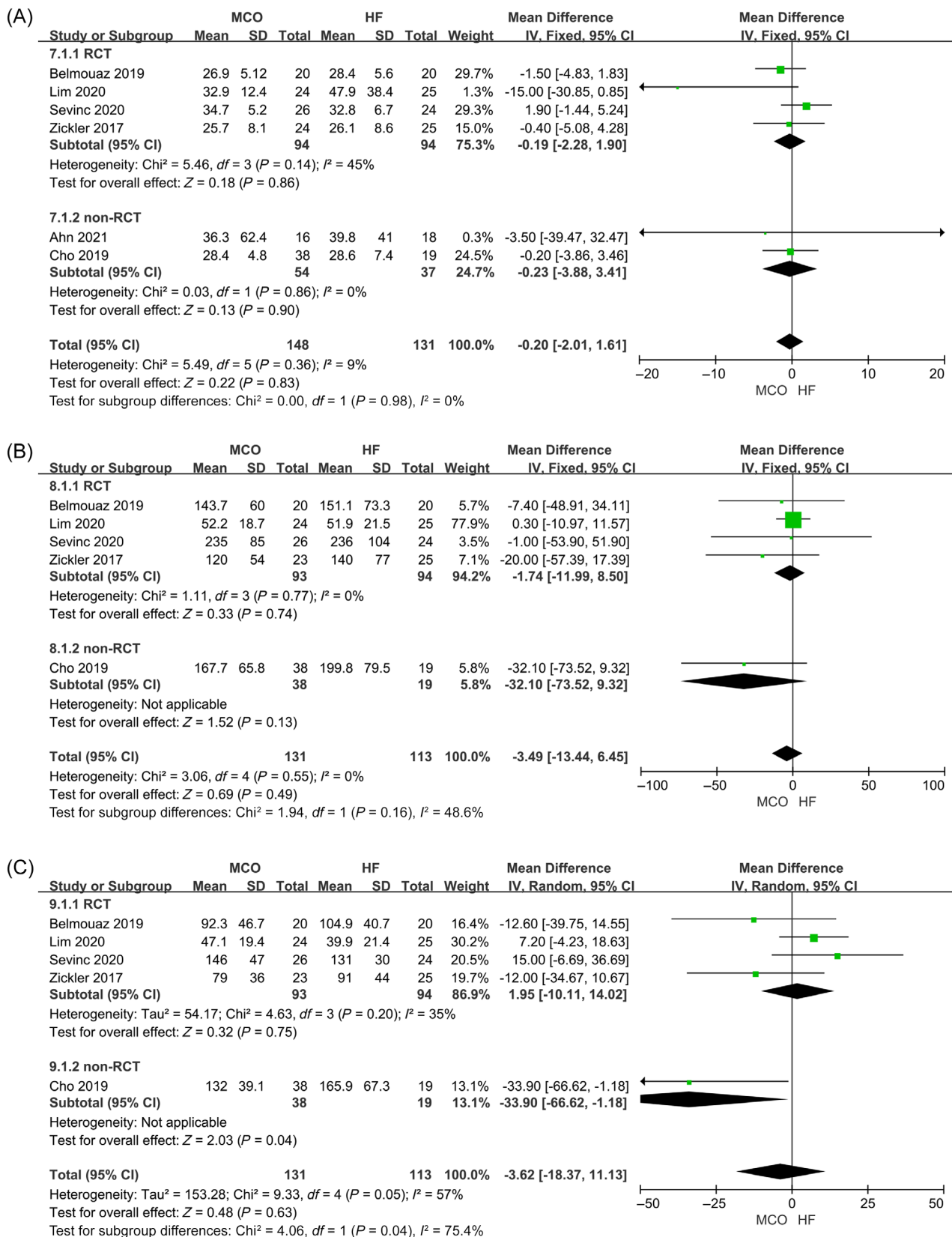
(A)

(B)

(C)

FIGURE 4 Forest plot of comparisons in MCO dialyzers vs. HF dialyzers. Outcomes included (A) the levels of β2-MG, (B) the levels of κFLC, and (C) the levels of λFLC
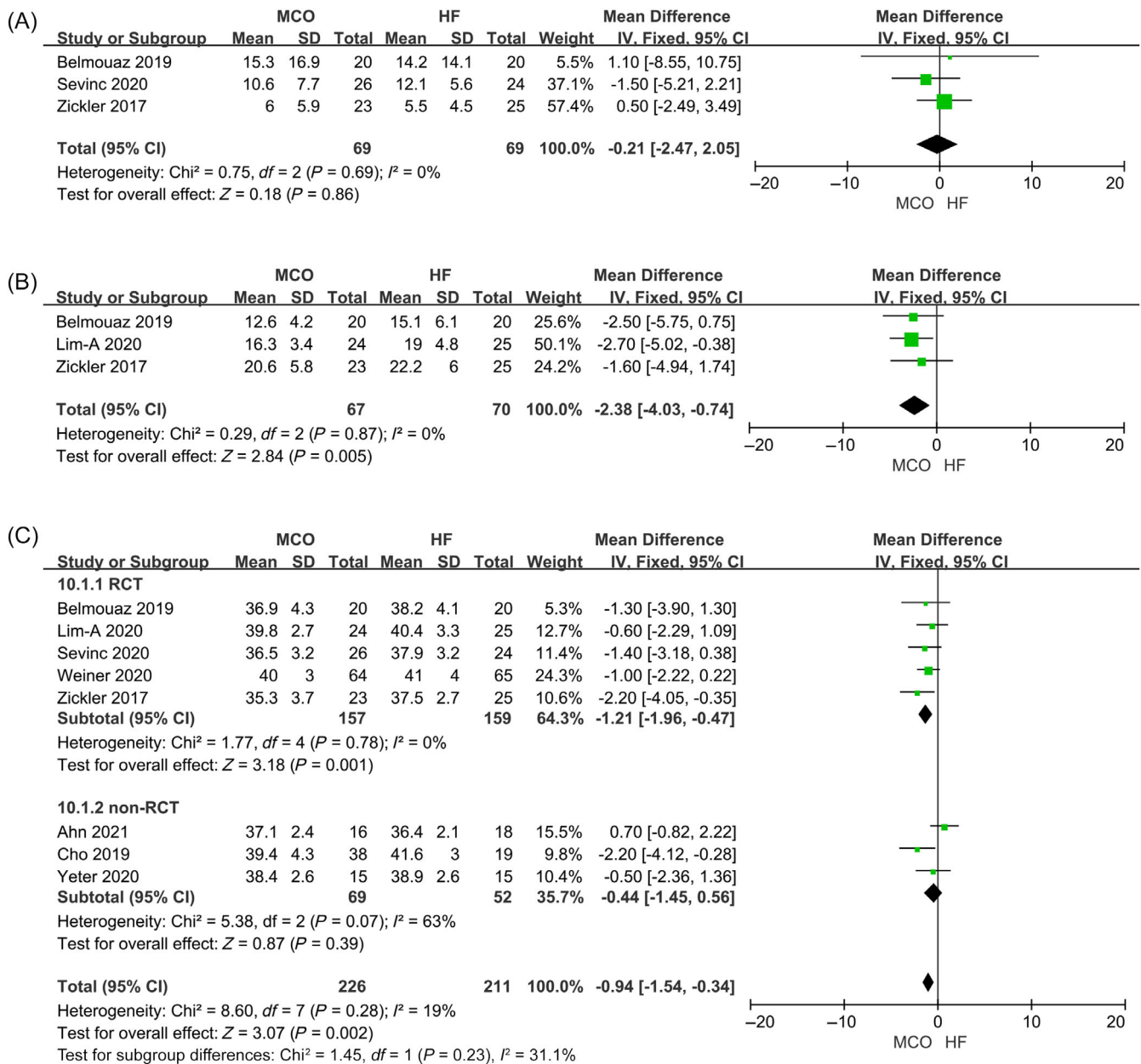
FIGURE 5 Forest plot of comparisons in MCO dialyzers vs. HF dialyzers. Outcomes included (A) the levels of IL-6, (B) the levels of TNF-α, and (C) the levels of albumin

3.5 | RR of middle molecule using MCO dialyzers compared with HF dialyzers

In a meta-analysis of six studies (512 patients) [19, 20, 22, 25, 26], the RR of β2-MG was significantly higher in patients using MCO dialyzers than those using HF dialyzers (MD = 9.16; 95% CI: 7.44, 10.88; $p < 0.00001$; Figure 3a). Subgroup analysis showed that the results of four RCTs and two non-RCTs were consistent. No heterogeneity was detected between studies (Chi^2 = 4.74, $p = 0.58$; $I^2 = 0\%$; Figure 3a).

In a pooled meta-analysis including five studies (479 patients) [19–22, 26], the RR of κFLC was significantly higher in the MCO group than in the HF group

(MD = 15.53; 95% CI: 12.96, 18.11; $p < 0.00001$; Figure 3b). We did not perform subgroup-analysis, as we only had one non-RCT. High heterogeneity (Chi^2 = 13.54, $p = 0.02$; $I^2 = 63\%$; Figure 3b) was detected among studies while that can be eliminated ($I^2 = 0\%$) after excluding data from the observational study [26].

In a pooled meta-analysis including five studies (479 patients) [19–22, 26], the RR of λFLC was significantly higher in the MCO group than in the HF group (MD = 22.99; 95% CI: 16.66, 29.32; $p < 0.00001$; Figure 3c). We did not perform subgroup-analysis, as we only had one non-RCT. There was high heterogeneity in this analysis (Chi^2 = 36.55, $p < 0.00001$; $I^2 = 86\%$;

Figure 3c) that was slightly reduced ($I^2 = 73\%$) after excluding data from the observational study [26].

3.6 | The levels of middle molecule after a period of HD using MCO dialyzers vs. HF dialyzers

In a meta-analysis of six studies (279 patients) [10, 18, 20, 21, 26], MCO dialyzers treatment led to no obvious difference in the levels of β2-MG compared with HF dialyzers therapy (MD = −0.20; 95% CI: −2.01, 1.61; $p = 0.83$; Figure 4a), with low heterogeneity in the analysis (Chi^2 = 5.49, $p = 0.36$; $I^2 = 9\%$;Figure 4a). Subgroup analysis also showed that the results of four RCTs and two non-RCTs were consistent.

In a meta-analysis of five studies (244 patients) [18–21, 26], there is no significant difference of the levels of serum κFLC between MCO group and HF group (MD = −3.49; 95% CI: −13.44, 6.45; $p = 0.49$; Figure 4b). Similarly, since we only use one non-RCT, we did not perform subgroup-analysis. No heterogeneity was detected between studies (Chi^2 = 3.06, $p = 0.55$; $I^2 = 0\%$; Figure 4b).

In a meta-analysis of five studies (244 patients) [18–21, 26], the levels of serum λFLC did not differ between the MCO group and High-flux group (MD = −3.62; 95% CI: −18.37, 11.13; $p = 0.63$; Figure 4c). Since we only had one non-RCT, we did not perform subgroup-analysis. Moderate heterogeneity was detected between studies (Chi^2 = 9.33, $p = 0.05$; $I^2 = 57\%$; Figure 4c). The heterogeneity was slightly reduced ($I^2 = 35\%$) after excluding data from the observational study [26].

3.7 | The levels of inflammatory cytokines and albumin after a period of HD using MCO dialyzers vs. HF dialyzers

In a meta-analysis of three studies (138 patients) [18–20], the levels of serum IL-6 in MCO dialyzers group was not obviously different with that in HF dialyzers group (MD = −0.21; 95% CI: −2.47, 2.05; $p = 0.86$; Figure 5a). No heterogeneity was detected between studies in this analysis (Chi^2 = 0.75, $p = 0.69$; $I^2 = 0\%$; Figure 5a).

In a meta-analysis of three studies (137 patients) [18, 19, 23], the levels of serum TNF-α in MCO dialyzers group was lower than that in HF dialyzers group (MD = −2.38; 95% CI: −4.03, −0.74; $p = 0.005$; Figure 5b). No heterogeneity was detected between studies (Chi^2 = 0.29, $p = 0.87$; $I^2 = 0\%$: Figure 5b).

In a meta-analysis pooling data from eight studies (437 participants) [18–20, 22–26], MCO dialyzers treatment led to obviously decrease the level of serum albumin compared with HF dialyzers therapy (MD = −0.94; 95% CI: −1.54, −0.34; $p = 0.002$; Figure 5c), with low heterogeneity in the analysis (Chi^2 = 8.6, $p = 0.28$; $I^2 = 19\%$; Figure 5c). Subgroup analysis showed that the results of five RCTs and three non-RCTs were inconsistent. In the RCT studies, the levels of albumin was reduced more by MCO dialyzers compared with HF dialyzers ($p = 0.001$). However, the effect MCO dialyzers and HF dialyzers treatments on the albumin levels were equivalent in the non-RCT ($p = 0.39$). All above indicated that the conclusion diverged between RCTs and non-RCTs.

4 | PUBLICATION BIAS

The potential publication bias detected by Egger's test and funnel plots. We found no publication bias for urea levels, RR of β2-MG, and albumin levels (Figure 6). Besides, apart from urea levels, RR of β2-MG, and albumin levels, we do not draw the funnel plots for the other parameters in this meta-analysis, due to the small size of these parameters in our included studies.

5 | DISCUSSION

The aim of this systematic review was to evaluate the efficacy of MCO dialyzers in comparison with HF-flux
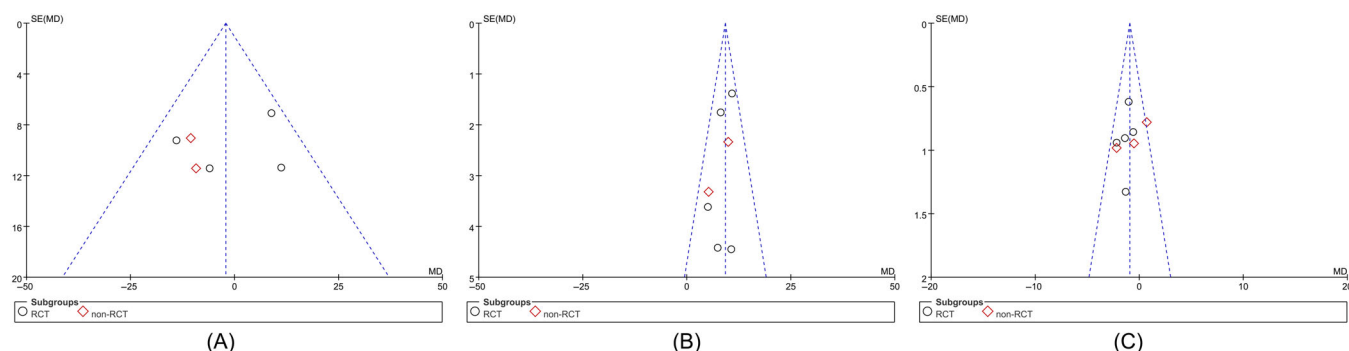

FIGURE 6 It shows publication bias assessment by funnel plot for (A) urea levels, (B) RR of β2-MG, and (C) albumin levels

dialyzers on the clearance and the circulating concentrations of uremic toxins, including small solutes, middle molecules, and inflammatory cytokines for maintenance HD patients. It also adds information about the safety of MCO dialyzers by detecting serum albumin level.

The URR, the levels of urea and creatinine were not significantly different between the two dialyzers, meaning that small solute clearance was as effective with the MCO dialyzers as compared with high-flux dialyzers. The small solutes are cleared through diffusion during HD, and the small solutes can easily pass the pores on both of the membrane.

High-flux dialyzers could clear middle molecules such as β2-MG (11.8 kDa), an smaller middle molecule, but the removal of molecules larger than 15–20 kDa is insufficient by HF dialyzers [6, 27, 28]. They cannot effectively reduce circulating levels of middle and large uremic toxins such as free kappa light chain (23 kDa) and free lambda light chain (45 kDa) [29]. Higher FLC levels could interfere with the function of neutrophil and may predispose to infections [30]. And, higher λFLC levels have been associated with increased mortality in patients with CKD [31, 32]. Compared with LF membranes, increased filtration in HF membranes considerably increases the removal of smaller middle molecules [7]. Convective therapies significantly increase lager middle molecule removal compared with diffusive therapies, especially when high transmembrane pressures (TMPs) are applied to obtain high convective volumes [33, 34]. Compared with HF dialyzers, MCO dialyzers combined the mechanism of diffusion and convection [35]. Findings from our meta-analysis demonstrate that greater clearance for β2-MG, free kappa, and lambda light chain by the MCO dialyzers than the HF dialyzers. On the basis of data from this meta-analysis, we noted a trend toward a decrease in the β2-MG, free kappa, and lambda light chain levels for maintenance HD patients in MCO dialyzers group than HF dialyzers group but without statistical significance. The factors that determine the concentrations of medium–large uremic toxins are not the dose of dialysis but mainly the residual renal function and the composition of the diet [36]. There are two possible strategies for lowering these toxins levels: first, increasing clearance by improving dialysis technologies and dialyzers, and second, reducing the formation and/or absorption of various toxins. Based on the above factors, the possible explanation for the results in our analysis may be due to that the usage of MCO membranes could not sufficiently overrides the continuous production of these toxins in the body, but the reasons need further research to explore.

It is well known that there is an inverse correlation between residual renal function and chronic inflammation. Among a large number of inflammatory markers,

IL-6 seems to be the most robust predictor of comorbidity and adverse outcome in CKD. Elevated concentration of serum IL-6 is a strong independent predictor of all-cause mortality in HD patients [37]. Moreover, studies have shown that elevated serum IL-6 levels, independent of traditional risk factors, predict accelerated atherosclerosis and cardiovascular events in maintenance dialysis patients [38]. Other inflammatory cytokines might also involve in the process of uremia complications. For example, TNF-α has been shown to down-regulate apolipoprotein E secretion, promote in vitro calcification of vascular cells, and cause endothelial dysfunction [39–41]. Most of the inflammatory markers are middle molecules, IL-6 (25 kDa) and TNF-α (17 kDa). This meta-analysis demonstrated that the use of MCO dialyzers significantly reduces the TNF-α levels than HF dialyzers, but could not obviously lower the IL-6 level. These may be explained that the size of IL-6 is bigger than TNF-α. Better removal of these molecules can be obtained by using large pore membranes with added increased convection by MCO dialyzers. While Heric et al. reviewing three studies, indicated that the reduction in inflammation markers (e.g., IL-6, TNF-α, and CRP) is not statistically different between the MCO dialyzers groups and HF dialyzers groups [42]. Further research is needed to explore the impact of MCO dialyzers on inflammatory cytokines as compared with HF dialyzers.

Current researches about whether MCO can retain albumin remains controversial. Our meta-analysis revealed that serum albumin level obviously decreased in MCO dialyzers as compared with high-flux dialyzers. This difference may suggest that use of MCO dialyzers led to more albumin loss than high-flux dialyzers. HF–HD albumin loss is usually absent or low (<2.4 g/4 h treatment) [43, 44]. While MCO dialyzers with convective therapies and highly permeable membranes may induce higher transmembrane albumin loss than the HF membranes. MCO dialyzers can remove middle and large uremic toxins close to the molecular size of albumin (68 kDa) [19, 45]. Low serum albumin level is a strong predictor of cardiovascular disease and all-cause mortality in dialysis patients. However, the correlation between hypoalbuminemia and mortality appears primarily related to chronic inflammation and inadequate albumin synthesis in malnourished patients, rather than the albumin loss during hemodialysis [46]. The consequences of a moderate decrease of serum albumin levels caused by dialytic removal are still unclear, and beneficial effect should not be ignored, as albumin is the major carrier of protein-bound toxins, such as oxidative stress markers, p-cresyl sulfate, and indoxyl sulfate.

However, further subgroup analysis stratified by study design found that in RCTs albumin level reduced

more in MCO dialyzer group while the effects of MCO dialyzer and HF dialyzer treatments on albumin levels were equivalent in non-RCT studies. Considering the multiple con-founders in non-RCTs, the differences are eliminated between the two dialyzers because of the bias of non-RCT studies. In Ahn's study [25], the albumin baseline in MCO dialyzers group is remarkably higher than that in HF dialyzers group. Although the MCO dialyzer caused more albumin loss, the final results showed that the albumin level in MCO dialyzers group was still higher than that of HF dialyzers group. Therefore, further better designed RCT studies were required to provide reliable evidences of the treatment of MCO dialyzers. The study duration is longer in non-RCT, some bias regarding albumin level might stem from the heterogeneity of measurement time. If more studies are included in the future study, stratification of study duration can be performed to exclude the bias originated from the length of dialyzers use leading to albumin loss.

There are several limitations to this systematic review and meta-analysis. First, the limitations of this review are mostly represented by the exclusive search for English-language articles and the number and quality of data available from studies. The majority of the included studies had a small number of patients. This may limit the reliability of findings from pooled meta-analyses. Second, residual renal functions of the HD patients were not adequately assessed because the amount of urine output was not collected in some of the included studies except three [20, 21, 23]. The dietary habits of the patients were not interfered in the included trials. Residual renal function and dietary are very important factors influencing the concentrations of middle molecules. Third, some of included trials are non-RCTs, which could lead to selection bias. Finally, as in many meta-analyses, we were limited by the data provided in the original studies.

In summary, the present systematic review of published trials suggested that novel MCO dialyzers show greater clearance for middle-molecules uremic toxins and obviously reduced the levels of TNF-α than HF dialyzers. We speculate that MCO dialyzers improved elimination of middle molecules uremic toxins by membranes with increased pore size and convective therapies. The effect of MCO and HF dialyzers on albumin levels diverges in RCT and non-RCT studies, so further studies are required to validate this new dialyzer.

CONFLICT OF INTEREST

All the authors have declared no competing interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. *Material preparation, data collection and analysis*:

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