Original Article

Efficacy and safety of Corbrin Capsule on malnutrition, inflammation, and atherosclerosis syndrome in patients with uremia: systematic review and meta-analysis

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Background: Uremia is a clinical syndrome caused by the development of chronic renal failure to the end-stage. Corbrin Capsule has the effect of tonifying the lungs and kidneys and improving the essence and qi, which can improve the metabolic disorders of the body. However, there is currently no systematic evaluation of the efficacy of Corbrin Capsule in the treatment of uremia malnutrition, inflammation, and atherosclerosis (MIA) syndrome. This paper aiming to provide a reference for improving the prognosis of uremic MIA patients.

Methods: According to the PICOS principle, the literature inclusion and exclusion criteria were formulated. The databases such as PubMed, Web of Science, Embase, and Cochrane Library were searched by computer using "Corbrin Capsule", "uremia", "MIA syndrome", and "kidney function" as search items. The outcome indicators were body mass index (BMI), C-reactive protein (CRP), blood urea nitrogen (BUN), and serum creatinine (sCr). Subsequently, the Cochrane Reviewer's Handbook 4.2.5 was adopted to assess the literature quality. The conventional treatment combined with Corbrin Capsule was defined as MIA/treatment group, and the conventional treatment was defined as the control group. The Review Manager (RevMan) 5.3 software was used to conduct a meta-analysis of the experimental data.

Results: A total of 6 suitable included articles were selected, including 894 patients. The included literature was analyzed and found that there was no obvious publication bias. According to the results of meta-analysis, the total BMI score was mean difference (MD) [95% confidence interval (CI)]: –0.10 (–3.44 to 3.24) with Z=0.06 and P=0.95. The CRP total score was MD (95% CI): 1.40 (0.34 to 2.46) with Z=2.58 and P=0.010. The BUN index was MD (95% CI): –1.15 (–3.05 to 0.75) with Z=1.18, P=0.24. Analysis result of sCr index data was MD (95% CI): –72.82 (–202.16 to 56.52) with Z=1.10 and P=0.27.

Discussion: Corbrin Capsule can effectively improve the relevant physiological indicators of patients with uremic MIA syndrome. However, the outcome indicators included in this study were insufficient, and it is necessary to further expand the sample size and outcome indicators in the future.

Keywords: Corbrin Capsule; uremia; malnutrition, inflammation, and atherosclerosis syndrome (MIA syndrome); renal function; meta-analysis

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Introduction

Uremia is an end-stage change in patients with chronic kidney disease (CKD), and maintenance hemodialysis treatment can remove toxic and side metabolites from the patient's body and maintain the homeostasis of the body's internal environment (1,2). However, patients undergoing maintenance hemodialysis for uremic disease develop a generalized microinflammatory state (3). In a long-term state of micro-inflammation, a series of changes in the heart structure and function of patients will also occur, which will eventually lead to the occurrence of cardiovascular disease (4). In addition, the release of inflammatory factors in the body of patients with uremia can reduce protein synthesis, further promote the decomposition and metabolism of muscle, and lead to malnutrition in patients (5). Malnutrition mainly refers to the lack of nutrients caused by protein or energy absorption disorders, insufficient intake levels, and a series of specific symptoms. It is therefore a common complication of end-stage renal disease (ESRD) and an important prognostic marker for patients with CKD (6-8). In uremic patients undergoing hemodialysis, inflammation affects the therapeutic effect and accelerates the progression of atherosclerosis, ultimately leading to cardiovascular disease (9). To this end, some scholars proposed the concept of malnutrition, inflammation, and atherosclerosis (MIA) syndrome, which emphasized the relationship between malnutrition, inflammation, and atherosclerotic cardiovascular disease in uremic patients (10,11).

Corbrin Capsule is mainly produced by low-temperature fermentation of Cordyceps sinensis strains. It has the effect of invigorating the lungs and kidneys and improving the essence and qi. It not only invigorates the lungs, kidneys, and spleen, but also regulates the metabolism of the organs, in turn promoting blood circulation and the excretion of toxins (12). Studies have confirmed that Corbrin Capsule is rich in Cordyceps polysaccharides, Cordyceps acid, nucleotides, and amino acids, which can improve the metabolic disorders of lipids and proteins in the body, and also have anti-inflammatory and antioxidant effects (13,14). Kai *et al.* showed that Corbrin Capsule could effectively reduce the levels of inflammatory factors and prevent the occurrence of contrast nephropathy when used for the protection of contrast nephropathy during coronary angiography in type 2 diabetic renal insufficiency (15). Zhao *et al.* studied the preventive effect of Corbrin Capsule on contrast agent nephropathy in patients with stable angina pectoris, and found that it can effectively prevent the damage of renal function caused by contrast agent (16). It can be concluded that most of the current research focuses on the prevention and treatment of contrast agent nephropathy, but there is no systematic evaluation of the clinical effect of Corbrin Capsule on MIA syndrome in uremia patients.

Therefore, in this study, we analyzed and explored Corbrin Capsule's impact on MIA syndrome in uremic patients, and aimed to provide a reference for the future clinical treatment and prognosis of uremic MIA patients. We present the following article in accordance with the PRISMA reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-291/rc).

Methods

Literature search

We performed a computer search of databases including PubMed, Web of Science, Embase, The Cochrane Library, and WanFang. The search time range was from January 2000 to September 2020. The search terms were set as "Bailing Capsule", "uremia", "Patients with end-stage renal disease", "MIA syndrome", "renal function", "traditional Chinese medicine".

Inclusion and exclusion criteria of literature

The inclusion and exclusion criteria were formulated according to the PICOS principle. Patients in the control group were given conventional treatment, while those in the treatment group were given Corbrin Capsule or Cordyceps sinensis on the basis of conventional treatment.

The inclusion criteria were as follows: (I) published literature exploring the effects of Corbrin Capsule on MIA syndrome in uremia patients; (II) direct or indirect evaluation of the indicators of MIA syndrome in patients with uremia; (III) at least 15 samples included in the study.

The exclusion criteria were as follows: (I) repeated publication of the same set of data; (II) review, conference report, experience lecture, case report, and research commentary; (III) research unrelated to the subject of this study; (IV) no control group set, or the samples between groups were not comparable; (V) studies where outcome indicators were not reported clearly and results data were incomplete.

Quality assessment of literature

The full texts of retrieved literature were read independently by two researchers, and they extracted relevant data. Disagreements between the two researchers were resolved through discussion, and if they failed to reach an agreement, a third researcher was invited to arbitrate. The Cochrane Reviewer's Handbook 4.2.5 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to evaluate the literature quality in terms of (I) randomized trial; (II) allocation concealment; (III) blind testing; (IV) complete result data; (V) selective reporting of results; and (VI) other bias. The specific evaluation methods of Cochrane Reviewer's Handbook 4.2.5 were shown in *Table 1*.

Data extraction

The data extracted included the following: (I) first author, year of publication, and evaluation results of the included literature; (II) the evaluation results such as the number of participants, experimental design, measures, study time, and outcome indicators; (III) baseline data of patients; (IV) indicators of feedback research quality.

Statistical methods

The software Review Manager 5.3 (RevMan 5.3; The Cochrane Collaboration, Denmark) was used for data statistics and analysis. First, heterogeneity testing was carried out for the test results at α=0.05. The heterogeneity among literatures was analyzed using the Peto method. No heterogeneity was indicated when I^2<50%, and the fixed effects model (FEM) was adopted. If I^2>50%, heterogeneity was indicated, and the random effects model (REM) was used for analysis. Continuous variables can be meta-analyzed using mean difference (MD), weighted mean difference (WMD), or standard mean difference (SMD). Dichotomous variables can be meta-analyzed using odds ratio (OR), relative risk (RR), etc. All results were expressed with 95% confidence interval (CI). A funnel plot was drawn and the publication bias was evaluated by the concentration of literature to the midline. Sensitivity analysis was used to assess the reliability and stability of the results.

Results

Literature search results and profile analysis

A total of 579 records were retrieved from the database search, and 267 abstracts were obtained after duplicates had been deleted. A total of 85 articles meeting the requirements were selected preliminarily. After further reading of full texts, articles that were not randomized, were repeatedly published, and for which full texts were unavailable were excluded, and 6 articles that met the requirements were finally included in this study (17-22). The specific retrieval process is shown in *Figure 1*, and *Table 2* shows the basic information of all literature.

Bias risk assessment of included literature

The literature quality was assessed by referring to the specific criteria in the Cochrane Handbook for Systematic Reviews of Interventions (The Cochrane Collaboration, Denmark), and the results are shown in *Figures 2,3*. None of these 6 studies had random sequence generation (selection bias), incomplete outcome data (selection bias), and selective reporting (reporting bias). Moreover, the overall risk of articles included in the study was low. As displayed in *Table 2*, all the 6 literatures included in the study had a low risk of bias, which met the requirements for subsequent analysis.

Meta-analysis of body mass index (BMI) of patients with MIA syndrome

Of the included articles, 4 studies evaluated the BMI scores of patients with MIA syndrome in the uremic patient population in detail. The BMI between the patients with MIA syndrome and the control group in the uremia patient group were compared, and the results are shown in *Figure 4*. The BMI scores of patients in the MIA group and the control group were heterogeneous (I^2=92%; P<0.00001). The REM analysis results showed that the total BMI scores of patients with MIA syndrome group and control group are analyzed as MD (95% CI): −0.10 (−3.44 to 3.24) with Z=0.06, P=0.95. This suggested that the BMI scores of the two groups of patients were not significantly different (P>0.05).

Meta-analysis of CRP levels in patients with MIA syndrome

Of the included literatures, 4 studies evaluated the CRP levels of patients with MIA syndrome in uremic patients in detail. The CRP index between the MIA syndrome patient group and the control group in the uremic patient

Table 1 Cochrane risk bias assessment tool

Field	Item	Descriptions		
		High risk of bias	Low risk of bias	Unknown risk of bias
Selection bias	Generation of random sequences	Selection bias due to improper random sequence generation	Random sequence generation can generate comparison groups	Insufficient description details
	Allocation hidden	Selection bias due to improper allocation concealment	The allocation of interventions cannot be predicted prior to enrolment	Insufficient description details
Implementation bias	Investigators and implementers were blinded	Workers understand the intervention implementation of the study and lead to performance bias	Blinding may work	Insufficient description details
Measurement bias	Blind evaluation of study results	Workers understand the intervention implementation of the study and lead to detection bias	Blinding may work	Insufficient description details
Follow-up bias	Integrity of the resulting data	Attrition bias due to incomplete outcome data	Missing outcome data have been treated with low potential for bias	Insufficient reporting of loss to follow-up and exclusion, leading to inability to judge
Reporting bias	Selective reporting of research findings	Bias due to selective reporting of results	No bias was detected in relation to selective reporting of results	Not giving enough information to make a judgment
Other bias	Other sources of bias	Bias due to issues not covered above	No other bias was detected	Possible risk of bias, insufficient information to assess other important risk of bias

group was compared, and the results are shown in *Figure 5*. The CRP index data of patients in the MIA group and the control group were heterogeneous (I^2=68%; P=0.02). The REM analysis showed the total CRP level of patients with MIA syndrome group and control group were MD (95% CI): 1.40 (0.34 to 2.46) with Z=2.58 and P=0.010. The results showed that the CRP index data of the two groups of patients were significantly different (P<0.05).

Meta-analysis of the influence of Corbrin Capsule on blood urea nitrogen (BUN) of MIA syndrome in patients with uremia

Of the included literatures, 2 studies evaluated the effect of Corbrin Capsule on MIA syndrome in patients with uremia in detail. Although other articles had simple descriptions, they did not evaluate in detail the impact of Corbrin Capsule on the specific physiological indicators of uremia patients with MIA syndrome. The BUN between the Corbrin Capsule treatment group and the control group of patients with MIA syndrome was compared, and the results are shown in *Figure 6*. The BUN of the treatment group and the control group were heterogeneous (I^2=82%; P=0.02). The REM analysis revealed that BUN of the treatment group and the control group were MD (95% CI): −1.15 (−3.05 to 0.75), Z=1.18, P=0.24. This showed that the BUN scores of the two groups were not significantly different (P>0.05).

Meta-analysis of the influence of Corbrin Capsule on serum creatinine (sCr) of MIA syndrome in patients with uremia

Of the included articles, 2 studies evaluated the effect of Corbrin Capsule on MIA syndrome in patients with uremia in detail. Although other articles had simple descriptions, they did not evaluate in detail the impact of Corbrin Capsule on the specific physiological indicators of uremia

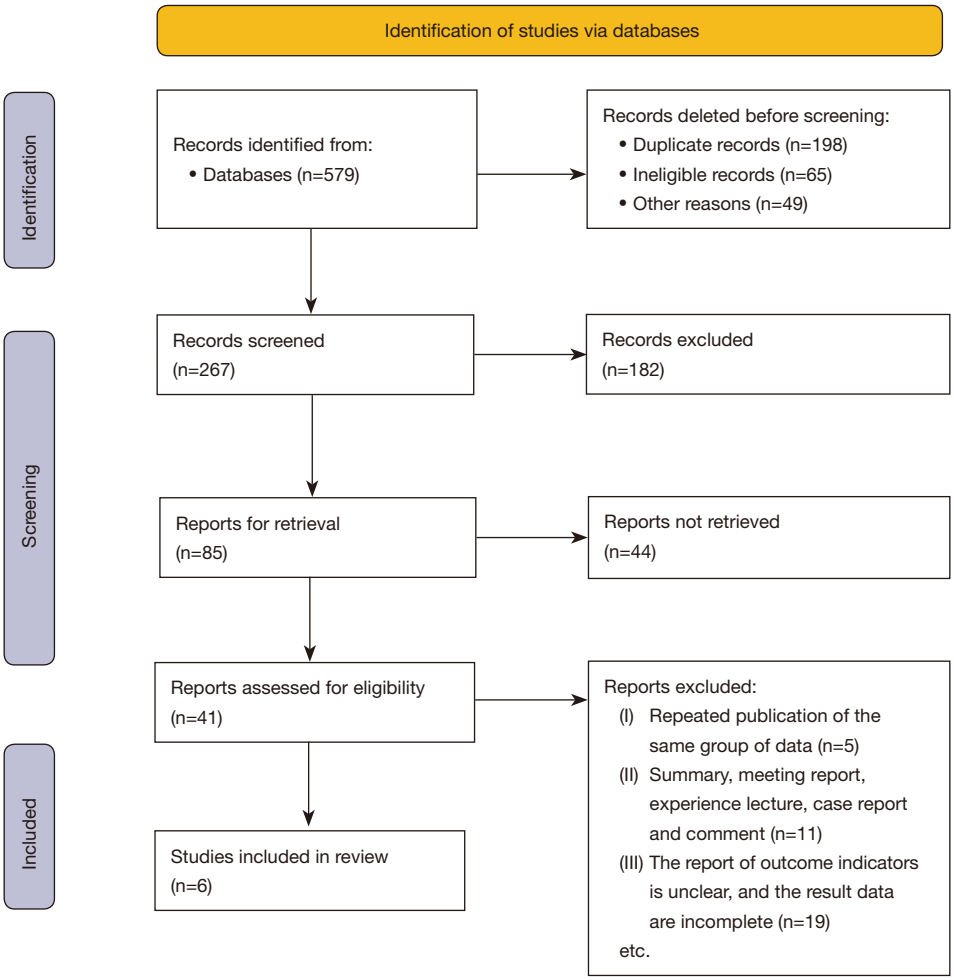

Figure 1 Literature screening process.

Table 2 Basic characteristics of the included literature

First author	Publish year	Outcome indicators	MIA/treatment	Control
Turkmen K	2013	BMI and CRP	79	20
Bammens B	2004	BMI and CRP	26	24
Terrier N	2005	BMI and CRP	57	120
Mutluay R	2019	BMI and CRP	79	78
Zhang Z	2011	BUN and sCr	122	109
Wang W	2013	BUN and sCr	80	100

BMI, body mass index; CRP, C-reactive protein; BUN, blood urea nitrogen; sCr, serum creatinine; MIA, malnutrition, inflammation, and atherosclerosis.

patients with MIA syndrome. The sCr between the Corbrin Capsule treatment group and the control group of patients with MIA syndrome was compared, and the results are shown in *Figure* 7. The sCr of patients in the treatment group and the control group were heterogeneous (I^2=100%; P<0.00001). The REM analysis results of sCr of patients in the treatment group and the control group were as follows: MD (95% CI): −72.82 (−202.16 to 56.52), Z=1.10, P=0.27. This showed that the sCr scores of the two groups of patients were not significantly different (P>0.05).

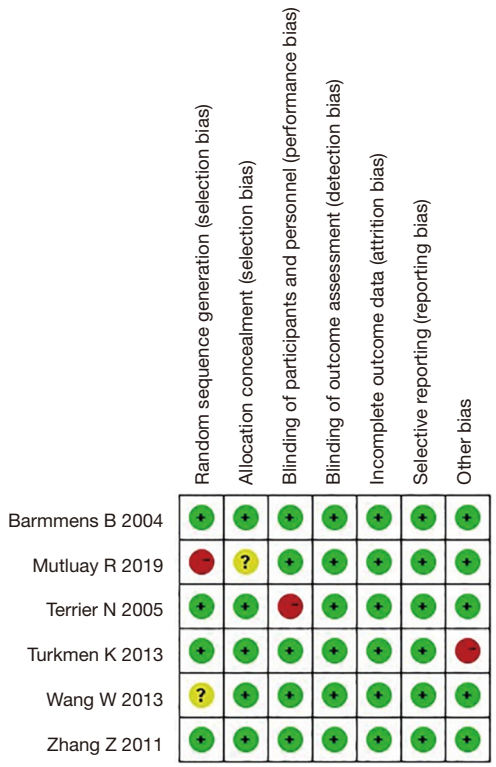

Figure 2 Bar chart of included literature bias risk assessment.

Publication bias analysis

A total of 4 evaluation indicators of patients with uremic MIA syndrome were analyzed, including BMI, CRP, BUN, and sCr, and the publication bias results are shown in *Figure 8*. The funnel charts of BMI, CRP, and BUN were basically symmetrical, and the data were also relatively concentrated. As shown in *Figure 8D*, there were individual samples in the funnel of sCr that did not fall into the funnel. This revealed that there was no big publication bias in the 4 functional indicators included in the literature of this study.

Discussion

As the terminal stage of chronic kidney failure, ESRD can be confirmed when the glomerular filtration rate (GFR) is lower than the specified level (15 mL/min/1.73 m^2) (23). Stage V CKD can be considered ESRD. After continual accumulation, toxins can cause uremia, and for this, hemodialysis must be performed for patients to maintain their normal life (24). In addition, if suitable kidney sources are found for transplant replacement, treatment can be carried out. However, patients with such diseases need to undergo prolonged hemodialysis to maintain normal physical indicators (25,26). Moreover, long-term hemodialysis often brings other types of complications to patients.

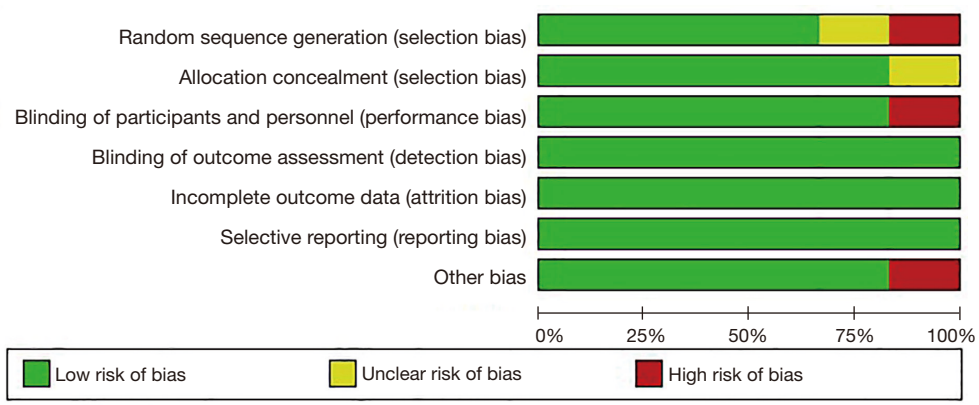

Figure 3 Summary chart of risk assessment.

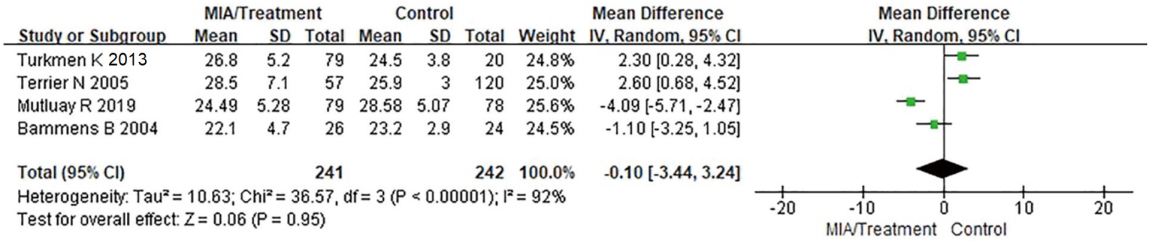

Figure 4 Forest plot of BMI scores of patients with MIA syndrome. SD, standard deviation; CI, confidence interval; BMI, body mass index; MIA, malnutrition, inflammation, and atherosclerosis.

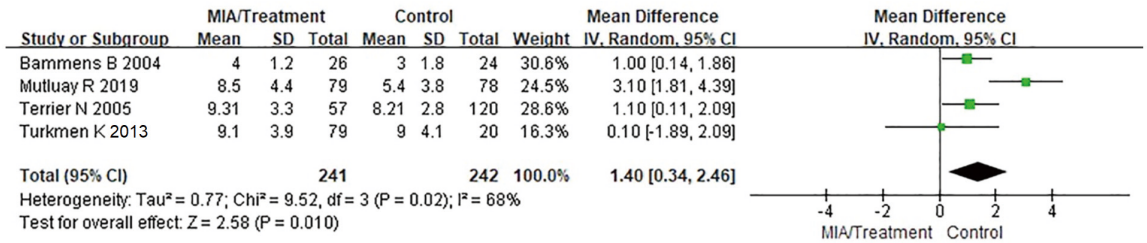

Figure 5 Forest plot of CRP scores in patients with MIA syndrome. SD, standard deviation; CI, confidence interval; CRP, C-reactive protein; MIA, malnutrition, inflammation, and atherosclerosis.

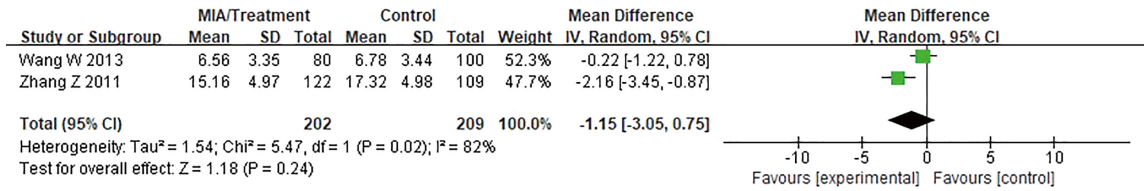

Figure 6 Forest plot of the influence of Corbrin Capsule on BUN of MIA syndrome. SD, standard deviation; CI, confidence interval; BUN, blood urea nitrogen; MIA, malnutrition, inflammation, and atherosclerosis.

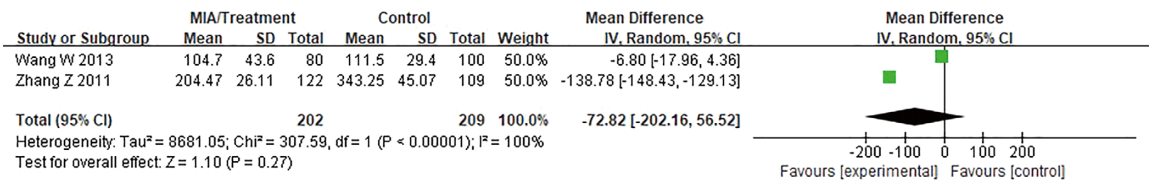

Figure 7 Forest plot of the effect of Corbrin Capsule on sCr in MIA syndrome. SD, standard deviation; CI, confidence interval; sCr, serum creatinine; MIA, malnutrition, inflammation, and atherosclerosis.

Patients with renal diseases such as uremia treated by dialysis have problems of poor quality of life and high mortality. Cardiovascular disease is the main cause of death in dialysis patients, and 30% to 60% of patients with ESRD suffer from malnutrition (27). In recent years, a large number of studies have confirmed that there is a causal relationship between malnutrition, inflammation and atherosclerosis (28,29). Due to the accumulation of toxins in the body, patients with uremia will experience problems such as anorexia, nausea and vomiting, and cause insufficient

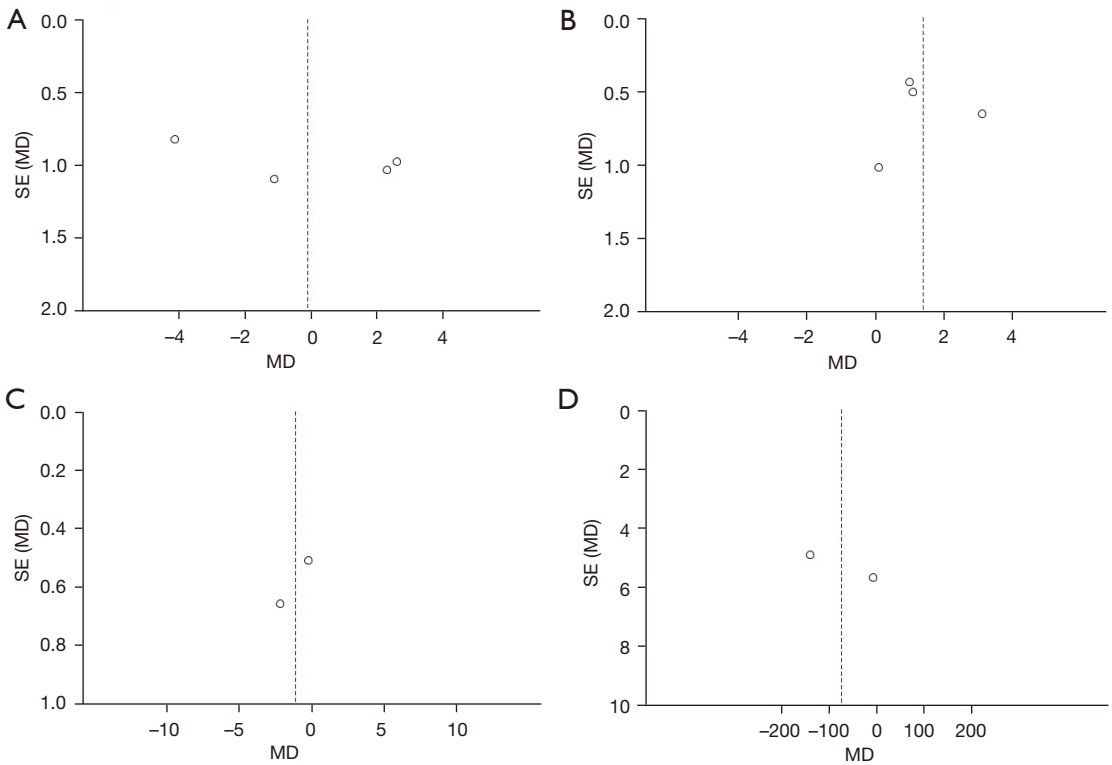

Figure 8 Funnel charts of related indicators. (A) The BMI total score funnel chart; (B) the CRP funnel chart; (C) the BUN funnel chart; (D) the sCr funnel chart. SE, standard error; MD, mean difference; BMI, body mass index; CRP, C-reactive protein; BUN, blood urea nitrogen; sCr, serum creatinine.

protein and calorie intake. Due to the above problems, patients with uremia will have problems such as abnormal metabolism and abnormal hormone levels, which will cause malnutrition in patients. MIA syndrome is prevalent in patients with renal insufficiency and affects the prognosis of patients (30).

According to relevant literature data, the incidence of MIA syndrome in patients with ESRD during perinatal hemodialysis treatment is up to 80%, and it has become the leading killer of kidney disease patients (31). Researchers have suggested that inflammation is a key issue in the 3 complications of MIA syndrome. Inflammation can lead to further accelerated kidney failure in patients with ESRD (32). In related studies, Corbrin Capsule has been shown to significantly reduce inflammation (33,34). The data showed that Corbrin Capsule has an ideal effect on reducing CRP levels in patients with inflammation (35). Corbrin Capsule is a product processed and extracted from cordyceps sinensis. It can effectively improve the inflammatory response of the human body, restore metabolic capacity, and have a good effect in accelerating the protein synthesis of the human body.

In short, the effects of Corbrin Capsule on MIA syndrome in patients with uremia were analyzed and compared. The results showed that patients with uremia syndrome and patients with MIA syndrome have significant differences in these indicators, which had effectively reduced BUN and sCr. However, due to the conditions for systematic review and meta-analysis, the analysis of evaluation indicators was still few, which should be further increased to more indicators analysis.

Conclusions

The objective of this study was to analyze the effects of Corbrin Capsule on MIA syndrome in uremia patients. A total of 6 appropriate references were selected, including 1,103 patients. Then, RevMan 5.3 was used to conduct meta-analysis of the experimental data. According to the results of meta-analysis, there were significant differences in BUN and CRP in patients after treatment. The effects of Corbrin Capsule on MIA syndrome in uremia patients

were analyzed and compared, and it was found that patients with uremia syndrome and patients with MIA syndrome have significant differences in these indicators, which had effectively reduced BUN and sCr. In summary, this study provides a further theoretical basis for subsequent studies on the efficacy of Corbrin Capsule in the treatment of MIA syndrome in uremia patients.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-291/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-291/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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