Original Article

A systematic review and meta-analysis of the efficacy of aerobic exercise combined with resistance training on maintenance hemodialysis patients

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Background: Chronic kidney disease (CKD) is a life-threatening illness that causes significant pain to patients, this serious impact on patient's physical fitness and quality of life. Previous studies have found that exercise training has a positive impact on improving CKD patients' symptoms. In order to improve patients' physical function and quality of life, this meta-analysis aimed to evaluate the application value of aerobic exercise combined with resistance training in maintenance hemodialysis (MHD) patients.

Methods: A computer search was conducted of PubMed, Cochrane Central Register of Controlled Trials, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang, and Weipu databases. The search keywords were: "chronic kidney disease", "end-stage renal disease", "hemodialysis", "maintenance hemodialysis", "exercise", "aerobic exercise", "resistance exercise", "combined exercise", and "physical exercise". Included studies should meet the following criteria, the study population is MHD patients, the intervention is aerobic exercise combined with resistance training, and a randomized controlled study with clearly documented outcome indicators. The Cochrane risk-of-bias tool was used to evaluate the quality of the included studies, and the meta-analysis was performed by RevMan 5.20 software (Cochrane Collaboration).

Results: A total of seven articles met the inclusion criteria. The included studies were assessed for risk of bias and met the inclusion criteria. The results of the meta-analysis showed significant differences between patients who received aerobic exercise combined with resistance training and control patients (the rest treatment was same as the study group) in the urea clearance index [mean difference (MD) =0.16, 95% confidence interval (CI): 0.10, 0.21], mental health (MD =7.54, 95% CI: 2.74, 12.35) and social functioning (MD =9.98, 95% CI: 1.52, 18.44). However, there was no significant difference in physical functioning between the two groups (MD =1.26, 95% CI: −1.20, 3.71).

Discussion: Although aerobic exercise combined with resistance training did not improve the physical functioning of MHD patients, it improved their urea clearance, mental health, and social functioning and positively affected their quality of life, risk of bias should also be considered. In the future, multi-center studies with larger samples should be used to explore the effects of aerobic exercise combined with resistance training on MHD patients.

Keywords: Aerobic exercise; resistance exercise; chronic kidney disease (CKD); hemodialysis; meta-analysis

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Introduction

Chronic kidney disease (CKD) is a type of disease that causes ongoing and irreversible damage to the function and structure of the kidneys over months or years due to various reasons. Common causes of CKD include glomerulonephritis, diabetes, high blood pressure, and poisoning. According to the definition and classification of CKD proposed by the National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKFKDOQI) in 2002, if kidney damage or a low glomerular filtration rate (GFR; <60 mL/min per 1.73 m^2) persists for three months or more, a diagnosis of CKD is made, and with the progression of the disease, it will eventually develop into end-stage renal disease (ESRD).

ESRD is the most serious stage of various CKDs and is characterized by high morbidity, irreversibility, and mortality. According to the Dialysis Outcomes and Practice Patterns Study (DOPPS) in 2011, the incidence of ESRD in the United States had reached 1,210 people per million. Japan's incidence had reached 2,213.4 people per million (1), and the number of patients who underwent hemodiafiltration (HDF) at the end of 2013 was 31,371, a marked increase from that in 2012 (2). Maintenance hemodialysis (MHD) is currently the most important treatment for patients with ESRD. According to the statistics (3), in 2011 alone, there were approximately 2.16 million patients on hemodialysis worldwide, a year-on-year increase of 6.4%. Therefore, CKD has a large impact on the population and a heavy economic burden, making it a major public health problem that needs to be urgently solved (4,5).

Drug therapy, dialysis, or kidney transplantation are the main treatment options for most patients with CKD. Both drugs and dialysis treatment are painful, and surgical medical procedures are costly, with a scarce supply of donor kidneys. Finding new interventions may provide hope for ESRD treatment. Some studies have found that exercise can be used to treat CKD. In these studies, patients with CKD were divided into three approximate cohorts before dialysis, maintenance dialysis treatment, or kidney transplantation, and exercise intervention was received. It was found that exercise had a positive effect (6-8), mainly because exercise has a targeted and positive impact on the causes of CKD, such as chronic inflammation, cardiovascular disease, and diabetes. Exercise also has a beneficial effect on many risk factors for CKD, such as high blood pressure. Exercise has been shown to improve the cardiovascular health and vascular function of patients with CKD (9-11).

Aerobic exercise, resistance training, and a combination of the two exercise regimes have attracted attention because of their efficacy. Resistance training is a method of muscle training that uses fitness equipment such as elastic bands to maintain a constant movement speed. However, it has been reported that aerobic exercise had no effect on the corresponding outcome indicators, and it has been difficult to explain the mechanism of aerobic exercise on patients with CKD (12). On the other hand, another study reported that after 35 weeks of aerobic training, the glomerular filtration rate and exercise endurance of patients with CKD were positively affected (13). There is also evidence that muscle strength significantly increases, and diastolic blood pressure decreases when CKD patients receive resistance training (14). However, the research conclusions on these issues remain controversial.

Based on the above reports and an understanding of the relevant literature, this study aims to use a meta-analysis to evaluate the effects of aerobic exercise combined with resistance training on patients with CKD requiring continuous hemodialysis. We present the following article in accordance with the PRISMA reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-226/rc).

Methods

Search strategy

We searched the English biomedical databases PubMed, Cochrane Central Register of Controlled Trials, Embase, and Web of Science. We also searched the major Chinese biomedical databases: China National Knowledge Infrastructure (CNKI), Wanfang, and Weipu. The language was limited to Chinese and English. The keywords for the search were as follows: "chronic kidney disease", "end-stage renal disease", "hemodialysis", "maintenance hemodialysis", "exercise", "aerobic exercise", "resistance exercise", "combined exercise", and "physical exercise". These keywords were searched individually and in combination, and the reference lists from relevant systematic reviews and meta-analyses were tracked to identify additional studies. The retrieval time was from the establishment of the databases to September 2021.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (I) patients over

18 years of age who met the diagnostic criteria for primary CKD. (II) The study design was a randomized controlled trial (RCT) comparing aerobic exercise combined with resistance training in patients with CKD. (III) Outcome indicators included one or more of the following: urea dialysis clearance rate, improvement in physical functioning, mental health status, and social functioning. (IV) The study group did not involve any other interventions except aerobic exercise combined with resistance training and MHD. (V) The intervention in the control group was the same as in the study group, except that the study group added aerobic exercise combined with resistance training. The following situations were excluded: (I) research on animals, children, adolescents, or pregnant women. (II) Non-randomized controlled trials. (III) Studies that included other interventions beyond the purpose of the study. (IV) Studies that did not include urea dialysis clearance rates, physical function improvement, mental health status, and social functioning as outcome indicators.

Literature screening and risk of bias

Two reviewers independently evaluated the titles and abstracts of articles to determine whether they were eligible to be selected for the study. If any reviewer believed that the article met the criteria, the full text was reviewed. Any differences of opinion between the two reviewers about the article qualifications were resolved by discussion. If the discussion failed to resolve the difference of opinion, a third reviewer was consulted for a final decision. If additional information about the study was required, the reviewers contacted the corresponding authors to obtain the relevant information. The Cochrane RoB 2.0 risk-of-bias tool was used to assess the quality of the included articles and the risk of bias.

Data extraction

The patients included in the meta-analysis were divided into two groups: an aerobic exercise combined with resistance training group and a control group. The data were independently extracted by two reviewers in accordance with the pre-established data tables. The basic data extracted included the author's name, country, publication date, journal name, and patient demographics. The recorded results included the urea dialysis clearance rate and improvements in physical functioning, mental health status, and social functioning. The two reviewers exchanged data sheets and cross-checked the extracted data. If there were any differences of opinion, these were resolved by discussion.

Statistical analysis

Percentages and relative risk (RR) or mean difference (MD) with 95% confidence interval (CI) were used to describe the data. The I^2 test was used to test for heterogeneity, and if the heterogeneity between studies was small ($P>0.1$, $I^2<50\%$), a fixed-effects model was used to merge the effect sizes; if there was apparent heterogeneity between studies ($P\leq0.1$, $I^2\geq50\%$), a random-effects model was used to merge the effect sizes. And a sensitivity analysis was carried out according to the Cochrane systematic review method. The statistical analysis and graphs were generated by RevMan 5.20 software (Cochrane Collaboration). A P value ≤0.05 was considered to be a statistically significant difference. A funnel plot was used to assess the risk of publication bias.

Results

Search results and study characteristics

There were 836 records initially identified in the databases. Of these, 49 duplicate records were removed. Preliminary screening of the remaining 787 records excluded 92 records due to low quality, leaving 695 records to be retrieved. A total of 612 articles were successfully retrieved, including 318 English articles and 294 Chinese articles. After a thorough full-text reading, studies were excluded that did not meet the inclusion and exclusion criteria, had incomplete data, or were not RCTs. A final number of seven articles were included in the present meta-analysis. The specific process is shown in *Figure 1*.

Of the seven articles available, four reported the urea dialysis removal rate, five reported physical functioning, four reported mental health, and three reported social functioning. All selected articles included patients with a clear diagnosis of CKD and met the inclusion and exclusion criteria. There were 164 patients in the aerobic exercise combined with resistance training group and 167 patients in the control group. The basic characteristics of the articles are shown in *Table 1*.

Results of the quality assessment revealed that of the seven included studies, only four described the random sequence generation, five reported allocation concealment, and only one article reported the double-blind method and

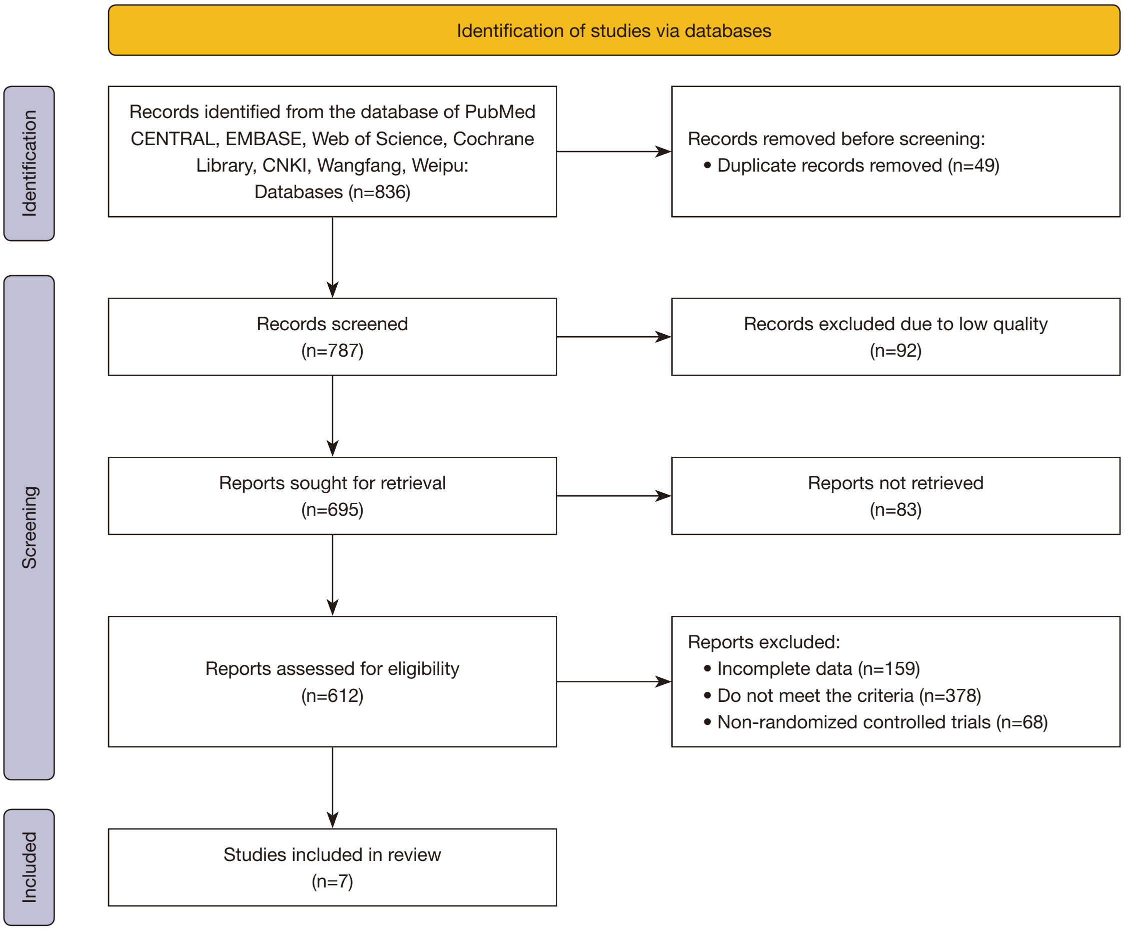

Figure 1 Flow diagram of the search, screening, and inclusion process.

Table 1 Basic characteristics of the included studies

Author	Country	Year	Journal	Exercise group (n)	Control group (n)
Abreu *et al.* (15)	Brazil	2017	*Life Sci*	25	19
Dong *et al.* (16)	China	2019	*Int Urol Nephrol*	21	20
Huang *et al.* (17)	China	2020	*Int Urol Nephrol*	16	16
Jamshidpour *et al.* (18)	Iran	2020	*J Bodyw Mov Ther*	15	13
Valenzuela *et al.* (19)	Spain	2018	*Front Physiol*	27	40
Xu *et al.* (20)	China	2016	*Zhengzhou University*	45	44
Zhao *et al.* (21)	China	2020	*Clin Nephrol*	15	15

the blinding of outcome assessments. All articles described incomplete data outcomes, selective report bias, and other risk biases. The quality assessment results are shown in *Figure 2*.

Meta-analysis results

Urea clearance index

According to the inclusion and exclusion criteria, four articles were included to analyze the effect of aerobic exercise combined with resistance training on the urea clearance index of MHD patients. There were 77 patients in the aerobic exercise combined with resistance training group and 70 patients in the control group. The heterogeneity analysis results showed P=0.61, I^2=0%, indicating homogeneity in the urea clearance rate between the training and control groups, so a fixed-effects model was used for the combined analysis. The combined effect size was MD =0.16, 95% CI: 0.10, 0.21, as shown in *Figure 3*. The comprehensive effect size test result was Z=5.29, P<0.00001, indicating that the difference in urea clearance between the aerobic exercise combined with resistance training group and the control group was statistically significant.

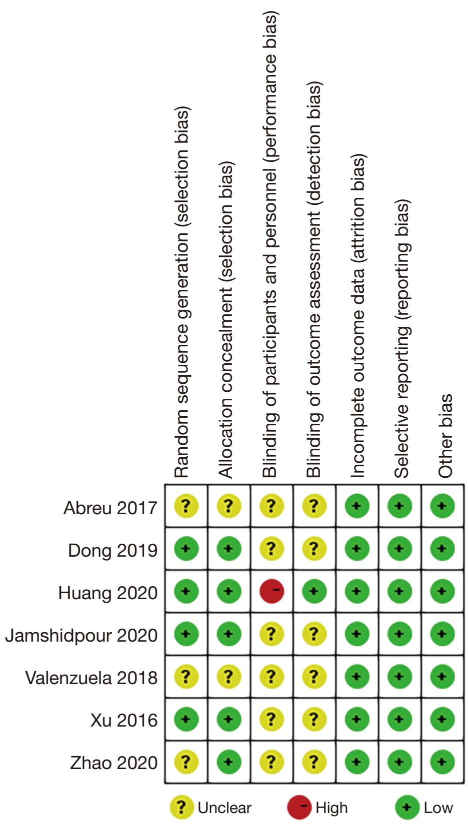

Figure 2 Literature quality evaluation details. "?" indicates that the risk is unclear; the red circle with a "-" indicates that the risk is high; the green circle with a "+" indicates that the risk is low.

Improvement in physical functioning

Five articles reporting on physical functioning were included to analyze the effect of aerobic exercise combined with resistance training on the physical functioning of MHD patients. There were 128 patients in the aerobic exercise combined with resistance training group and 132 patients in the control group. The heterogeneity analysis results showed P=0.86, I^2=0%, indicating that homogeneity existed in the physical functioning measures between the training and control groups, so a fixed-effects model was used for the combined analysis. The combined effect size was MD =1.26, 95% CI: −1.20, 3.71, as shown in *Figure 4*. The result of the comprehensive effect size test was Z=1.00, P=0.31, indicating that there was no statistically significant difference in physical functioning between the aerobic exercise combined with resistance training group and the control group.

Mental health improvement

A total of four articles were included that studied the effects of aerobic exercise combined with resistance training on the mental health of MHD patients. There were 83 patients in the aerobic exercise combined with resistance training group and 88 patients in the control group. The heterogeneity analysis results showed P=0.19, I^2=36%, indicating that homogeneity existed in the mental health improvement between the training and control groups, so a

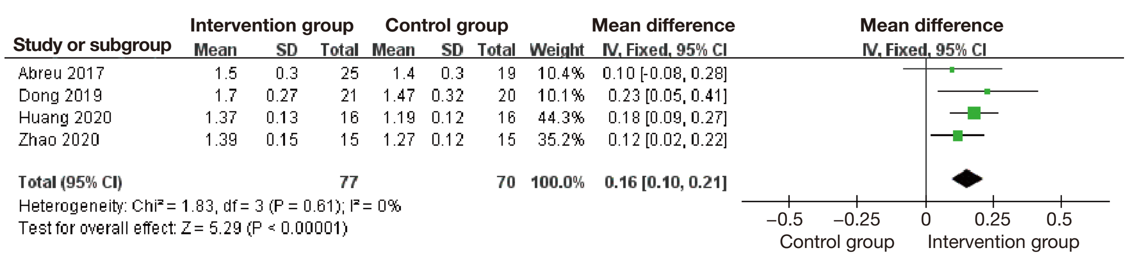

Figure 3 Forest plot of urea clearance index. Comparison of urea clearance index between the aerobic exercise combined with resistance exercise training group and the control group. Statistical method: inverse variance of fixed effects model (MD and 95% CI). MD, mean difference; CI, confidence interval.

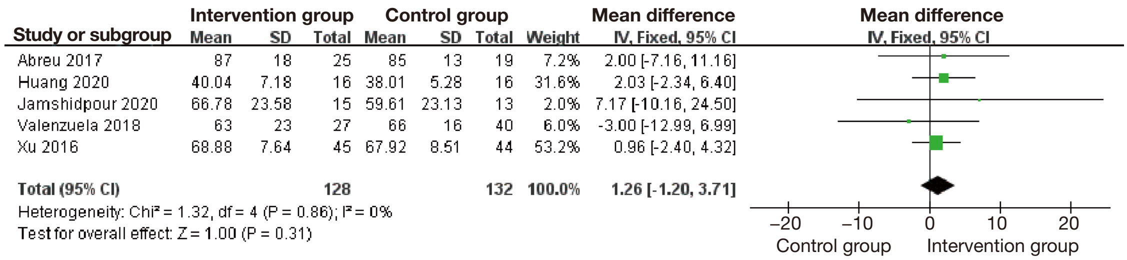

Figure 4 Forest plot of physical function improvement. Comparison of physical function improvement between the aerobic exercise combined with resistance exercise training group and the control group. Statistical method: inverse variance of the fixed effects model (MD and 95% CI). MD, mean difference; CI, confidence interval.

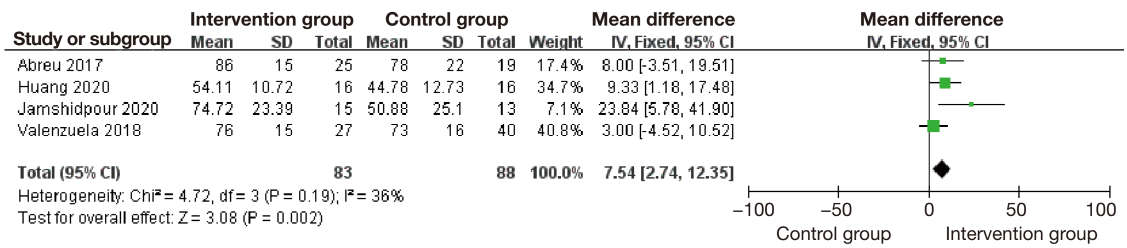

Figure 5 Forest plot of mental health improvement. Comparison of mental health improvement between the aerobic exercise combined with resistance exercise training group and the control group. Statistical method: inverse variance of the fixed effects model (MD and 95% CI). MD, mean difference; CI, confidence interval.

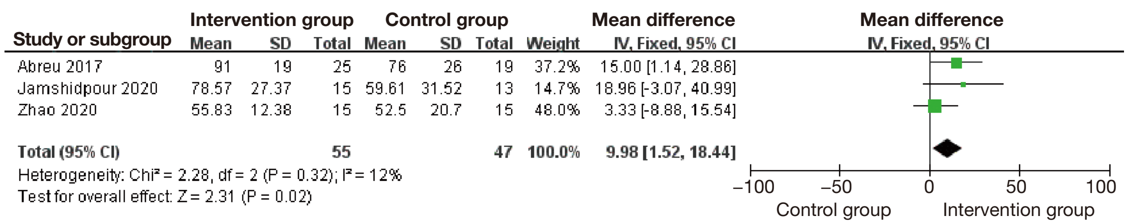

Figure 6 Forest plot of social function improvement. Comparison of social function improvement between the aerobic exercise combined with resistance exercise training group and the control group. Statistical method: inverse variance of the fixed effects model (MD and 95% CI). MD, mean difference; CI, confidence interval.

fixed-effects model was used for the combined analysis. The combined effect size was MD =7.54, 95% CI: 2.74, 12.35, as shown in *Figure 5*. The comprehensive effect size test result was Z=3.08, P=0.002, indicating that the difference in mental health between the aerobic exercise combined with resistance training group and the control group was statistically significant.

Improvement in social functioning

Three articles were included in the meta-analysis that studied the effects of aerobic exercise combined with resistance training on the social functioning of MHD patients. There were 55 patients in the aerobic exercise combined with resistance training group and 47 patients in the control group. The heterogeneity analysis results showed P=0.32, I^2=12%, indicating that homogeneity existed in the social functioning between the training and control groups, so a fixed-effects model was used for the combined analysis. The combined effect size was MD =9.98, 95% CI: 1.52, 18.44, as shown in *Figure 6*. The comprehensive effect size test result was Z=2.31, P=0.02, indicating that the difference in social functioning between the aerobic exercise combined with resistance training group and the control group was statistically significant.

Publication bias

A funnel plot was used to check the publication bias of the improvement in physical functioning. As shown in *Figure 7*, the funnel plot showed asymmetry, indicating the possibility of publication bias.

Risk of bias

Among the seven eligible studies, four articles displayed a low risk of bias in random sequence generation (16-18,20), and three articles had an unclear risk of random sequence bias (15,19,21). Five articles displayed a low risk of bias for allocation concealment (16-18,20,21), and two articles had an unclear risk of allocation concealment bias (15,19). One article had a high risk of bias in the blinding of participants and researchers (17), while six articles had an unclear risk of bias (15,16,18-21). One article displayed a low risk of bias in the assessment of the blinded results (17), while the risk of bias in the other six articles was unclear (15,16,18-21). All studies were judged to have a low risk of bias for incomplete outcome data, selective reporting domains, and other biases, as shown in *Figure 8*.

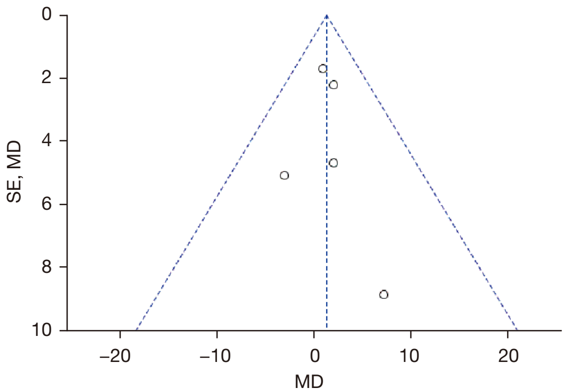

Figure 7 Funnel plot analysis of possible publication bias for physical function improvement. MD, mean difference; SE, standard error of the mean.

Discussion

CKD is a clinical syndrome caused by damage to the structure or function of the kidneys caused by various reasons, including the accumulation of metabolites and water-electrolyte and acid-based balance disorders (13,22). The clinical manifestations include impaired physical and cognitive functioning, which can lead to a decline in physical ability and quality of life (23). Exercise therapy has been developed by the American Medical Association and the American College of Sports Medicine. Exercise assessments can be carried out for specific patients, and exercise or treatment models can be formulated to achieve individualized treatment. The American Kidney Disease Quality of Life Guidelines (KDOQI) recommends exercise therapy as an important adjunct to the treatment of MHD patients. It is recommended that patients without contraindications should exercise as much as possible to improve their health (12,24). In clinical practice, it is a common exercise method to take the aerobic exercise capacity that the patient can withstand and the appropriate resistance force for muscle strength training. Exercise therapy for MHD patients has become a recent focus of research, but there are few studies on aerobic exercise combined with resistance training interventions.

This study shows that aerobic exercise combined with resistance training can significantly improve patients' urea

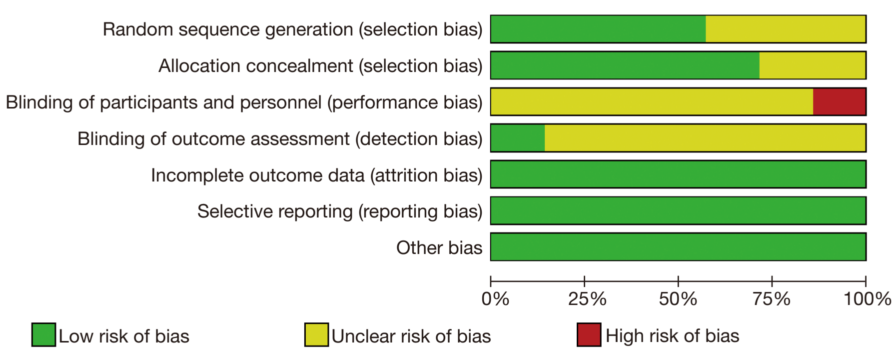

Figure 8 The intensity and distribution of the quality risk of the articles included in the study.

dialysis clearance rates, similar to results from the previous study (25). The possible reasons that exercise can improve urea removal are as follows: in hemodialysis at rest, the exchange of serum urea between the systemic circulation and the dialysate is slow. In hemodialysis combined with exercise, muscles are compressed during exercise, blood circulation is accelerated, and the exchange of metabolites between tissue cells and blood is accelerated (6,8). The increase of metabolites in the blood promotes the clearance of urea. Exercise will cause sweat excretion, and urea in the body will be excreted together with sweat, thereby increasing the excretion of urea and water.

Quality of life refers to the comprehensive evaluation of an individual's physical, mental, and social functioning. The quality of life of MHD patients is significantly lower than that of the general population and is closely related to the long-term survival rate (26). This study shows that aerobic exercise combined with resistance training does not significantly improve the physical functioning of MHD patients but does significantly improve their mental health and social functioning compared with control patients. One reason for this finding could be as follows: exercise does not improve the patient's physical functioning because the patient's underlying cause has not been completely removed, but increased exercise can enhance musculoskeletal strength and athletic ability, thereby improving the patient's self-confidence and social range and enabling the recovery of mental health and social functioning.

The present study is limited due to the small sample size and the insufficient power of the analysis to provide conclusive results. In the future, multi-center, large-sample research should be performed, and RCTs should be used to comprehensively study the effects of aerobic exercise combined with resistance training on MHD patients.

Conclusions

In summary, although aerobic exercise combined with resistance training does not improve the physical functioning of MHD patients, it can significantly improve the urea dialysis clearance rate, mental health status, and social functioning of MHD patients and has a positive impact on the quality of life of MHD patients. However, the present study has shortcomings, such as the small sample size. In the future, multi-center and larger sample size studies should be conducted to comprehensively research the effect of aerobic exercise combined with resistance training on MHD 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-22-226/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https:// apm.amegroups.com/article/view/10.21037/apm-22-226/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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