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Review Article

Different hemodialysis methods for survival of patients with maintenance hemodialysis: a meta-analysis

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Abstract: Objective: To compare the effects of low flux hemodialysis (LFHD) and high flux hemodialysis (HFHD) on survival of patients undergoing maintenance hemodialysis (MHD) with a meta-analysis. Methods: Data on randomized controlled trials and prospective controlled ones involving survival of MHD patients by LFHD or HFHD were retrieved from the computer-based databases (CNKI, EM-BACE, Cochrane Library, PubMed, VIP Chinese database, Wanfang database), with the retrieval period ranging from the date of database establishment to November 5th, 2016. The eligible studies were selected according to the pre-specified inclusion and exclusion criteria. After data extraction and quality assessment by independent reviewers, a meta-analysis was conducted using the RevMan5.2 software, with all-cause mortality as the primary outcome and the rate of death from vascular diseases and the rate of death from infection as secondary outcomes. Results: Nine studies involving 8,662 patients were enrolled. The meta-analysis showed significant lower all-cause mortality in the patients with HFHD than those with LFHD (pooled hazard ratio (HR)=0.71, 95% confidence interval (CI): 0.63-0.82; $P < 0.001$). Analysis on subsets of follow-up < 3 years and > 3 years revealed that all-cause mortality in HFHD patients was evidently lower than that in LFHD patients ($P < 0.001$). Among all the hemodialysis patients, there were more deaths from cardiovascular diseases than deaths from infection (P=0.005). The rate of death from cardiovascular diseases was markedly higher in the patients with LFHD than those with HFHD (pooled OR=0.79, 95% CI: 0.65-0.96, P=0.02); but there was no statistical difference in the rate of death from infection between patients with LFHD and HFHD (pooled OR=0.90, 95% CI: 0.69-1.18, P=0.45). Conclusion: Scientific application of HFHD in the treatment of MHD patients resulted in a pronounced improvement in survival and a reduction in death from cardiovascular disease in patients.

Keywords: Different hemodialysis methods, maintenance hemodialysis, survival rate, meta-analysis

Introduction

Patients with chronic renal disease at the fifth stage are required to undergo hemodialysis. Although hemodialysis improves the quality of life of patients, it still causes high annual mortality [1]. One study revealed inadequate clearance of small-molecular-weight uremic toxins was a key determinant for high mortality from chronic renal disease [2]. And some studies have indicated that high flux hemodialysis (HFHD) results in a remarkable reduction in the mortality of chronic renal disease [3]. In 1992, Santoro et al. reported an 88% drop of risk for death in patients having chronic renal disease, of whom HFHD instead of low flux hemodialysis (LFHD) had been used in a dialysis center in the USA [4]. In another study, the HFHD patients were reported to be at more than 40% lower risk for death. However, as it was a retrospective study, there might exit some bias [5]. Therefore, a meta-analysis was conducted to pool the randomized controlled trials and prospective controlled ones regarding survival of the patients with HFHD or LFHD to explore the effects of the two hemodialysis methods on survival of the patients undergoing maintenance hemodialysis (MHD).

Materials and methods

Bibliographic search

Computer-based retrieval was conducted to search for literature regarding the effects of LFHD and HFHD on survival of patients with maintenance hemodialysis from journals in China and other countries. The common Chinese databases, Wanfang, VIP and CNKI databases were used for searching for the data, with the keywords divided into three types: firstly, LFHD and HFHD; secondly, chronic renal disease, diabetic nephropathy and hypertensive nephropathy; thirdly, case-fatality rate, mortality rate, all-cause mortality, infection, and cardiovascular mortality. The word "OR" was used to link the above individual keywords within each subtype, and the word "AND" to link the keyword among the three subtypes. The foreign-language databases included the Cochrane CENTRAL Registry, PubMed, and EM-BACE; the retrieval methods were as follows: first, "CKD" chronic kidney disease and hypertensive nephropathy were linked by the word "OR"; second, low flux hemodialysis "LFHD" and High flux hemodialysis "HFHD" were linked by the word "OR"; third, death rate or mortality, all-cause mortality (ACM), cardiovascular death rate and infection by the word "OR". The word "AND" was used to link the keyword among the three subtypes. The retrieval period lasted from the time of database establishment to November 5 th, 2016. Besides, the references of the documents reviewed in this study were also reviewed.

Inclusion and exclusion criteria

The previous studies were included in this meta-analysis if they were prospective controlled trials or randomized controlled ones exploring the effect of LFHD or HFHD on survival of patients with maintenance hemodialysis, regardless of the use of double blinding; routine hemodialysis was carried out with the use of a HFHD dialyzer, with the membrane ultrafiltration coefficient (kuf) ≥ 20 $mL*h^{-1}*mmHg^{-1}$; routine hemodialysis was conducted with a LFHD dialyzer with the membrane ultrafiltration coefficient (kuf) of less than < 20 $mL*h^{-1}*mmHg^{-1}$, or β2-microglobulin clearance of less than 10 mL/min; the primary outcomes in the studies included were death from cardiovascular disease and all-cause mortality. Studies were excluded if they met any of the following conditions: Related studies were non-clinical and designed as non-randomized trials, with the included patients without chronic kidney disease; the study including less than 60 cases; the study was longer than 8 years, with poorly-evaluated results, and the full texts lacking support from important data or only providing abstracts; uncertain diagnostic criteria or the studies similar with those in published articles. Moreover, the studies in which the patients had renal dysfunction induced by acute nephritis, fever, acute urinary infection and acute metabolic dysfunction or medication were also excluded for this meta-analysis.

Data inclusion and quality evaluation of the articles

The system reviewers reviewed the eligible literature by the article quality evaluation method from the Hand-book 5.2 statistical software of Cochrane Collaboration. In case of disagreement, agreement reached through collective discussion. When evaluating the quality of the articles, the following aspects should be taken into consideration: accuracy of randomization, blinding implementation, the integrity of the data and results, masking ways of the protocol, other bias, or no results of selective reports. The extracted data included: intervention methods, statistical methods, sampled grouping methods, inclusion criteria for the patients and the sample size, the clinical basic data of the subjects and the follow-up period. In case of data deficiencies, additional data on the control and experimental groups related to this meta-analysis could also be extracted and used.

Statistical analyses

A meta-analysis was conducted by using Handbook 5.2 statistical software of Cochrane Collaboration. The heterogeneity among the similar studies was analyzed with the use of chi-square tests and I^2 tests. Clinical non-heterogeneity was $P \geq 0.1$ and $I^2 \leq 50\%$, and the fixed effect model was applied. When heterogeneity ($P < 0.1$ or $I^2 > 50\%$) was present, clinical heterogeneity should be analyzed first. There was no difference in heterogeneity among the results of the studies ($P > 0.05$) after subset analysis (follow-up < 3 years or > 3 years), indicating that heterogeneity might be derived from the data and factors obtained after subset analysis. Then a meta-analysis was conducted regarding the results of each subset. If the causes of heterogeneity remained unclear, the random effect model was used for re-analysis. Odds ratio (OR) or hazard ratio (HR) and 95% confidence interval (CI) were utilized in statisti-

Table 1. Basic characteristics and data of the included literature

Author	Country	Study design	Sample size/n		Age/n		Gender (male, female)/n		Follow-up (year)
			HFHD	LFHD	HFHD	LFHD	HFHD	LFHD	
Petar S 2015	Seville	Prospective single-center randomized controlled	64	69	59.9±11.8	67.2±10.8	44, 20	35, 34	2
Hyung 2014 Dialysis < 3 mon	Korea	Prospective multicenter randomized controlled	334	831	59±14	59±14	205, 129	507, 324	2
Hyung 2014 Dialysis > 3 mon	Korea	Prospective multicenter randomized controlled	807	834	58±13	59±13	463, 344	458, 376	2
Asci G 2013	Turkey	Randomized controlled	352	352	58.5±13.8	58.7±14.5	272, 80	187, 165	3
MPO 2009	Italy	Prospective multicenter randomized controlled trial with parallel design	318	329	59.4±14.5	60.2±12.7	200, 118	215, 114	Median time of 3
Angela K 2008	Germany	Prospective multicenter randomized controlled	166	236	66.1±7.8	68.7±8.3	91, 75	129, 107	Maximum 7.5
Yokoyama H 2008	Japan	Prospective multicenter randomized controlled	595	612	59.3±0.5	59.1±0.5	339, 256	392, 220	4
Chauveau P 2005	France	Prospective multicenter randomized controlled	301	349	58±16	63±16	175, 126	203, 146	2
HEMO 2003	US	Prospective multicenter randomized controlled	921	925	57.7±13.9	57.6±14.2	399, 522	409, 516	6

Note: HFHD, high flux hemodialysis; LFHD, low flux hemodialysis.

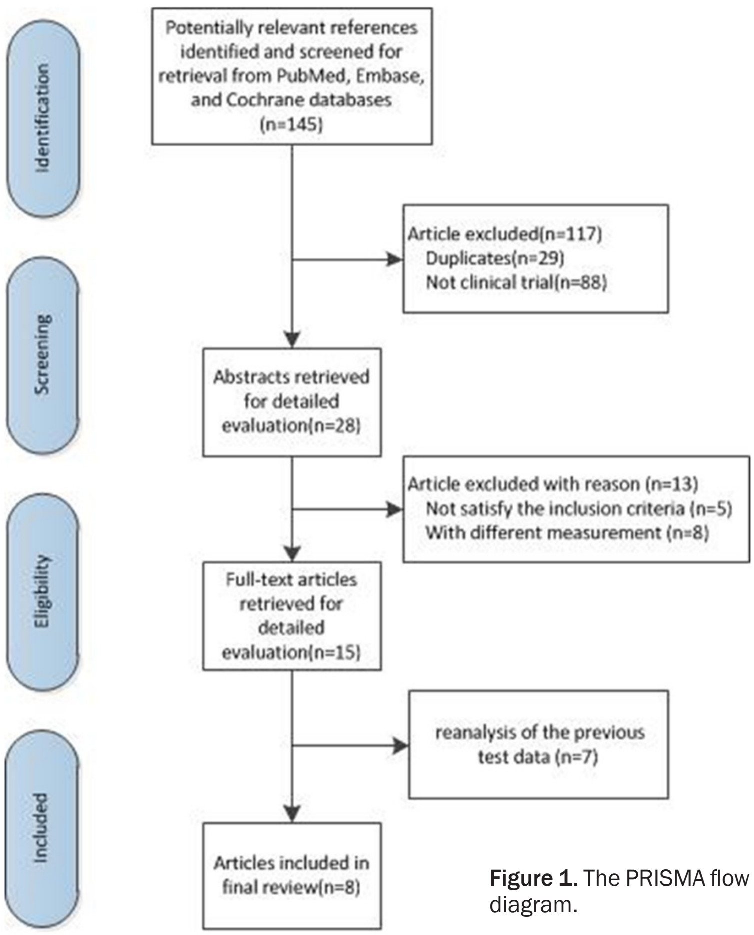

Figure 1. The PRISMA flow diagram.

cal analysis for count data. The publication biases were plotted by the Hand-book 5.2 statistical software: If there were no publication biases, the data obtained from each study would present symmetric inverted-funnel-shaped distribution on the chart; otherwise, the asymmetric inverted-funnel distribution indicated the existence of sample bias.

Results

Basic data

In this study, 145 associated articles were preliminarily retrieved, and all the articles were imported into the literature management software Endnote X7 for screening. One hundred and sixteen articles were left after removal of repetitive articles. Eighty-eight articles, which did not meet the inclusion criteria (only the trial methods were introduced in the review or the full text, etc.), were excluded after the titles and the full texts had been reviewed. In this manner, the remaining 28 articles were obtained. Of the remaining 28 articles, 5 were excluded because the interventions did not meet the inclusion criteria; 8 were also excluded due to different measurement indicators; 7 were excluded for the trials in which should be re-analyzed. Finally, only 8 articles were included in this study, including 9 studies (two of which were found in one article) involving a total of 8,395 patients [6-13]. See **Table 1** and **Figure 1**.

Bias risk assessment of included studies

The 9 included studies at baseline were rather comparable but had different degrees of deviation. The data on the results of the studies were at high risk of loss, which might be due to the long follow-ups in the studies. The development of the patients' disease was related to the protocols. The quality of the overall literature enrolled in this meta-analysis was relatively high (**Figure 2**).

Meta-analysis

Nine eligible studies including 8,395 patients were recruited in this meta-analysis. Inverted funnel plot showed no significant biases (**Figure 3**). The results of this meta-analysis indicated that all-cause mortality was obviously lower among MHD patients undergoing HFHD than among those with LFHD ($P < 0.00001$). According to the results of subset analyses, for the patients (four studies including 3,589 patients) with follow-up < 3 years, the mortality of the patients with HFHD was markedly lower than that of those with LFHD ($P < 0.00001$). Likewise, for those with follow-up > three years (five studies including 4,806 patients), deaths with HFHD were much fewer than those with LFHD ($P < 0.00001$), as seen in **Figure 4A**.

LHFD vs. HFHD for death from cardiovascular disease

Three studies were enrolled in the meta-analysis. The result of the heterogeneity test revealed that $P=0.84$ and $I^2=0\%$, which indicates that

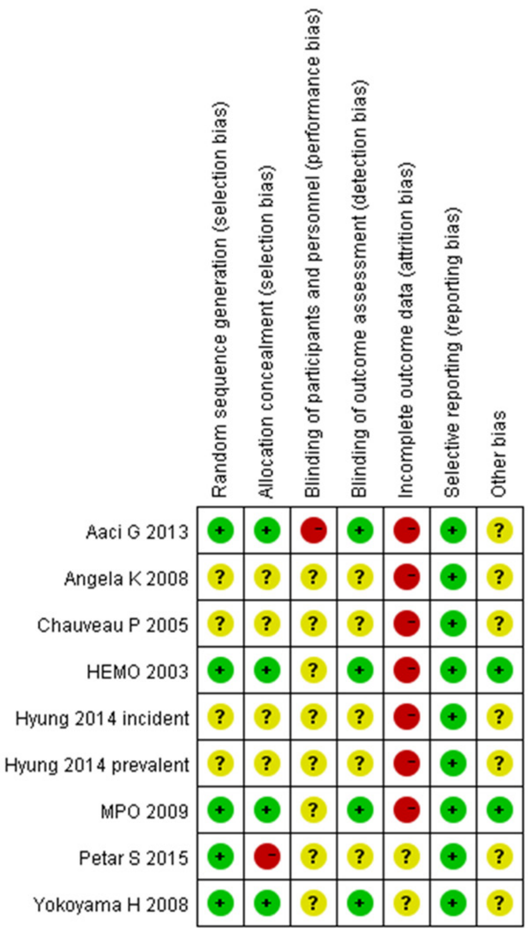

Figure 2. Bias risk map + low risk; -, high risk; ?, unclear risk.

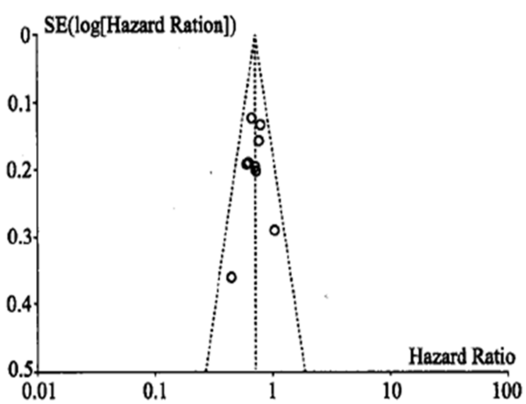

Figure 3. The bias funnel plot of studies comparing all-cause mortality.

homogeneity of each study was good and the fixed-effect model was used. The comparison between the 1,591 patients with HFHD and 1,606 with LHFD showed that HFHD resulted in a lower rate of death from cardiovascular disease among MHD patients (OR=0.79, 95% CI 0.65, 0.96, P=0.02), as shown in **Figure 4B**.

Death from infection vs. cardiovascular disease

Three articles with 1,298 patients were enrolled for the meta-analysis. The result of the heterogeneity test revealed that P=0.03, I^2=66%, which indicates the homogeneity of each study was poor. The random-effect model was used for analysis. The meta-analysis suggested that the mortality of cardiovascular disease was higher in the LHFD group than in the HFHD group and the difference was significant (P=0.005, **Figure 5**).

LHFD vs. HFHD for death from infection

Two studies were included for the meta-analysis. The result of the heterogeneity test revealed that P=0.61, I^2=0%, which indicates that homogeneity of each study was good and the fixed-effect model was used. The rates of death from infection was insignificantly different between the patients in the HFHD group (n=1,239) and those in the LHFD group (n= 1,254) (OR=0.90, 95% CI: 0.69-1.18, P=0.45, **Figure 6**).

Discussion

The studies included in this meta-analysis were large-scale trials, and all the ones with small sample size were excluded in the process of screening. Additionally, the patients in the experimental groups and the control group in the studies included had different dialysis membrane materials used, with followed ups ranging from 2 to 7.6 years. The course of dialysis and flow of dialyzing fluid were imbalanced among the eligible patients. The specificity of this meta-analysis led to the difficulty in double blinding, which might directly affect the results of the current meta-analysis. Because of the limited clinical data available, in this meta-analysis, we were unable to make normal analysis and reparative subset analyses on types of dialysis membranes as well as dialysis fluid and biocompatibility.

In our study, the meta-analysis demonstrated considerably better long-term survival in the MHD patients with HFHD than those with LHFD, which was substantially different from the results of conventional analysis that LHFD and

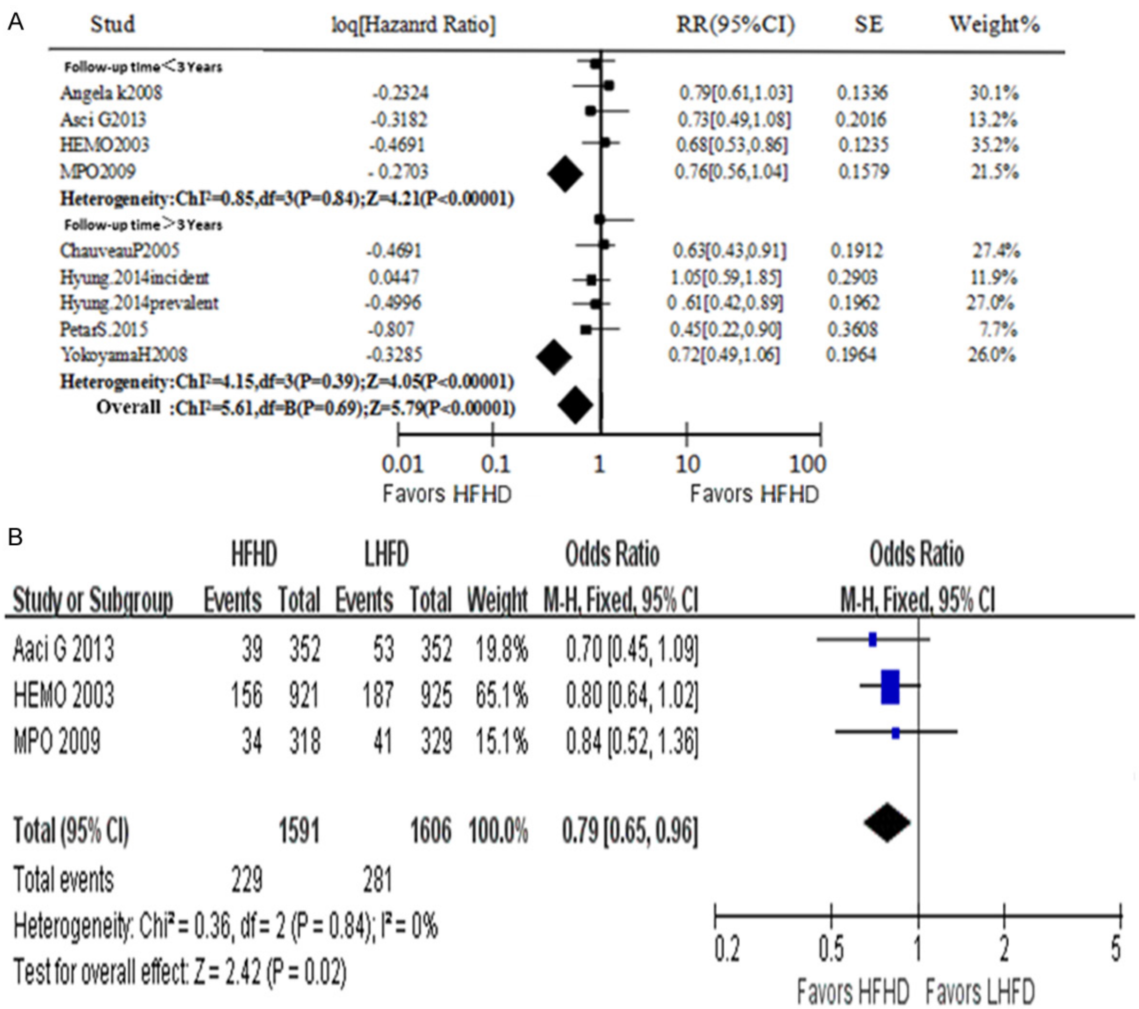

Figure 4. A. HFHD vs. LHFD for the risks for all-cause mortality; B. HFHD vs. LHFD for the risks for death from cardiovascular events HFHD, high flux hemodialysis; LFHD, low flux hemodialysis.

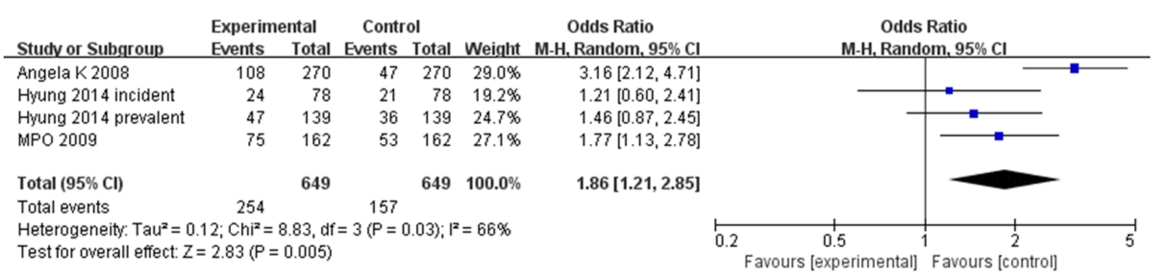

Figure 5. Comparison of mortality caused by cardiovascular events and post infection mortality.

HFHD could not change all-cause mortality in patients. Related studies have shown that the rates of survival and death risk of patients with HFHD were lower than 76.61% and 50%, respectively [6]. In addition, the mortality of diabetes patients was reduced by about 38% after HFHD treatment. Some scholars argued that HFHD improved the long-term survival of the patients with hemodialysis duration < 3.7 years [6]. The current meta-analysis showed that HFHD significantly improved all-cause mortality among the patients with follow ups > 3 years or < 3 years. Given the limited enrolled samples, additional studies with larger sample sizes are

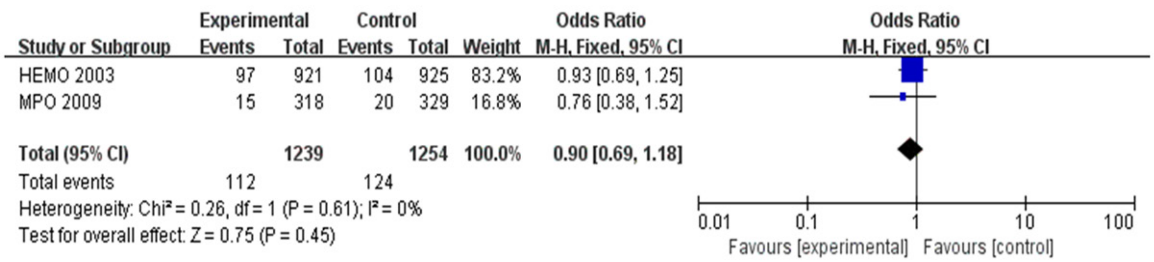

Figure 6. LHFD vs. HFHD for deaths from infection HFHD, high flux hemodialysis; LFHD, low flux hemodialysis.

needed for further research. For the MHD patients, most of deaths from cardiovascular disease were caused by infection, but HFHD was effective in reducing the rate of deaths from cardiovascular disease. This might be related to the fact that HFHD has the advantages of better β2 microglobulin clearance, improved lipid and vascular endothelial functions, more effective clearance of inflammatory mediators in the blood circulation and a lower level of B-type natriuretic peptide (BNP).

The results of this meta-analysis indicated that HFHD was effective in the treatment of some special patients with chronic kidney disease. This may be explained by the cause that HFHD could in some extent protect the cardiovascular system. If a patient undergoes long hemodialysis, HFHD can effectively protect the patient from having cerebrovascular diseases [13]. Nevertheless, the MPO study involving the clinical data of many enrolled subjects revealed that HFHD was not more effective than LFHD in the treatment of patients with chronic kidney disease. And if the patient's serum albumin is below 40 g per liter, then the survival rate of the patients with HFHD will increase by 51% [14]. The patients with long term hemodialysis are clinically at high risk for infection, mostly infected in the lung [15, 16]. HFHD has shown to effectively clear inflammatory cytokines, but there is a two-way forced ultrafiltration in the process of HFHD [17, 18]. In this case, anti-ultrafiltration is inevitable, and the safety of HFHD use can be effectively improved by elevating the purity of dialysis fluid [19, 20]. The results of the current meta-analysis indicated no notable difference between HFHD and LHFHD in the morbidity of patients.

In conclusion, the results of this meta-analysis showed that long-term survival of patients with HFHD are significantly superior to that of those with LFHD, and the finding can bring some insights into the clinical hemodialysis.

Disclosure of conflict of interest

None.

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