Original Article

Cost-effectiveness analysis of hemodialysis plus hemoperfusion versus hemodialysis alone in adult patients with end-stage renal disease in China

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Background: This study evaluates the cost-effectiveness of hemodialysis (HD) plus hemoperfusion (HP) with HD alone in adult patients with end-stage renal disease (ESRD) in China.

Methods: A Markov model was constructed to assess the cost-effectiveness of interventions over a lifetime horizon. Model parameters were informed by the HD/HP trial, the first randomized, open-label multicenter trial comparing survival outcomes and incidence of cardiovascular disease (CVD) for HD + HP versus HD alone, and supplemented by published literature and expert opinion. The primary outcome was the incremental cost-effectiveness ratio (ICER) with respect to quality adjusted life-years (QALY). The robustness of the results was examined in extensive sensitivity analyses. Analyses were conducted from a healthcare perspective. Costs were reported in both Chinese Renminbi (RMB) and US Dollars (USD) in 2019 values.

Results: The base case ICER of HD + HP is RMB 174,486 (USD 25,251) per QALY, which is lower than the RMB 212,676 (USD 30,778) willingness-to-pay threshold of three times Gross Domestic Product. This conclusion is sensitive to the mortality for patients with no severe CVD events, the incidence of CVD events, and the cost of HP and HD. At a willingness-to-pay threshold of RMB 212,676 (USD 30,778) per QALY gained, the probability that HD + HP is cost-effective is 58%.

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Conclusions: Our results indicate a potential for HD + HP to be cost-effective for patients with ESRD. Further evidence on the longer-term impact of HD + HP on CVD event rates and mortality unrelated to CVD is needed to robustly demonstrate the cost-effectiveness of HD + HP.

Trial Registration: The HD/HP trial was registered with the Chinese Clinical Trial Registry (ChiCTR-IOR-16009332).

Keywords: End-stage renal disease (ESRD); cost-utility analysis; Markov model; hemodialysis (HD); hemoperfusion (HP)

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Introduction

End-stage renal disease (ESRD) is a serious illness associated with significant health consequences and substantial financial burden. The number of ESRD patients in China was estimated at 20 million in 2017 (1). The options of renal replacement treatment for ESRD include hemodialysis (HD), peritoneal dialysis, and kidney transplant. According to the China National Hemodialysis and Peritoneal Dialysis Registry (1), the majority of patients who required renal replacement treatment received HD (86.7%), with the remaining patients receiving peritoneal dialysis (13.3%). Kidney transplant is rare in China due to high treatment costs and shortage of kidneys.

Although HD can efficiently remove small water-soluble uremic toxins, such as urea or parathyroid hormone, it is less efficient in removing medium or large, protein-bound uremic toxins such as phenolic or indolic compounds. The latter uremic toxins are closely associated with a high incidence of cardiovascular disease (CVD), which accounts for over 50% of all-cause mortality for patients with ESRD in maintenance HD. Hemoperfusion (HP) allows for the removal of uremic toxins by direct contact with activated charcoal or resin via adsorption. Several small-scale clinical trials have demonstrated that HD combined with HP can effectively remove small water-soluble solutes, medium-sized molecules and protein-bound uremic toxins (2-6). However, none of the previous trials directly assessed the impact of HP on clinical outcomes such as CVD events or survival. In addition, use of HP is associated with increased cost. The monthly cost of HP per patient in China is estimated to be $333 US dollars (7). To our knowledge, none of the existing studies have assessed the cost-effectiveness of HP for patients with ESRD. In 2014, the first clinical trial which aimed to compare the survival outcomes of HD + HP with HD alone for patients with ESRD was conducted in China ("HD/HP trial", registration number: ChiCTR-IOR-16009332) (8). This study exploits data collected by the HD/HP trial along with data from the literature to evaluate the cost-effectiveness of HD + HP as an alternative to HD alone for patients with ESRD. We present the following article in accordance with the Consensus on Health Economics Evaluation Report Standards (CHEERS) reporting checklist (available at https://dx.doi.org/10.21037/atm-21-1100) (9).

Methods

This analysis compared the cost-effectiveness of HD + HP versus HD alone for a hypothetical cohort of 54-year-old adults with ESRD in China requiring renal replacement treatment. Following the revised Brennan's toolkit (10), a Markov model was chosen to simulate the incidence, costs and outcomes of CVD events and calculate the life-time costs and quality adjusted life expectancy. The model was parameterized using data from the HD/HP trial and published literature.

HD/HP trial

The HD/HP trial is a randomized, open-label multicenter trial which compared the clinical effectiveness and safety of HD/HP versus HD alone for patients with ESRD in China. The protocol of the study was reported in Lu *et al.* (8) and is briefly summarized below. The inclusion criteria of the HD/HP trial were:

- Aged 18–75 years;
- Receiving regular blood purification treatment for at least 3 months before enrolment in the study;

- Standard Kt/V≥1.2.[1]

Patients were excluded if they had a life expectancy less than 1 year; had abnormal white cell count; or had major cardiovascular events in the past eight weeks. Patients were randomly allocated to the two arms with a 1:1 ratio, without stratification by patient characteristics. The following data were collected at baseline and six follow-ups (4, 12, 24, 48, 72 and 96 weeks): major CVD events and cause of death (CVD or non-CVD). Quality of life was measured by the Kidney Disease Quality of Life Short Form (KDQOL-SF) at baseline and 96-week follow-up. Major CVD events included angina pectoris, myocardial infarction, severe arrhythmia, congestive heart failure, cerebral infarction, heart surgery, and peripheral vascular disease. Treatments in the HD group were specified as low-flux HD treatment at a frequency of two times a week and online hemodiafiltration treatment at a frequency of once a week, with each treatment session lasing 4 hours. Treatments in the HD + HP group were specified as all treatments in the HD group, as well as HP (HA130 HP cartridge, Jafron Biomedical Co., Ltd, China) once every 2 weeks.

The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethical Committee of the 30 participating centers (Xinhua Hospital, Shanghai, China; Renji Hospital Shanghai Jiao Tong University School of Medicine, Shanghai, China; Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; Shanghai General Hospital (Songjiang District), Shanghai, China; Jinshan Hospital Affiliated to Fudan University, Shanghai, China; the Fifth People's Hospital of Shanghai, Fudan University, Shanghai, China; Changhai Hospital Affiliated to The Second Military Medical University, Shanghai, China; Tongji Hospital Affiliated Tongji University of Shanghai, Shanghai, China; Hongshan Hospital of Shanghai, Shanghai, China; Dongfang Hospital Affiliated Tongji University of Shanghai, Shanghai, China; Yangpu Hospital Affiliated to Shanghai Tong Ji University, Shanghai, China; Longhua Hospital Shanghai University of Traditional Chinese Medicine, Shanghai, China; 455 Hospital of Chinese Liberation Army, Shanghai, China; 85 Hospital of People's Liberatlon Army, Shanghai, China; Armed Police Corps Hospital of Shanghai, Shanghai, China; Shanghai Construction Group (SCG) Hospital, Shanghai, China; Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine Chongming Branch, Shanghai, China; Central Hospital of Minhang District, Shanghai, China; the Fifth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine Songjiang Branch, Shanghai, China; Seventh People's Hospital of Shanghai University of Traditional Chinese Medicine, Shanghai, China; Changning District Central Hospital of Shanghai, Shanghai, China; Jing'an District Central Hospital of Shanghai, Shanghai, China; Tongren Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; Renji Hospital Shanghai Jiaotong University School of Medicine, Jiading Branch, Shanghai, China; Zhabei District Central Hospital of Shanghai, Shanghai, China; the Sixth Hospital Affiliated to Shanghai Jiao Tong University School of Medicine Jinshan Branch, Shanghai, China; Shanghai Fengxian District Central Hospital, Shanghai, China; Shanghai Punan Hospital of Pudong New District, Shanghai, China; Shanghai Pudong New District Zhoupu Hospital, Shanghai, China; and the Tenth People's Hospital Affiliated to Tongji University, Shanghai, China). It has been assigned the following protocol ID: XHEC-C-2014-046-2. Written informed consent was obtained from all the study participants.

Perspective and outcomes

A costing perspective of the Chinese healthcare system was adopted. All costs were expressed in Chinese Renminbi (RMB) (2019 value) and converted to United States Dollars (USD) using the Organization of Economic Cooperation and Development (OECD) annual exchange rate for 2019 (1 USD =6.91 RMB) (11). The primary outcome was quality adjusted life-years (QALYs), which are a composite measure of quality of life and survival (12).

Model structure

Lifetime costs and outcomes were estimated using a Markov model (*Figure 1*) to simulate outcomes following each of the treatment strategies. The model was developed using Excel 2010 (Microsoft Corporation, US). In *Figure 1*, each circle represents a health state and arrows represent possible

[1] Kt/V is defined as clearance of urea multiplied by dialysis duration and normalized for urea distribution volume.

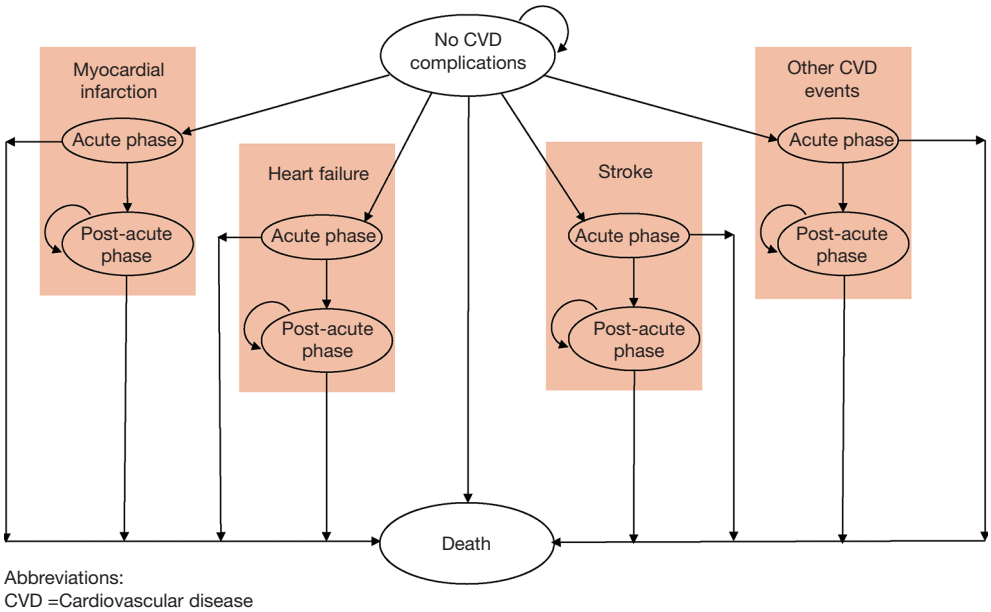

Figure 1 Model structure.

transitions at the end of each 1-month time cycle. Following treatment with either HD/HP or HD, all patients start in the "No CVD complications" health state in the model. During treatment, they may or may not experience severe CVD complications, including myocardial infarction, heart failure, stroke, and other CVD events. Patients surviving severe CVD complications progress through two stages: acute (0–30 days), and post-acute (after 30 days). Each stage is associated with different mortality rates and treatment costs. All patients are at risk of death, which includes both CVD-death and non-CVD-death. The four key assumptions of the model are:

(I) The incidence of non-CVD severe complications was assumed to be the same across different treatment groups. Therefore, non-CVD severe complications were not simulated in the model.

(II) Patients continue renal replacement treatment during treatment for severe CVD complications.

(III) Deaths within three days of a CVD event were assumed to be caused by the CVD event.

(IV) The disutility of severe CVD events after the acute phase was assumed to last for a lifetime.

The three key simplifications of the model are:

(I) Patients can only experience one severe CVD complication.

(II) Patients who die from a CVD complication do not accrue any QALYs after the CVD event.

(III) The acute treatment cost of CVD complications was assumed to be the same for all patients experiencing a CVD event regardless of the survival outcome.

Input data

The model required input parameters for transitions between health states, treatments costs, and health related quality of life in each health state. The short-term (96-week) clinical effectiveness of HD/HP and HP alone were obtained from the HD/HP trial, including incidence of severe CVD events, CVD mortalities, and non-CVD mortality. The effect of treatment on quality of life and the relative risk (RR) of CVD events was estimated using regression analysis to control for patient baseline characteristics including age, sex, baseline utility value, and frequency of dialysis before entering the trial. The long-term (i.e., from week 96 onwards) rates of severe CVD events were extrapolated from short-term trial data using standard parametric distributions, following the methods suggested by Latimer (13). The model fit parameters of alternative parametric models are reported in Supplementary file (available online: https://cdn.amegroups.cn/static/public/atm-21-1100-1.pdf), Section 1. The long-term RR of death for ESRD patients with and without severe CVD events was calculated from data on 175,840 patients

with CKD recorded in the US Renal Data System (14). The long-term non-CVD mortality was calibrated to the reported 10-year survival rate (27%) for patients on maintenance HD in China (15), using the RR of death (CVD versus no CVD) obtained from the US Renal Data System.

Health state utility values for patients according to treatment arm and prior to experiencing severe CVD events were obtained from the HD/HP trial. Yang *et al.* (16) have published mapping algorithms from KDQOL-SF to EQ-5D tariffs for six countries: France, Germany, Italy, Spain, UK and Singapore. Mapped values for patients not experiencing severe CVD events ranged from 0.66 (French tariffs) to 0.91 (UK tariffs). Tariff values for Singapore were considered the best match for mainland China and were used in this study. After controlling for patient baseline characteristics including age, sex, baseline utility value, and frequency of dialysis before entering the trial, the mapped utility values at 96 weeks were 0.839 for the HD group and 0.844 for the HD + HP group. The Cost-Effectiveness Analysis Registry (17) was searched for literature to provide disutilities for severe CVD events (18-20). The retrieved disutilities were combined with utility by treatment arm using an additive model.

Patients accrued costs for interventions (HD alone or HD + HP), outpatient follow-ups, and treatment of severe CVD complications. Unit costs were predominantly obtained from the Shanghai healthcare reference costs 2018 (7), as no more recent unit costs were available. The frequencies of HD, HP and hemodiafiltration for each treatment group were informed by the HD/HP trial. The costs of treating acute and post-acute CVD events were estimated based on data from the China Statistical yearbook 2019 (21), the Chinese CVD clinical guideline (22), other published literature (23-26), and expert opinion. A discount rate of 5% was applied to both costs and QALYs, as recommended by the China Guideline for Pharmacoeconomic Evaluations (27). All input data for cost-effectiveness analysis are reported in *Table 1*.

Cost-effectiveness analysis

Patients accrued QALYs in each health state as the product of the quality of life tariff attached to the health state and the time spent in that health state. Costs and QALYs were summed over the lifetime model time horizon, after discounting. Cost-effectiveness is reported as the incremental cost-effectiveness ratio (ICER), which is the ratio of the additional cost divided by the additional effectiveness of a treatment strategy compared to the next most effective strategy. Where one strategy is more effective and less costly than a comparator, the comparator is dominated. In line with the WHO recommendations (29), (I) interventions with an ICER less than the average Chinese GDP per capita (RMB 70,892 (USD 10,259) per QALY) are considered very cost-effective, (II) interventions with an ICER less than three times GDP per capita (RMB 212,676 (USD 30,778) per QALY) are considered cost-effective, and (III) interventions with an ICER exceed there times GDP per capita are considered not cost-effective.

Sensitivity analysis

Extensive sensitivity analyses were undertaken to test the robustness of the results to different sets of assumptions and different input data, including one-way sensitivity analysis, probabilistic sensitivity analysis (PSA) and structural sensitivity analysis. Sensitivity analysis assessed the impact of variation in each parameter singly across plausible ranges, and scenario analysis examined impact of variation in key parameters. The impact of joint uncertainty across all sampled parameters was examined simultaneously in PSA. A distribution reflecting underlying uncertainty was specified for each parameter, and a value sampled from the respective distribution prior to evaluating the model. Outputs from 5,000 simulations of the model allow estimation of the mean value and distribution of incremental costs and outcomes derived from Monte Carlo simulation of the joint impact of parameter uncertainty. Details on the specification of distributions for each parameter are provided in *Table 1*. Structural sensitivity analysis was undertaken to assess the impact of alternative modelling assumptions. In the base case, the long-term incidence rates of severe CVD events for both treatment groups were extrapolated from trial data using standard parametric distributions. In structural sensitivity analysis, the long-term incidence rates of CVD events in the HD group were obtained from published literature. The incidence of severe CVD events in Chinese patients on dialysis have been assessed by two large-scale multi-center cohort studies (30,31). Of these two studies, the study conducted by Hou *et al.* (31) in 2012 has a larger sample size (2,388) and was more recent. Therefore, the data reported by Hou *et al.* 2012 was tested in the structural sensitivity analysis. The long-term incidence rates of CVD events in the HD + HP group were calculated by multiplying the incidence rates in the HD group by the RR data taken from the HD/HP trial.

Table 1 Summary of input data

Variable	Base case value	95% CI	Distribution	Source
Monthly probability of developing CVD complications—HD group				
Myocardial infarction (year 1)	0.02%	0.01–0.06%	Lognormal (ln(mean) =–8.517, ln(SE) =–12.159)	HD/HP trial
Myocardial infarction (year 2 onwards)	0.13%	0.07–0.25%	Lognormal (ln(mean) =–6.645, ln(SE) =–10.928)	HD/HP trial
Heart failure	0.04%	0.02–0.09%	Lognormal (ln(mean) =–7.824, ln(SE) =–11.898)	HD/HP trial
Stroke	0.21%	0.14–0.30%	Lognormal (ln(mean) =–6.166, ln(SE) =–11.097)	HD/HP trial
Other severe CVD events	0.03%	0.01–0.08%	Lognormal (ln(mean) =–8.112, ln(SE) =–11.909)	HD/HP trial
HR of developing CVD complications (HD + HP *vs.* HD alone)				
Myocardial infarction (year 1)	0.586	0.264–1.301	Lognormal (ln(mean) =–0.539, ln(SE) =0.407)	HD/HP trial
Myocardial infarction (year 2 onwards)	0.586	0.264–1.301	Lognormal (ln(mean) =–0.539, ln(SE) =0.407)	HD/HP trial
Heart failure	1.001	0.388–2.581	Lognormal (ln(mean) =–0.001, ln(SE) =0.484)	HD/HP trial
Stroke	0.699	0.406–1.203	Lognormal (ln(mean) =–0.358, ln(SE) =0.277)	HD/HP trial
Other severe CVD events	0.699	0.164–2.978	Lognormal (ln(mean) =–0.359, ln(SE) =0.740)	HD/HP trial
Monthly probability of developing CVD complications—HD + HP group				
Myocardial infarction (year 1)	0.01%	0.00–0.04%	Lognormal (ln(mean) =–9.210, ln(SE) =–12.614)	HD/HP trial
Myocardial infarction (year 2 onwards)	0.08%	0.04–0.17%	Lognormal (ln(mean) =–7.131, ln(SE) =–11.257)	HD/HP trial
Heart failure	0.04%	0.02–0.08%	Lognormal (ln(mean) =–7.824, ln(SE) =–11.097)	HD/HP trial
Stroke	0.15%	0.10–0.22%	Lognormal (ln(mean) =–6.502, ln(SE) =–11.301)	HD/HP trial
Other severe CVD events	0.02%	0.01–0.06%	Lognormal (ln(mean) =–8.517, ln(SE) =–12.012)	HD/HP trial

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Base case value	95% CI	Distribution	Source
Monthly mortality rate—patients with no severe CVD events				
HD group—year 1	0.19%	0.13–0.28%	Lognormal (ln(mean) =–6.266, ln(SE) =–11.132)	HD/HP trial
HR of mortality for patients with no severe CVD events (HD + HP *vs.* HD alone)	0.691	0.395–1.208	Lognormal (ln(mean) =–0.370, ln(SE) =0.285)	HD/HP trial
HD + HP group—year 1	0.13%	0.08–0.21%	Lognormal (ln(mean) =–6.645, ln(SE) =–11.345)	HD/HP trial
RR of death for both groups (year 3 onwards *vs.* year 1)	5.00	–	Assume fixed	Calibrated based on Sun *et al.* (15) and RR of death (CVD versus no CVD, reported below)
Immediate mortality rate for patients with severe CVD events (death within 3 days of a CVD event)				
Patients with myocardial infarction	85.71%	70.84–95.81%	Beta (α=24, β=4)	HD/HP trial
Patients with heart failure	82.14%	71.20–90.92%	Beta (α=46, β=10)	HD/HP trial
Patients with stroke	50.00%	27.81–72.19%	Beta (α=9, β=9)	HD/HP trial
Patients with other severe CVD events	37.50%	9.90–70.96%	Beta (α=3, β=5)	HD/HP trial
Relative risk of mortality (patients who survived severe CVD events *vs.* non-CVD patients)				
Myocardial infarction	2.27	–	Lognormal (ln(mean) =0.82, ln(SE) =0.06)	US Renal Data System (14)
Heart failure	1.76	–	Lognormal (ln(mean) =0.57, ln(SE) =0.05)	US Renal Data System (14)
Stroke	1.78	–	Lognormal (ln(mean) =0.58, ln(SE) =0.06)	US Renal Data System (14)
Other severe CVD events	1.74	–	Lognormal (ln(mean) =0.56, ln(SE) =0.04)	US Renal Data System (14)
Unit cost of renal replacement treatment, including material and labour (RMB)				
HD (per session)	400	198–662	Gamma (α=11, β=36)	Shanghai Unit Cost book (7)
HP (per session)	1,149	566–1,894	Gamma (α=11, β=103)	Shanghai Unit Cost book (7)
Online haemodiafiltration (per session)	940	467–1,563	Gamma (α=11, β=85)	Shanghai Unit Cost book (7)
Resource use of renal replacement treatment—HD group				
HD (per week)	2	–	Assumed fixed	HD/HP trial
Online haemodiafiltration (per week)	1	–	Assumed fixed	HD/HP trial
Resource use of renal replacement treatment—HD + HP group				
HD (per week)	2.5	–	Assumed fixed	HD/HP trial
HP (per week)	0.5	–	Assumed fixed	HD/HP trial
Online haemodiafiltration (per week)	0.5	–	Assumed fixed	HD/HP trial
Cost per follow up (RMB)				
Follow-up	214	104–349	Gamma (α=11, β=19)	HD/HP trial

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Base case value	95% CI	Distribution	Source
Cost of treating severe CVD complications—per acute episode (RMB)				
Myocardial infarction	38,788	25,850–53,863	Gamma (α=29, β=1,331)	China Statistical yearbook (21)
Heart failure	33,796	21,199–48,430	Gamma (α=23, β=1,454)	Huang *et al.* (23)
Stroke	9,958	7,390–13,131	Gamma (α=47, β=214)	China Statistical yearbook (21)
Other severe CVD events	6,482	2,680–11,192	Gamma (α=8, β=776)	He *et al.* (24)
Cost of treating severe CVD complications—post-acute phase, per month (RMB)				
Myocardial infarction	322	135–562	Gamma (α=8, β=39)	Zhao *et al.* (25)
Heart failure	1,451	1,144–1,735	Gamma (α=89, β=16)	Zhang *et al.* (26)
Stroke	304	88–710	Gamma (α=4, β=81)	He *et al.* (24) and CVD clinical guideline (22)
Other severe CVD events	222	93–389	Gamma (α=8, β=27)	He *et al.* (24)
Utility				
Utility for patients with no severe CVD complications—HD group	0.907	0.905–0.908	Lognormal (ln(mean) =–0.098, ln(SE) =–10.206)	HD/HP trial
The incremental impact of HP on utility of patients with no severe CVD events	0.004	0.001–0.006	Lognormal (ln(mean) =–5.521, ln(SE) =–6.562)	HD/HP trial
Utility for patients with no severe CVD complications—HD/HP group	0.910	0.908–0.912	Lognormal (ln(mean) =–0.094, ln(SE) =–10.180)	HD/HP trial
Disutility of myocardial infarction—acute phase	0.147	0.140–0.155	Beta (α=1,948, β=11,301)	Kongpakwattana *et al.* (19)
Disutility of heart failure—acute phase	0.117	0.111–0.123	Beta (α=1,897, β=14,314)	Borisenko *et al.* (20)
Disutility of stroke—acute phase	0.226	0.215–0.237	Beta (α=2,082, β=7,129)	Kongpakwattana *et al.* (19)
Disutility of other CVD events—acute phase	0.058	0.054–0.060	Beta (α=1,796, β=29,280)	De Smedt *et al.* (28)
Disutility of myocardial infarction—post-acute phase	0.039	0.037–0.041	Beta (α=1,764, β=43,474)	Deng and Liu (18)
Disutility of heart failure—post-acute phase	0.039	0.037–0.041	Beta (α=1,764, β=43,474)	Deng and Liu (18)
Disutility of stroke—post-acute phase	0.069	0.063–0.071	Beta (α=1,815, β=24,492)	Deng and Liu (18)
Disutility of other CVD events—post-acute phase	0.041	0.039–0.043	Beta (α=1,767, β=41,550)	Borisenko *et al.* (20)
Other data				
Discount rate for both costs and QALYs	5.00%	–	Not varied	China Guideline for Pharmacoeconomic Evaluations (27)

CVD, cardiovascular disease; HD, haemodialysis; HP, haemoperfusion; HR, hazard ratio; QALY, quality adjusted life-year; RR, relative risk.

Table 2 Base case and structural sensitivity analyses for patients with ESRD

Intervention	Cost (RMB)	LYs	QALYs	Incremental cost (RMB)	Incremental LYs	Incremental QALY	ICER (RMB)	ICER (USD)
Base case results[†]								
HD	510,329	7.84	5.35	–	–	–	–	–
HD + HP	740,705	10.70	6.68	230,376	2.87	1.32	174,486	25,251
Results of structural sensitivity analysis[‡]								
HD	405,460	5.52	4.14	–	–	–	–	–
HD + HP	551,716	6.80	4.86	146,256	1.28	0.72	202,396	29,290

[†], In the base case, the long-term (i.e., 96-week onwards) incidence rates of severe CVD events for the HD and the HD + HP group were extrapolated from trial data using standard parametric distributions. For the HD group, the long-term monthly incidence rates for myocardial infarction, heart failure, stroke and other CVD events are 0.13%, 0.04%, 0.21% and 0.03%, respectively. For the HD + HP group, the long-term monthly incidence rates for myocardial infarction, heart failure, stroke and other CVD events are 0.08%, 0.04%, 0.15% and 0.02%, respectively. [‡], In structural sensitivity analysis 1, the long-term incidence rates of severe CVD events for the HD group were obtained from Hou et al. (31). The incidence rates of severe CVD events for the HD + HP group were calculated based on the incidence rates for the HD group, and the RR of severe CVD events derived from the HD/HP trial. For the HD group, the long-term monthly incidence rates for myocardial infarction, heart failure, stroke and other CVD events are 0.39%, 0.93%, 0.14% and 0.05%, respectively. For the HD + HP group, the long-term monthly incidence rates for myocardial infarction, heart failure, stroke and other CVD events are 0.25%, 0.74%, 0.09% and 0.03%, respectively. Lys, life years; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality-adjusted life of years; WTP, willingness to pay threshold.

Model verification and validation

Model verification and validation steps included: checking appropriateness of the model structure and input data (HJ, HW and MP), testing extreme values (HW), and checking the plausibility of results with clinical experts in ESRD (WL and ZY).

Results

Results of the HD/HP trial

Between 2014 and 2016, 1,407 patients with ESRD were recruited to the HD/HP trial from 30 participating clinical centers in Shanghai. The baseline demographics and clinical information of the recruited patients, and the unadjusted clinical outcomes of the trial are reported in Supplementary file, Sections 2 and 3, respectively. The regression models used for estimating the incidence of severe CVD events and mortality rates are reported in Supplementary file, Section 4. Analyses of the KDQOL-SF scores indicate a significant improvement associated with HD + HP, in concordance with the analysis of mapped EQ-5D values (Supplementary file, Section 4.3, 4.4 and 5). As shown in *Table 1*, compared to the HD group, patients in the HD + HP group had lower monthly probabilities of myocardial infarction (HR: 0.58), stroke (HR: 0.70), other severe CVD events (HR: 0.70) and lower monthly non-CVD mortality (HR: 0.69). HD + HP did not appear to reduce probability of heart failure (HR: 1.00).

Base case, structural sensitivity analysis and PSA

Table 2 reports costs, life years (LYs), QALYs and cost-effectiveness derived from the simulation model. In the base case analysis, compared with HD alone, HD + HP results in 2.87 LYs saved, 1.32 QALY gains and an additional cost of RMB 230,376 per patient. The probabilistic ICER of HD + HP is RMB 174,486 (USD 25,251) per QALY, which is lower than the RMB 212,676 (USD 30,778) willingness-to-pay threshold. Therefore, HD + HP is considered to be cost-effective. In structural sensitivity analysis (*Table 2*), where the long-term incidence rates of severe CVD events were obtained from a previously published cohort study (31), the ICER of HD + HP increased to RMB 202,396 (USD 29,290) per QALY, but was still lower than the pre-defined willingness-to-pay threshold.

The results of the PSA are illustrated in the cost-effectiveness acceptability curve (CEAC) in *Figure 2*. The CEAC is the plot of the likelihood an intervention is cost-effective as the value placed on the outcome (i.e., QALY)

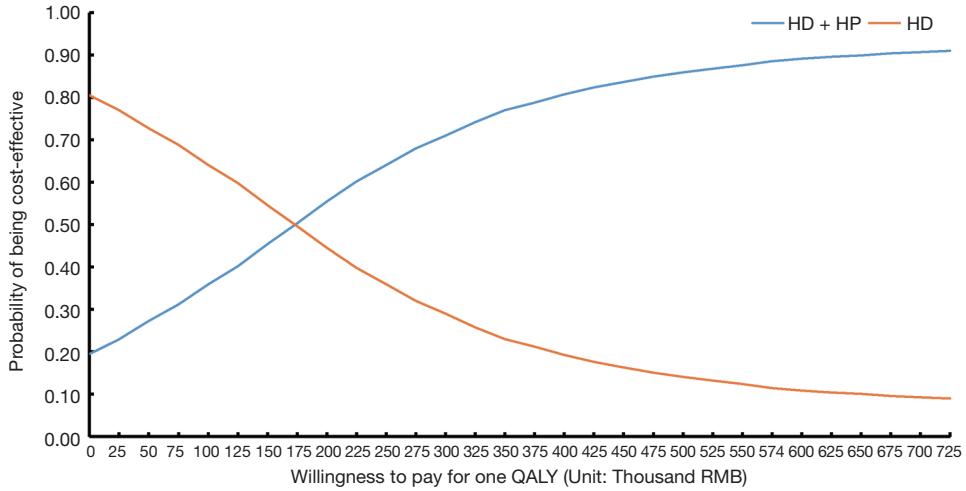

Figure 2 Cost-effectiveness acceptability curve.

is varied. At a willingness-to-pay threshold of three times GDP per capita per QALY gained (RMB 212,676/USD 30,778), the probability that HD + HP is cost-effective is 58%. At a willingness-to-pay threshold of one times GDP per capita per QALY gained [RMB 70,892 (USD 10,259)] and two times GDP per capita per QALY gained [RMB 141,784 (USD 20,518)], the probability that HD + HP is cost-effective compared to HD alone is 30% and 44%, respectively.

One-way sensitivity analyses

The results of one-way sensitivity analysis for all 39 parameters tested are reported in the Supplementary file, Section 6. The top 10 most sensitive parameters and their impacts on the results are illustrated in *Figure 3*. The base case conclusion (HD + HP being the most cost-effective intervention) is reversed with the following changes to parameters:

- HR of non-CVD mortality increased to 0.83 (base case value: 0.69);
- Frequency of HP increased to 0.63 per week (base case value: 0.50 per week);
- Cost of HP increased to 1,446 RMB (base case value: 1,149 RMB);
- Discount rate for costs reduced to 3.00% (base case value: 5.00%);
- Discount rate for QALYs increased to 6.78% (base case value: 5%);
- Cost of HD per session increased to 566 RMB (base case value: 400 RMB);
- Monthly incidence rate of heart failure in the HD group increased to 0.85% (base case value: 0.04%).

Discussion

The main findings and interpretation

Our findings indicate a potential for HD + HP to be cost-effective for the treatment of ESRD in China. Compared to HD alone, HD + HP reduces incidence of severe CVD events and subsequent CVD deaths. It is also associated with a modest improvement in quality of life and a reduction in mortality for patients with no severe CVD events. All of these effects contribute to additional QALYs for patients receiving HD + HP compared to HP alone, which are sufficient to justify the additional cost. The gain in quality of life associated with HD + HP over and above the impact on CVD events may arise from reductions in non-CVD adverse events, such as cutaneous pruritus (32) and infection (33). Further evidence on the longer-term impact of HD + HP on CVD event rates and on mortality unrelated to CVD is needed to robustly demonstrate the cost-effectiveness of HD + HP.

In structural sensitivity analysis, when the incidence rates of CVD events reported by Hou *et al.* (31) were used in the model, the ICER of HD + HP increased from 174,486 RMB (25,251 US dollars) to 202,396 (29,290 US dollars), but remained lower than the pre-defined willingness-to-pay

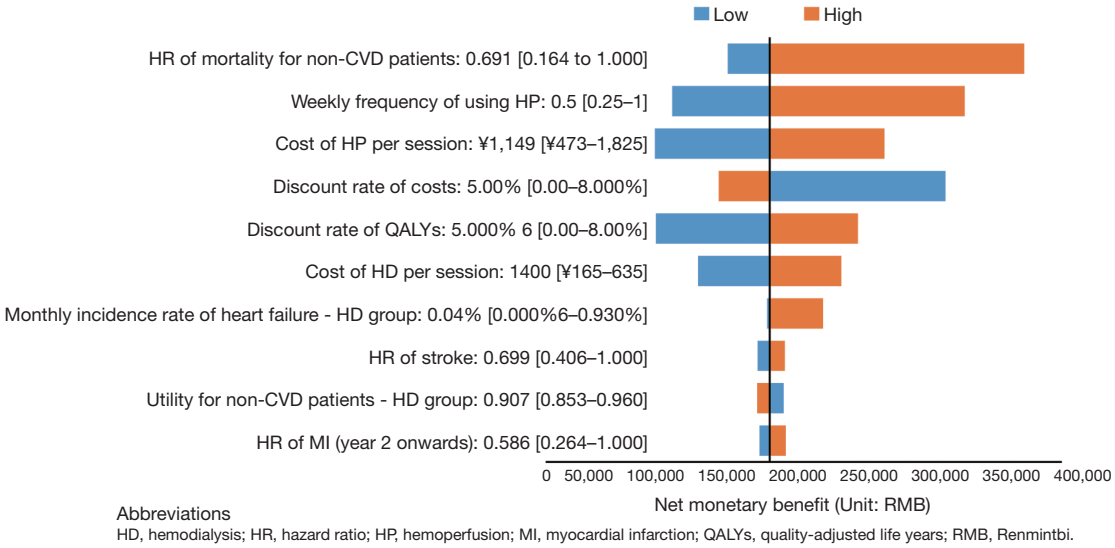

Figure 3 Result of one-way sensitivity analysis.

threshold. The reasons for an increase in the ICER are (I) the monthly incidence rate of heart failure reported by Hou *et al.* (31) (0.93%) is 23 times higher than the incidence rate observed in the HD/HP trial (0.04%); and (II) the HD/HP trial showed that use of HD + HP resulted in longer life expectancy but not reduced incidence of heart failure (HR: 1.00). Therefore, the impact of an increase in the incidence rate of heart failure was greater in the HD + HP group. Increases in the incidence rate of the other three types of CVD events (myocardial infarction, stroke and other severe CVD events) reduced the ICER for HD + HP, reflecting the reduced the incidence of myocardial infarction, stroke and other severe CVD events (HR: 0.58, 0.70 and 0.70, respectively) associated with HD + HP.

There are three reasons why the incidence rate of heart failure reported by Hou *et al.* (31) is much larger than the incidence rate observed in the HD/HP trial: rarity of heart failure in the trial; varying risk of CVD across China; and a healthy patient effect associated with trial enrolment. By the end of the HD/HP trial (96-week), only 18 out of 1407 patients (1.28%) in the HD/HP trial developed heart failure. Evidence suggests the risk of CVD varies greatly across different regions in China (34). The patients in Hou *et al.* were recruited from six cities in China (Beijing, Shanghai, Guangzhou, Hangzhou, Wuhan, and Xian), whilst all patients in the HD/HP trial were recruited from Shanghai, which is in the region with the lowest risk of CVD (35). Hou *et al.* is a retrospective cohort study whilst the HD/HP trial is a randomized trial, and it has been reported that patients participating in trials experienced better outcomes compared with those outside trials (36,37).

The cost-effectiveness of HD + HP was most sensitive to the HR of mortality for patients not experiencing a CVD event, rather than HD + HP's effectiveness in preventing CVD events. This reflects the low numbers of CVD events in the trial—by the end of the HD/HP trial (96-week), only 7.8% patients experienced severe CVD events, whereas non-CVD mortality was 4.2%. Increased costs of HD increased the ICER for HD + HP. This is because patients in the HD + HP group received all treatments in the HD group, as well as HP, and patients in the HD + HP have a longer life expectancy than patients in the HD group. Hence patients in the HD + HP arm accrued more HD treatments.

Implications for clinical practice and future research

Our findings indicate a potential for HD + HP to be cost-effective for the treatment of ESRD in China. Sensitivity analysis indicates that the cost-effectiveness of HD + HP improves for patients at higher risk of myocardial infarction, stroke and other severe CVD events. This finding supports the prioritization of HD + HP for patients at higher risk of CVD, for example, individuals who reside in northeast and north China, as those regions were reported to be associated with the highest risk of CVD (35).

The generalizability of our results to other countries is limited by two factors. Firstly, the characteristics

of ESRD patients in China differ from those in other countries. As observed in the HD/HP trial and previous studies (30,31,38,39), the leading cause of ESRD in China is chronic glomerulonephritis. In contrast, in the US and Europe, diabetes and hypertension are the main causes of ESRD (40,41). In addition, the average age at commencement of dialysis in China is ten-years younger than in western countries (30,38). Therefore, the risk and pattern of CVD in China might be different from other countries. Second, differences in clinical practice and treatment costs can limit the transferability of economic analysis to different countries (42,43). However, our study demonstrated a potential for HD/HP to be cost-effective for patients with ESRD, and identified factors which are likely to impact on the cost-effectiveness of HD + HP. Three priorities for future research are warranted: (I) the longer-term impact of HD + HP on CVD event rates and mortality unrelated to CVD; (II) the application of a generic preference based measure, such as the EQ-5D (44), to quantify changes in patients' quality of life associated with HD + HP; and (III) exploration of the mechanisms driving improved survival and quality of life for patients receiving HD + HP.

Strengths and limitations

There are several strengths of this study. To our knowledge, this study presents the first economic analysis of the cost-effectiveness of HD + HP for patients with ESRD. The analysis exploits individual patient data from the HD/HP trial, a large clinical trial (n=1,407) which is the first to assess the impact of HD + HP on incidence of severe CVD complications and mortality in patients with ESRD. Previous economic evaluations for dialysis either did not model any adverse events (45,46) or only modelled general severe adverse events (47,48), whilst our study explicitly modelled the cost and health impacts of four different types of severe CVD events (myocardial infarction, heart failure, stroke and other CVD events). In addition, extensive sensitivity analyses have been conducted to test the robustness of the base case inference under different assumptions and different sets of input data, in addition to capturing parameter uncertainty in a fully probabilistic model.

There are some limitations of this study, arising predominantly from limitations in the input data. First, patients recruited to the HD/HP trial were allocated to treatment using simple randomization without stratification on patient characteristics. There were some significant differences in baseline characteristics, notably sex, which might influence CVD event rates. In our analyses we adjusted for patient characteristics when estimating event rates and differences in quality of life across trial arms, which should have mitigated any risk of bias. Second, the follow-up period of the HD/HP trial is only 96 weeks, necessitating extrapolation of event rates beyond this point to capture the lifetime impact of HD + HP. A robust approach to selecting the most appropriate extrapolations was implemented (13), and the impact of alternative assumptions on the event rate beyond two years was explored. However, extrapolation of data inevitably introduces uncertainty into the analysis. Third, in the model, we assumed that patients can only experience one severe CVD complication. In reality, some patients will experience multiple, severe CVD complications during their lifetime. This simplification is likely to disfavour HD + HP, as the primary benefit of using HD + HP is to reduce the incidence of severe CVD complications. Finally, the quality of life data in the HD/HP trial were measured using KDQOL-SF rather than EQ-5D recommended by the China guideline for Pharmacoeconomic Evaluations (27). As a result, we had to use the mapping algorithm developed by Yang *et al.* (16) to estimate EQ-5D utility values from the KDQOL-SF scores. However, our analyses of KDQOL-SF scores indicates a significant improvement associated with HD + HP, in concordance with our analysis of mapped EQ-5D values.

Conclusions

Our analyses indicate a potential for HD + HP to be cost-effective for adult patients with ESRD in China. Compared to HD alone, HD + HP reduces incidence of severe CVD events and subsequent CVD deaths. It is also associated with a modest improvement in quality of life and a reduction in mortality for patients with no severe CVD events. All of these effects contribute to additional QALYs for patients receiving HD + HP compared to HP alone, which are sufficient to justify the additional cost. The cost-effectiveness of HD + HP improves for patients at higher risk of myocardial infarction, stroke and other severe CVD events. Our finding supports the prioritization of HD + HP for patients at higher risk of CVD in China. Further evidence on the longer-term impact of HD + HP on CVD event rates and mortality unrelated to CVD is needed to robustly demonstrate the cost-effectiveness of HD + HP.

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Footnote

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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. The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethical Committee of the thirty participating centers (Xinhua Hospital, Renji Hospital Shanghai Jiao Tong University School of Medicine, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai General Hospital (Songjiang District), Jinshan Hospital Affiliated to Fudan University, the Fifth People's Hospital of Shanghai, Fudan University, Changhai Hospital Affiliated to The Second Military Medical University, Tongji Hospital Affiliated Tongji University of Shanghai, Hongshan Hospital of Shanghai, Dongfang Hospital Affiliated Tongji University of Shanghai, Yangpu Hospital Affiliated to Shanghai Tong Ji University, Longhua Hospital Shanghai University of Traditional Chinese Medicine, 455 Hospital of Chinese Liberation Army, 85 Hospital of People's Liberatlon Army, Armed Police Corps Hospital of Shanghai, Shanghai Construction Group (SCG) Hospital, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine Chongming Branch, Central Hospital of Minhang District, the Fifth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine Songjiang Branch, Seventh People's Hospital of Shanghai University of Traditional Chinese Medicine, Changning District Central Hospital of Shanghai, Jing'an District Central Hospital of Shanghai, Tongren Hospital, Shanghai Jiaotong University School of Medicine, Renji Hospital Shanghai Jiaotong University School of Medicine, Jiading Branch, Zhabei District Central Hospital of Shanghai, the Sixth Hospital Affiliated to Shanghai Jiao Tong University School of Medicine Jinshan Branch, Shanghai Fengxian District Central Hospital, Shanghai Punan Hospital of Pudong New District, Shanghai Pudong New District Zhoupu Hospital, and Tenth People's Hospital Affiliated To Tongji University). Informed consent was taken from all individual participants.

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