



**Original Article**

**Cost-Utility Analysis of four Chelation Regimens for  $\beta$ -thalassemia Major: a Chinese Perspective**

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**Abstract. Objective:** The Iron chelation is essential to prevent iron overload damage of vital organs, like heart, liver, and endocrine glands, in patients with transfusion-dependent thalassemia. The most common chelation regimens for  $\beta$ -thalassemia major ( $\beta$ -TM) patients used in China are a combination therapy of deferoxamine and deferiprone (DFO+DFP), deferoxamine (DFO) monotherapy, deferiprone (DFP) monotherapy and deferasirox (DFX) monotherapy. Such patients use iron chelators their whole lives, resulting in enormous treatment costs. This study analyses the cost-utility of these four regimens from the Chinese healthcare system perspective.

**Methods:** A Markov decision model was used over a 5-year time horizon and was populated using clinical data from a systematic literature review. We obtained utility data from local and previous research. Costs were estimated using Chinese national sources.

**Results:** From the base-case analysis results, DFP was the most cost-effective chelation regimen, followed by DFO, DFX, and DFO+DFP. DFP had 97.32%, 99.43%, and 58.04% likelihood of being cost-effective versus DFX, DFO+DFP, and DFO, respectively, at a payment threshold of 193,932.00 CNY/QALY (QALY, quality-adjusted life-year).

**Conclusions:** DFP was the most cost-effective chelation regimen for  $\beta$ -TM patients, followed by DFO, DFX, and DFO+DFP. Using DFP as the primary treatment regimen may potentially result in cost-savings and QALY gains for the Chinese healthcare system. To increase these benefits, the Chinese government should take measures to lower DFX and DFO drug costs, and Chinese clinicians should choose the cheaper DFX and DFO, increase the utility of DFO+DFP and reduce mortality and morbidity of DFP. Changes in influential parameters easily affect the results of DFX versus DFO+DFP and of DFP versus DFO; clinicians should focus on such parameters and adjust the regimens accordingly.

**Keywords:** Cost-Utility analysis;  $\beta$ -thalassemia major; Deferoxamine; Deferiprone; Deferasirox.

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**Introduction.**  $\beta$ -thalassemia is an autosomal recessive hereditary anemia characterized by reduced or absent  $\beta$ -globin chain synthesis.<sup>1</sup> Patients with  $\beta$ -thalassemia

have been typically categorized as minor, intermedia, or major based on their  $\alpha$ -globin or  $\beta$ -globin chain imbalance, the severity of the anaemia, and clinical

picture at presentation.<sup>2</sup>  $\beta$ -thalassemia is known to be highly prevalent in Southeast and South Asia, the Middle East, the Mediterranean countries, and North and Central Africa.<sup>1</sup> Additionally, because of continued migration,  $\beta$ -thalassemia is now becoming increasingly common in Europe and North America, making it a global health concern.<sup>2</sup> Approximately 1.5% of the world's population carries the  $\beta$ -thalassemia gene,<sup>3</sup> and every year, the number of new-born children diagnosed with  $\beta$ -thalassemia major ( $\beta$ -TM) exceeds 23,000.<sup>4,5</sup> In China, the average prevalence rate of  $\beta$ -thalassemia was 0.67%-2%.<sup>6</sup>

$\beta$ -thalassemia may be classified clinically as transfusion-dependent or non-transfusion-dependent.<sup>7,8</sup>  $\beta$ -TM patients require since early childhood regular red blood cell (RBC) transfusions to maintain adequate hemoglobin levels improving quality of life while reducing mortality.<sup>7,8</sup> Unfortunately, the human body does not have an iron excretory pathway, which leads to the accumulation of iron from the transfused blood, known as iron overload.<sup>6</sup> The cumulative iron overload subsequently leads to organ toxic effects and dysfunction, for example, in the heart, liver, or endocrine glands, eventually leading to death.<sup>8</sup> Three iron chelators are currently available for the treatment of iron overload in  $\beta$ -TM patients: deferoxamine (DFO), deferiprone (DFP), and deferasirox (DFX). The four most commonly used chelation regimens in China are combination therapy of DFO and DFP (DFO+DFP) (38.9%), DFO monotherapy (19.1%), DFP monotherapy (19.0%) and DFX monotherapy (16.0%).<sup>6</sup>

DFO was the first iron chelator to be marketed, and it is the first-line drug for  $\beta$ -TM patients 2 years of age and older.<sup>2</sup> Because DFO is administered as a subcutaneous infusion, the quality of life and compliance of patients are low. Low compliance with DFO poses a higher risk of iron overload-related complications and death.<sup>9,10</sup> To obtain a higher quality of life, and better compliance, oral iron chelators, DFP and DFX, were introduced. DFP is the second-line drug for  $\beta$ -TM patients six years of age and older.<sup>2,11</sup> DFX is the first-line drug for patients 6 years of age and older in China and Europe.<sup>2,12</sup> Because cardiac complications related to iron overload is the leading cause of death in 52.3% of these patients,<sup>13</sup> the guidelines of the US, Italy, Australia, and China all recommend that  $\beta$ -TM patients with iron overload-related cardiac complications should receive DFO+DFP.<sup>11,14-16</sup>

Because  $\beta$ -TM patients need to use iron chelators throughout their whole lives, the treatment cost is enormous. Paramore *et al.* reported that the annual average chelation treatment cost of transfusion-dependent  $\beta$ -thalassemia patients in the US was approximately USD 53,000.<sup>17</sup> Esmailzadeh *et al.* found that the treatment of approximately 18,000  $\beta$ -TM patients led to an annual loss of nearly USD 150

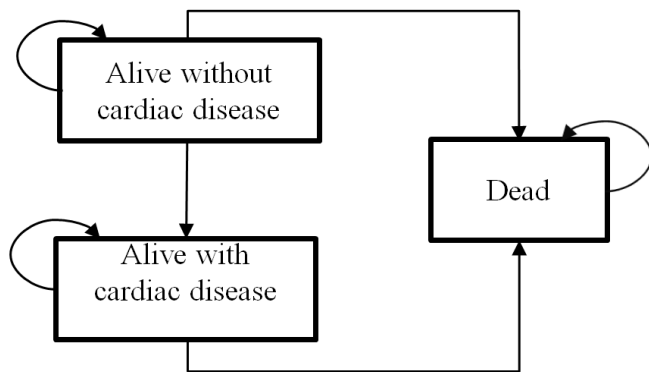
million for Iran's healthcare system.<sup>18</sup> In China, the annual average treatment cost of blood transfusion and iron excretion for  $\beta$ -TM patients was over CNY 100,000, but the annual income of over 90% of families with  $\beta$ -TM patients was less than CNY 60,000, which means that most families with  $\beta$ -TM patients will fall into poverty due to the illness.<sup>6</sup> As a result, it is crucial to analyse the cost-effectiveness of iron chelation regimens from a Chinese perspective.

According to a previous systematic review, there is no published analysis of the relative cost-effectiveness of iron chelator therapies from a Chinese perspective.<sup>19</sup> Cost-effectiveness is not an entire issue when in different countries (regions), the results are the opposite for other countries (regions). The specific legislation of regions where clinicians operate has a substantial influence on the economics of drugs.<sup>19</sup> Thus, this study aims to compare the cost-utility of the four iron chelation regimens (DFO, DFP, DFX, DFO+DFP) from the Chinese healthcare system perspective.

**Methods.** A Markov model was developed to determine the cost-utility of the four chelation regimens (DFO, DFP, DFX, and DFO+DFP) for  $\beta$ -TM patients with iron overload from the perspective of the Chinese healthcare system. The data used in the Markov model included cost, utility, and clinical transition probabilities. To obtain these data, we conducted a systematic literature review. If the data collected by the systematic review were insufficient, we conducted local research to supplement the data.

*Outline of the economic model.* The model considered adults and children, regardless of treatment history or disease status. A 5-year time horizon was specified in the model, and the cycle length was one year. The People's Bank of China regulates that for financial institutions, the national guiding interest rate for one-year deposits is 1.5%.<sup>20</sup> Hence, we used a 1.5% discount rate to discount future costs and QALYs (quality-adjusted life year).<sup>21</sup> The National Bureau of Statistics of China announced that in 2018, per capita GDP was CNY 64,644.<sup>22</sup>

Additionally, a study by the World Health Organization (WHO) proposed that when the incremental cost-effectiveness ratio (ICER) was less than three times per capita GDP, the increased costs were acceptable, and the intervention was cost-effective.<sup>21</sup> As a result, the payment threshold used in the model was CNY 193,932. We constructed our Markov model with three health statuses:  $\beta$ -thalassemia without cardiac complications,  $\beta$ -thalassemia with cardiac complications, and death (**Figure 1**). In addition to the cardiac complication, the major complications of iron overload include chronic liver disease, diabetes mellitus, hypogonadism, hypoparathyroidism, and hypothyroidism.<sup>19,23,24</sup> The



**Figure 1.** Markov model.

cost and morbidity of these complications were also calculated in a model.

**Systematic literature review.** A systematic literature search in MEDLINE (PubMed), EMBASE (Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL, Cochrane Library), the Cochrane Database of Systematic Reviews (CDSR, Cochrane Library), China Biology Medicine (CBM, SinoMed), the China National Knowledge Infrastructure (CNKI), VIP Data, and Wanfang Data was conducted on March 2019, with no restrictions on the date. Besides, a manual search was performed to identify conferences. Both Chinese and English search terms were used. The search terms included “thalassemia,” “beta-thalassemia,” “iron overload,” “iron-chelating agents,” “deferoxamine,” “deferiprone,” and “deferasirox,” and their variations. The study selection and data extraction were conducted independently by two researchers to confirm that they met the pre-defined inclusion/exclusion criteria and data extraction form. Any inconsistencies were resolved through discussion. The inclusion criteria for the systematic review were as follows: *population*:  $\beta$ -TM patients or transfusion-dependent thalassemia major patients; *intervention/comparison*: DFO, DFP, DFX, or DFO+DFP; *outcomes*: (1) clinical data: cardiac complication morbidity, cardiac complication mortality, and non-cardiac complication mortality; (2) utility data: the utility associated with cardiac complication or without cardiac complication; and (3) cost data: the chelator cost, DFO administration cost, cardiac complication therapy cost, and monitoring cost; study design: randomized controlled trials (RCTs), non-RCTs, observational studies, and pharmacoeconomic reviews. Because local/national context has a substantial influence on the results of pharmacoeconomic evaluations,<sup>7</sup> we used valuable localized in this study. For the clinical data, we preferred to use data from China (including Mainland China, Hong Kong, Macao, and Taiwan), followed by data from Asia or all around the world. For the utility data, we used data from China (including Mainland

China, Hong Kong, Macao, and Taiwan). For the cost data, we used data from Mainland China.

**Data used in the model.** The detailed data were shown in **Table 1**.

Cost data:

- a) **Chelator cost:** The chelator cost was calculated according to the drug cost, chelator dosage, and patient weight. Lau *et al.* reported that the mean weight of 381 TM (age ranging from 3 months to 56 years) was 46.5kg,<sup>25</sup> and it was used in the model. We searched the official websites of 31 provincial-level administrative units in Mainland China to obtain the government wholesale acquisition cost. The average unit cost of drugs was used in the model. The government official websites showed that there were only brand-name drugs: Desferal®, Ferriprox®, and Exjade®. Luangasanatip *et al.* reported that the cost of the generic version of DFO, USD 0.20 per gram, was only 9.57% that of the brand-name drug (USD 2.09 per gram).<sup>27</sup> As a result, we used 10% of the average unit cost of drugs in a sensitivity analysis. In this study, we assumed that the patient compliance rate was 100%. The dosage levels and frequencies of the four iron chelation regimens were based on Chinese guidelines.<sup>11,27</sup> The average dosage was used in the base-case analysis. The maximum dosage and minimum dosage were used in the sensitivity analysis.
- b) **DFO administration cost:** We searched the official websites of 31 provincial-level administrative units in Mainland China to obtain the DFO administration cost. The average cost was used for the base-case analysis, while the maximum cost was used in the sensitivity analysis. If DFO patients purchased an infusion pump and used it at home, the DFO administration was free. Therefore, CNY 0 was used in the sensitivity analysis.
- c) **Monitoring cost:** Reduction of severe adverse reactions requires that the vision and hearing of patients on DFO therapy should be monitored every three months,<sup>28</sup> the blood cell count of patients on DFP therapy should be monitored weekly,<sup>27,29</sup> and the renal function of patients on DFX therapy should be monitored monthly.<sup>27,12</sup> We searched the official websites of 31 provincial-level administrative units in Mainland China to obtain those monitoring costs. The average cost was used for the base-case analysis, while the minimum and maximum costs were used in the sensitivity analysis.
- d) **Complications therapy cost:** Luangasanatip *et al.* reported that the cost of treating iron overload-related cardiac complications in thalassemia patients was the same as the cost of treating chronic heart failure complications in patients with diabetes mellitus.<sup>26</sup> In China, the annual medical cost of treating chronic heart failure complications in patients with type 2 diabetes mellitus was CNY 9897.37,<sup>31</sup>

and the data were used in the model. We used the cost data of hypogonadism, hypoparathyroidism, and

hypothyroidism from Ho *et al.*<sup>31</sup> The rate was USD 1= CNY 7.0328.<sup>32</sup>

**Table 1.** values used in the model.

Parameters	Value used in the model	Variation in sensitivity analysis
<b>Patient weight (assumption)</b>	46.5kg [25]	1.0-100.0 <sup>d</sup>
<b>Dosage</b>		
DFO: dose (mg/kg)	40 [11]	20-60 <sup>a</sup>
DFP: dose (mg/kg)	75 [11]	75-100 <sup>a</sup>
DFX: dose (mg/kg)	30 [11]	20-40 <sup>a</sup>
DFO/DFP/DFX: days in a week/days in a year	7/365 [11]	—
DFO+DFP: dose (mg/kg)	DFO:40; DFP: 75 [27]	—
DFO+DFP: days in a week/days in a year	DFO:2/104; DFP: 7/365 [27]	DFO: 2/104-5/260 <sup>a</sup>
<b>Cost</b>		
drug cost		
DFO (CNY/g)	106.6	10.7-114.9 <sup>a</sup>
DFP (CNY/g)	38.6	3.9-50.1 <sup>a</sup>
DFX (CNY/g)	566.1	56.6-578.6 <sup>a</sup>
DFO administration (CNY/day)	41.3	0-95.0 <sup>a</sup>
monitoring cost		
DFO: vision monitoring (CNY/time)	1.7	0-5.0 <sup>a</sup>
DFO: hearing monitoring (CNY/time)	34.2	10.0-86.0 <sup>a</sup>
DFP: complete blood count (CNY/time)	13.3	5.0-24.0 <sup>a</sup>
DFX: renal function test (CNY/time)	16.2	11.0-21.3 <sup>a</sup>
Complications' treatment cost		
Cardiac complication (CNY/year)	9897.4 [30]	7423.0-12371.7 <sup>b</sup>
Chronic liver disease (CNY/year)	61606.8 [51]	21824.3-123571.8 <sup>a</sup>
Diabetes mellitus (CNY/year)	9897.4 [30]	7423.0-12371.7 <sup>b</sup>
Hypogonadism (CNY/year)	7124.2 [31]	5343.2-8905.3 <sup>c</sup>
Hypoparathyroidism (CNY/year)	2060.6 [31]	1545.5-2575.8 <sup>c</sup>
Hypothyroidism (CNY/year)	8678.5 [31]	6508.9-10848.1 <sup>c</sup>
<b>Utility</b>		
without cardiac complication		
DFO	0.59	0.46-0.72 <sup>a</sup>
DFP	0.62	0.38-0.86 <sup>a</sup>
DFX	0.76	0.63-0.89 <sup>a</sup>
DFO+DFP	0.66 [33]	0.49-0.82 <sup>a</sup>
with cardiac complication		
DFO	0.50	0.38-0.63 <sup>c</sup>
DFP	0.53	0.40-0.66 <sup>c</sup>
DFX	0.65	0.49-0.81 <sup>c</sup>
DFO+DFP	0.56	0.42-0.70 <sup>c</sup>
<b>Transition probability data</b>		
cardiac complication morbidity		
DFO	0.148 [35-37]	0,018-0.587 <sup>a</sup>
DFP	0.262 [38]	0.197-0.328 <sup>c</sup>
DFX	0.040 [34]	0.030-0.050 <sup>c</sup>
DFO+DFP	0.133 [39]	0.100-0.166 <sup>c</sup>
cardiac complication mortality		
DFO	0.046 [36]	0.034-0.058 <sup>c</sup>
DFP	0.061 [38]	0.046-0.076 <sup>c</sup>
DFX	0.500 [34]	0.375-0.625 <sup>c</sup>
DFO+DFP	—	—
non-cardiac complication mortality		
DFO	0.008 [40]	0.006-0.010 <sup>c</sup>
DFP	0.009 [41]	0.007-0.011 <sup>c</sup>
DFX	0.001 [42]	—
DFO+DFP	—	—
<b>Other complications' morbidity</b>		
Chronic liver disease	0.857 [44]	0.643-1 <sup>c</sup>
Diabetes mellitus	0.052 [45,46]	0.033-0.070 <sup>a</sup>
Hypogonadism	0.632 [47,48]	0.579-0.684 <sup>a</sup>
Hypoparathyroidism	0.098 [49]	0.074-0.123 <sup>c</sup>
Hypothyroidism	0.121 [47,50]	0.105-0.136 <sup>a</sup>

PM: the final transition probabilities inputs for the model; a. Reported in source. b. Calculated based on standard error reported in source. c. Calculated by varying the reported value  $\pm 25\%$ . d. Calculated value would be outside the plausible range, value set to plausible maximum (i.e., maximum SC infusion utility cannot be higher than the standard oral utility, and the minimum oral utility cannot be lower than the standard SC infusion utility)

**Utility data.** Eighteen patients (32 person-time) who were treated at a hospital between 2015 and 2017 completed an assessment to get their utility values for DFO (12 person-time), DFP (9 person-time), and DFX (11 person-time) by a time trade-off (TTO) method. Participants were queried to identify the number of years of life with  $\beta$ -TM treated with either DFO, DFP, or DFX that they would be willing to trade off for years of life with perfect health. The average utility was used in the model. Kuo *et al.* reported that the utility value for DFO+DFP.<sup>33</sup> For patients with cardiac disease, their quality of life is estimated to be approximately 15% less than that of individuals without cardiac disease.<sup>26</sup>

**Clinical data.** From the systematic review, there was one paper from China reported cardiac complication morbidity and mortality with DFX,<sup>34</sup> where the morbidity was 7.7%, and mortality was 100% over 2 years. Three reported cardiac complication morbidity and mortality with DFO from Asia.<sup>35-37</sup> Ayyub *et al.* reported cardiac complication morbidity and mortality with DFP from Pakistan,<sup>38</sup> where the morbidity was 54.5%, and mortality was 16.7% over 3 years. Tanner *et al.* paper reported cardiac morbidity with DFO+DFP,<sup>39</sup> where the morbidity was 13.3% over one year. There was one paper reported non-cardiac complication mortality with DFO from Iran,<sup>40</sup> where the mortality was 4.0% over 5 years. However, there were two papers reported non-cardiac complication mortality from Europe, where the mortality was 2.6% over 3 years with DFP<sup>41</sup> and 1.0% over 6.9 years with DFX<sup>42</sup> respectively. These were converted into an annual rate for use in the model using actuarial life-table methods;<sup>43</sup> the mean of different annual rates with the same iron chelation was used in the model. The morbidity of diabetes mellitus, hypogonadism, and hypothyroidism were both reported from China,<sup>44-50</sup> and the mean of different morbidity was used in the

model.

**Sensitivity analysis.** One-way sensitivity analysis was performed to investigate the effects of altering the parameters, including the dosage, costs, utilities, and transition probabilities, within plausible ranges. To assess the main drivers of cost-effectiveness, we generated tornado diagrams representing the one-way sensitivity analysis for each comparison combination (DFO+DFP versus DFO, DFO+DFP versus DFP, DFO+DFP versus DFX, DFX versus DFO, DFX versus DFP and DFP versus DFO). A tornado diagram plotted the results of the effects of the ten most influential parameters on the outcomes from a sensitivity analysis exercise. These parameters were ordered such that the most influential parameter is at the top of the tornado diagram. In addition, all parameters were simultaneously varied in a probabilistic sensitivity analysis in which the doses and costs assumed to follow gamma distributions, while the utilities and transition probabilities were assigned beta distributions, in line with best practices.<sup>52,53</sup>

To analysis the influence of these key parameters of the one-way sensitivity analysis, which resulted in an ICER being greater or less than the payment threshold, we valued and calculated the fraction of these. Firstly, we valued key parameters according to the influence in each comparison. The most influential key parameter was valued 10, decreasing successively, and the least influential key parameter was valued 1. Secondly, we added up the value of the key parameter.

**Results. Base-case analysis.** The results from the base-case analysis are presented in **Table 2**. The ICER results showed that DFP was the most cost-effective treatment over a 5-year time horizon, followed by DFO, DFX, and DFO+DFP. DFP had the lowest cost of the four chelation regimens. Additionally, DFX had the longest QALYs.

**Table 2.** Results of base-case analysis.

	DFO	DFP	DFX	DFO+DFP
<b>cost(CNY)</b>				
not discounted	718535.21	541994.90	1642642.50	1592794.17
discounted	687581.85	509242.46	1572726.50	1523421.10
<b>QALYs(year)</b>				
not discounted	2.72	2.73	3.60	3.16
discounted	2.62	2.64	3.48	3.05
<b>Incremental analysis (discounted)</b>	<b>Inc. cost(CNY)</b>	<b>Inc. QALYs</b>	<b>ICER(CNY)</b>	<b>outcome</b>
DFX versus DFO	885144.65	0.86	1029237.97	NE
DFX versus DFP	1063484.04	0.84	1266052.43	NE
DFX versus DFO+DFP	49305.40	0.43	114663.72	Dominated
DFO+DFP versus DFO	835839.25	0.43	1943812.21	NE
DFO+DFP versus DFP	1014178.64	0.41	2473606.44	NE
DFP versus DFO	-178339.39	0.02	-8916969.50	Dominated

a. NE: not cost-effective.

**Sensitivity analysis.** One-way sensitivity analysis. The one-way sensitivity analysis results are represented in tornado diagrams in **Figure 2**.

For DFX versus DFO (tornado diagram **A.**), the patient weight and DFX drug cost resulted in an ICER < payment threshold, indicating that DFO was not cost-effective.

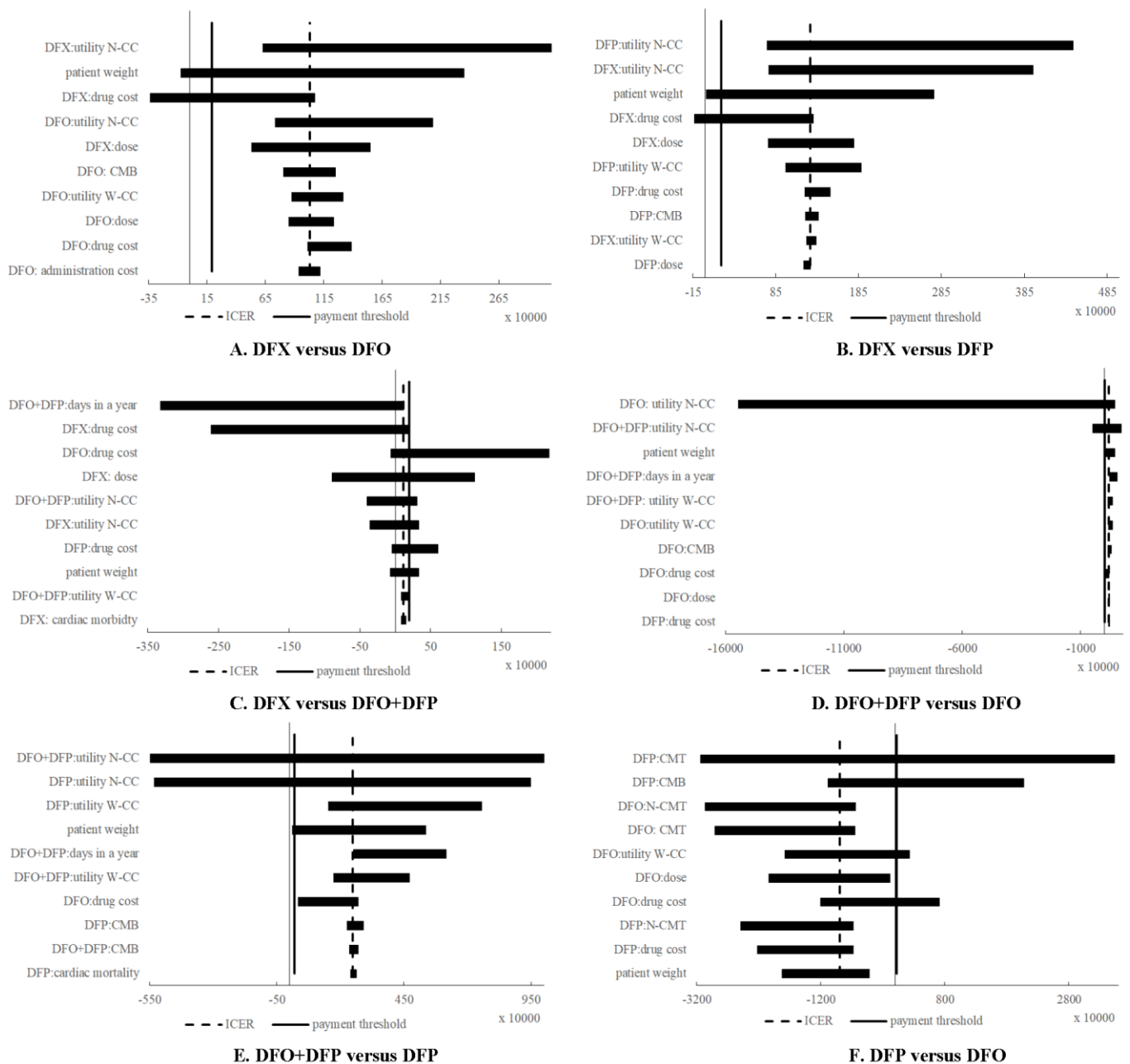
For DFX versus DFP (tornado diagram **B.**), the patient weight and DFX drug cost resulted in an ICER < payment threshold, indicating that DFP was not cost-effective.

For DFX versus DFO+DFP (tornado diagram **C.**), the DFO drug cost, DFX dose, utility without cardiac complication of DFO+DFP, utility without cardiac

complication of DFX, DFP drug cost, patient weight, utility with cardiac complication of DFO+DFP resulted in an ICER > payment threshold, indicating that DFX was not cost-effective.

For DFO+DFP versus DFO (tornado diagram **D.**), the utility without cardiac complication of DFO, utility without cardiac complication of DFO+DFP and patient weight resulted in an ICER < payment threshold, indicating that DFO was cost-effective.

For DFO+DFP versus DFP (tornado diagram **E.**), the utility without cardiac complication of DFO+DFP, utility without cardiac complication of DFP, and patient weight resulted in an ICER < payment threshold, indicating that DFP was cost-effective.



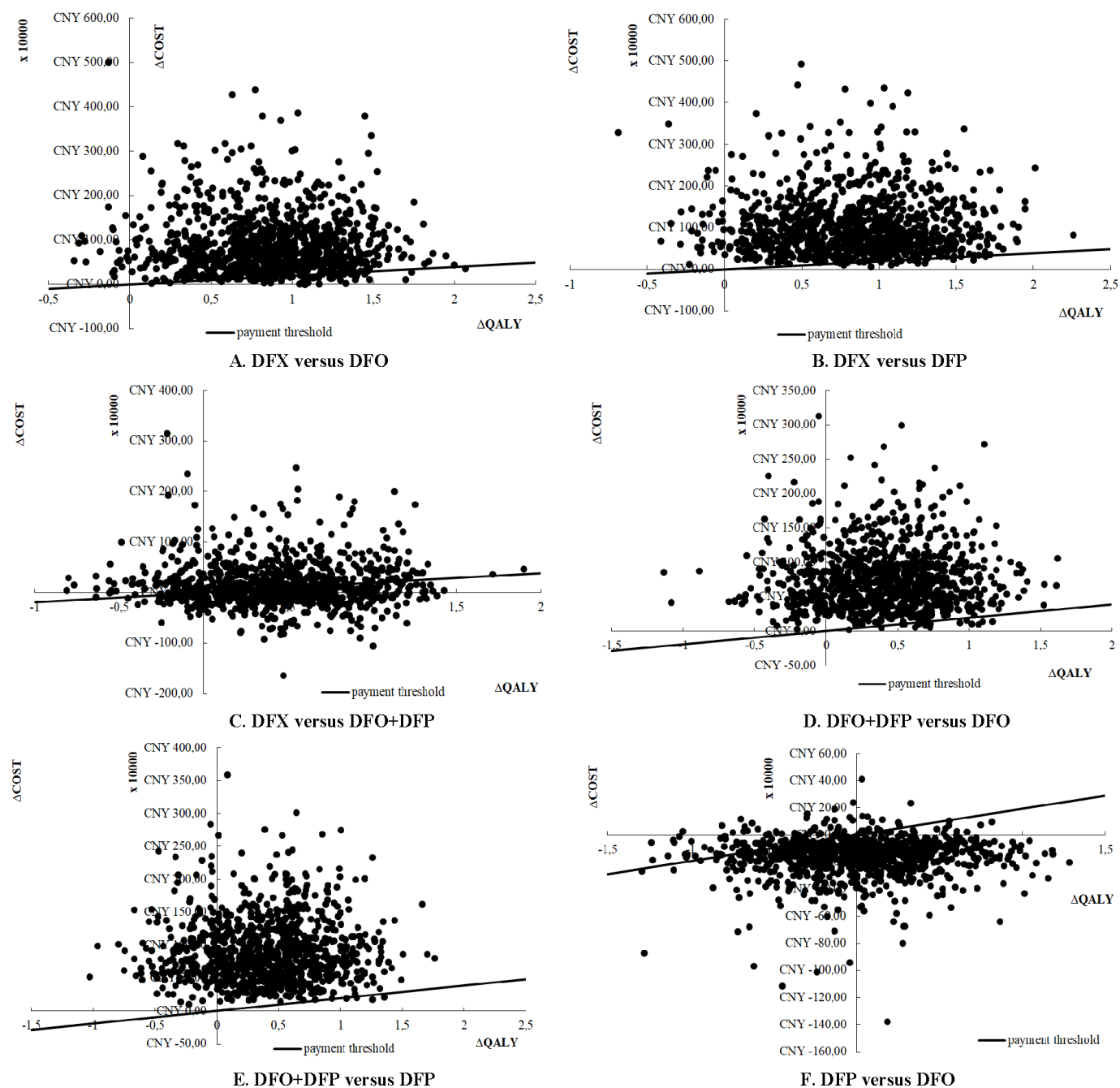
**Figure 2.** tornado diagrams for the one-way sensitivity analyses of **A.** DFX versus DFO, **B.** DFX versus DFP, **C.** DFX versus DFO+DFP, **D.** DFO+DFP versus DFO, **E.** DFO+DFP versus DFP and **F.** DFP versus DFO. N-CC: without cardiac complication; W-CC: with cardiac complication; CMB: cardiac complication morbidity; CMT: cardiac complication mortality; N-CMT: non-cardiac complication mortality; the vertical dotted line represents the base-case ICER, and the vertical solid line represents the payment threshold.

For DFP versus DFO (tornado diagram **F.**), the cardiac complication mortality of DFP, cardiac complication morbidity of DFP, utility with cardiac complication of DFO, DFO drug cost resulted in an ICER > payment threshold, indicating that DFP was not cost-effective.

**Probabilistic sensitivity analysis.** **Figure 3** shows the results of the probabilistic sensitivity analysis, represented by scatter plots. We simulated 10,000 sets of doses, costs, utilities, and transition probabilities estimated for each strategy by simultaneously sampling from the assigned probability distributions of the

variables. At the payment threshold, 193,932.00 CNY/QALY, compared with DFX, DFO+DFP, and DFO, the likelihood of DFP being cost-effective was 97.32%, 99.43% and 58.04%. Compared with DFX and DFO+DFP, the likelihood of DFO being cost-effective was 92.84% and 98.01%. Compared with DFO+DFP, the likelihood of DFX being cost-effective was 53.97%.

**The influence of key parameters of the one-way sensitivity analysis.** The calculation results of the influence of key parameters of the one-way sensitivity analysis were shown in **Table 3**.



**Figure 3.** Scatter plots for the probabilistic sensitivity analyses of **A.** DFX versus DFO, **B.** DFX versus DFP, **C.** DFX versus DFO+DFP, **D.** DFO+DFP versus DFO, **E.** DFO+DFP versus DFP and **F.** DFP versus DFO.

**Table 3.** The influence of key parameters of the one-way sensitivity analysis.

Sort	Key parameter	Fraction	Number of occurrences
1	patient weight	41	5
2	utility without cardiac complication of DFO+DFP	27	3
3	DFX drug cost	18	2
4	DFO drug cost	17	2
5	cardiac complication mortality of DFP	10	1
6	utility without cardiac complication of DFO	10	1
7	cardiac complication morbidity of DFP	9	1
8	DFX dose	9	1
9	utility without cardiac complication of DFP	9	1
10	utility with cardiac complication of DFO	8	1
11	utility without cardiac complication of DFX	7	1
12	DFP drug cost	6	1
13	utility with cardiac complication of DFO+DFP	4	1

**Discussion.** In this study, an analysis was conducted to evaluate the cost-utility of the four chelation regimens for  $\beta$ -TM from the Chinese healthcare system perspective. The results from the base-case analysis indicated that DFP was the most cost-effective chelation regimen, followed by DFO, DFX, and DFO+DFP. As a result, using DFP as the primary treatment regimen for  $\beta$ -TM patients has the potential to result in cost-savings and QALY gains for the Chinese healthcare system.

A systematic literature review of the cost-effectiveness of the four chelation regimens for  $\beta$ -TM<sup>19</sup> showed that DFP was the dominant strategy, which was consistent with the findings of this study. In the systematic literature review, DFX and DFO were tied as the second most cost-effective treatment regimen, and we could not judge which one was more cost-effective. In our study, DFO was the second most cost-effective treatment regimen, and DFP was the third. The systematic literature review and our study both thought DFO+DFP was the least cost-effective treatment regimen.

The one-way sensitivity analysis results and the influence of key parameters of the one-way sensitivity analysis reported that the utility without cardiac complication of DFO+DFP, DFX drug cost, DFO drug cost, cardiac complication mortality of DFP and the utility without cardiac complication of DFO were important. As a result, we have some suggestions to save more on costs or to obtain more QALYs. Firstly, for the Chinese government, DFX and DFO drug cost needs to be reduced. The available measures included incorporating these drugs into the National Reimbursement Drug List, negotiating drug prices, imposing a zero tariff on imported chelators, and encouraging the development of generic drugs. For Chinese clinicians, the following measures can be taken: (1) choosing the DFX and DFO that is cheaper or that is incorporated into the National

Reimbursement Drug List to make the drug cost lower, (2) acting in accordance with patients' parameters to make the utility of drugs higher (especially DFO+DFP), and (3) standardizing the use of chelators to reduce morbidity and mortality (especially DFP).

The results of the probabilistic sensitivity analysis showed that the likelihood of DFX being cost-effective compared to DFO+DFP was 63.97%, and the likelihood of DFP being cost-effective compared to DFO was 58.04%. These findings meant that changes in influential parameters easily changed the results of DFX versus DFO+DFP and DFP versus DFO. The key parameters of DFX versus DFO+DFP and of DFP versus DFO were shown in **Figure 2**. As a result, clinicians should pay more attention to the key parameters to save more on costs or to obtain more QALYs.

Generally, one utility is used for oral iron chelation therapy (DFP or DFX), and a different utility is used for the subcutaneous infusion. However, in our study, the utility of DFP was different from DFX. The main reason for the difference was that some patients who used DFP had experienced severe adverse reactions. In other papers, this difference also existed. Luangsanatip *et al.* reported that the utility of DFP and DFX was 0.61 and 0.85, respectively.<sup>26</sup>

We needed data on the cardiac complication morbidity, cardiac complication mortality, and non-cardiac complication mortality of the four chelation regimens from China (including Mainland China, Hong Kong, Macao, and Taiwan) to input them into the Markov model. Unfortunately, at the time of the study, there were not enough clinical data from China. To ensure the quality of this study, we performed a systematic literature review and used clinical data from the rest of the world. The clinical data may vary among different races. Therefore, they may bias the results.

**Conclusions.** In this study, DFP was the most cost-



effective chelation regimen for  $\beta$ -TM patients, followed by DFO, DFX, and DFO+DFP. As the most cost-effective treatment, using DFP as the primary treatment regimen has the potential to result in cost-savings and QALY gains for the Chinese healthcare system. To save more on costs or to obtain more QALYs, the Chinese government should take measures

to lower DFX and DFO drug costs, and Chinese clinicians should choose the cheaper DFX and DFO, increase the utility of DFO+DFP and reduce mortality and morbidity of DFP. Changes in key parameters easily affect the results of DFX versus DFO+DFP and of DFP versus DFO; clinicians should focus on such parameters and adjust the regimens accordingly.

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