

Cost-effectiveness Analysis of Intravitreal Aflibercept versus Laser Photocoagulation and ranibizumab PRN in the Treatment of Visual Impairment Due to Diabetic Macular Edema in China

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Background & Objectives

- Diabetic macular edema (DME) is a common microvascular complication of diabetes mellitus, which is the leading cause of visual impairment among working-age populations worldwide including Asia¹.
- Intravitreal aflibercept (IVT-AFL) is the first anti-VEGF agent approved for the treatment of DME in China, as it has demonstrated clinically meaningful superiority over macular laser photocoagulation in the Chinese population in the VIVID-EAST study².
- Mainly, three treatments are currently licensed and recommended for the treatment of visual impairment due to DME in China: macular laser photocoagulation, IVT-AFL, and ranibizumab. Each strategy is well-studied in terms of clinical efficacy and safety³⁻⁵, however there are no studies addressing the cost-effectiveness issue of DME treatment in China.
- This study aims to conduct a cost-effectiveness analysis to enable a comprehensive evaluation of the long-term economic benefits of IVT-AFL compared with macular laser photocoagulation and ranibizumab PRN in the treatment of DME from a Chinese societal perspective.

Methods

- A Markov model was developed to compare IVT-AFL 2 mg every 8 weeks after five initial monthly doses versus macular laser and ranibizumab 0.5 mg pro-re-nata (ranibizumab PRN) from a societal perspective. The model was condensed into an efficacy, maintenance, and non-intervention phase to reflect the vision changes in treated patients. Eight health states were defined based on the number of Early Treatment Diabetic Retinopathy Study letters read⁶ (**Figure 1**). This economic model was originally developed for Health Technology Assessment Submissions to regulatory agencies in Europe, including the National Institute for Health and Care Excellence (NICE)⁷, and then it was further adapted to fit for China's current situation in 2018.
- An external validation of the model was conducted via in-depth interviews of five key opinion leaders (KOL) from five top tertiary hospitals in four cities in China. Fifteen ophthalmologists from 15 tertiary hospitals in 12 cities were enrolled to finish a questionnaire-based survey verifying data inputs and closing data gaps.
- Efficacy data were derived from the VIVID-EAST trial and published indirect comparison⁸. Other parameters were estimated from the VIVID-EAST trial data, published literature, local reference price tables, or physician surveys (**Table 1**). Both costs and utilities were discounted at 5% each year.
- Productivity loss and caregiver costs were included for low vision states and blindness state. The days off for patients and caregivers were derived from the China physician survey, average national annual salary and annual allowance for blindness were used in calculation.
- One-way sensitivity analysis (OWSA) (variance was set as +/- 20% for all parameters except for the discount rate, which was set as 3% and 8%) and probabilistic sensitivity analyses were conducted

Figure 1. Visual acuity over time (3-phase model) and health states transition

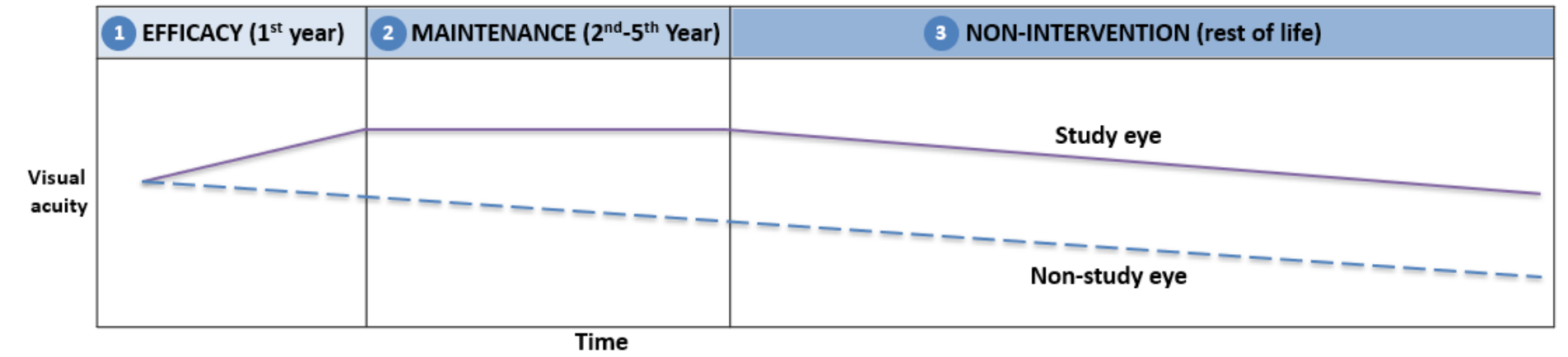


Table 1. Key model inputs

Parameter	Parameter detail	Source
Clinical transition probabilities		
IVT-AFL	Transition matrix	VIVID-EAST Trial
Laser	Transition matrix	VIVID-EAST Trial
ranibizumab PRN	Transition matrix	VIVID-EAST Trial & Korobelnik et al. 2015
Health utility inputs		
Key unit cost	Two-eye utility value	Czoski-Murray et al. 2009 ⁹
IVT-AFL 2 mg	5,850	Retail price in China's market
Ranibizumab10 mg/ml 0.2 ml/vial	5,700	Retail price in China's market
Laser	388	China physician survey
Resources use per eye per year		
IVT-AFL injections	Year 1: 8.6; Year 2-5: varies	Year 1: VIVID-EAST trial; Year 2-5: China physician survey
Laser treatments	Year 1: 2.4; Year 2-5: varies	Year 1: VIVID-EAST trial; Year 2-5: China physician survey
Ranibizumab injections	Year 1: 7.8; Year 2-5: varies	Year 1: REVEAL trial ¹⁰ ; Year 2-5: China physician survey

Results

IVT-AFL vs. laser

- In the base case of a 20-year lifetime horizon, an IVT-AFL-treated patient was associated with 7.825 quality adjusted life years (QALYs) and 217,841 CNY (32,264 USD; average exchange rate 2017: 1 USD=6.75 CNY), and a laser-treated patient was associated with 7.189 QALYs and 135,489 CNY (20,067 USD) (**Table 2 & Figure 2**)
- The incremental cost-effectiveness ratio (ICER) for IVT-AFL versus laser was 129,397 CNY (19,165 USD)/QALY, which was lower than the willingness-to-pay threshold (triple GDP per capita 178,980 CNY in China in 2017)
- OWSA showed that the ICER was most sensitive to variations due to starting age of cohort, IVT-AFL drug costs, number of IVT-AFL injections, and discontinuation rates (**Figure 3a**)
- Probabilistic sensitivity analyses projected that IVT-AFL has a higher probability of being cost-effective compared with laser under the willingness-to-pay threshold (triple GDP per capita) (**Figure 4a**)

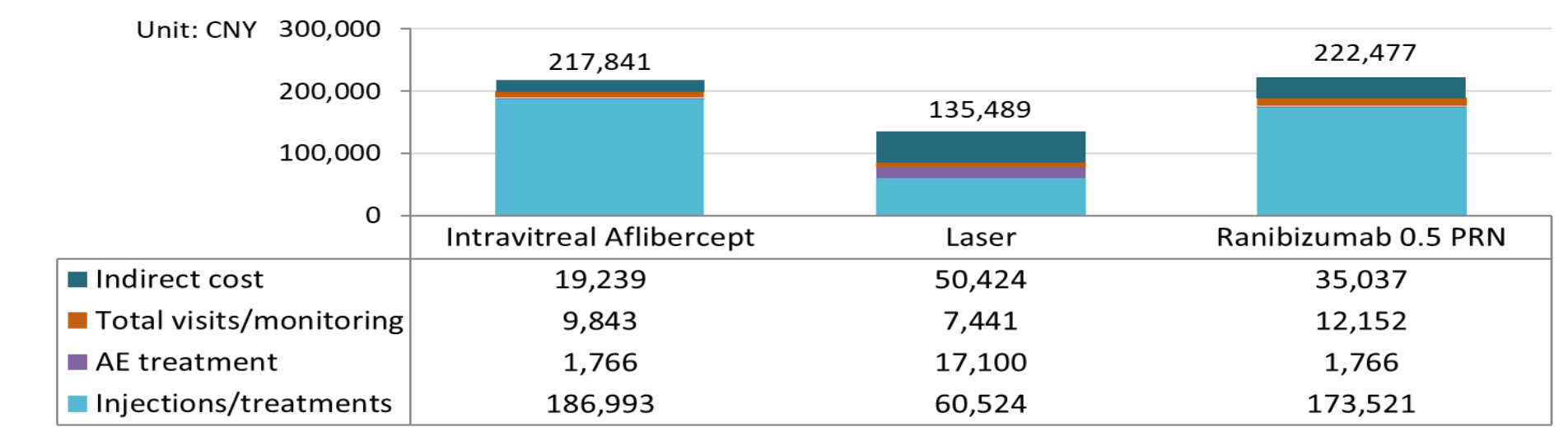
IVT-AFL vs. ranibizumab PRN

- A ranibizumab PRN-treated patient was associated with 7.462 QALYs and 222,477 CNY (32,951 USD). When comparing with ranibizumab PRN, IVT-AFL was associated with better outcomes with lower treatment cost, resulting the ICER of -12,774 CNY (-1,892 USD)/QALY (**Table 2 & Figure 2**)
- OWSA showed that ranibizumab PRN and IVT-AFL drug costs had the largest impact on the ICER results, followed by the number of injections of IVT-AFL and ranibizumab PRN (**Figure 3b**)
- Probabilistic sensitivity analyses showed that IVT-AFL is dominant in most scenarios (**Figure 4b**)

Table 2. Base case results

Treatment	Costs (CNY, ¥)			QALYs	ICER (CNY per QALY)
	Direct	Indirect	Total		
IVT-AFL	198,602	19,239	217,841	7.825	—
Laser	85,065	50,424	135,489	7.189	
ranibizumab PRN	187,439	35,037	222,477	7.462	IVT-AFL vs ranibizumab PRN: -12,774 (dominant)

Figure 2. Lifetime total cost breakdown



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Figure 3. OWSA tornado diagram

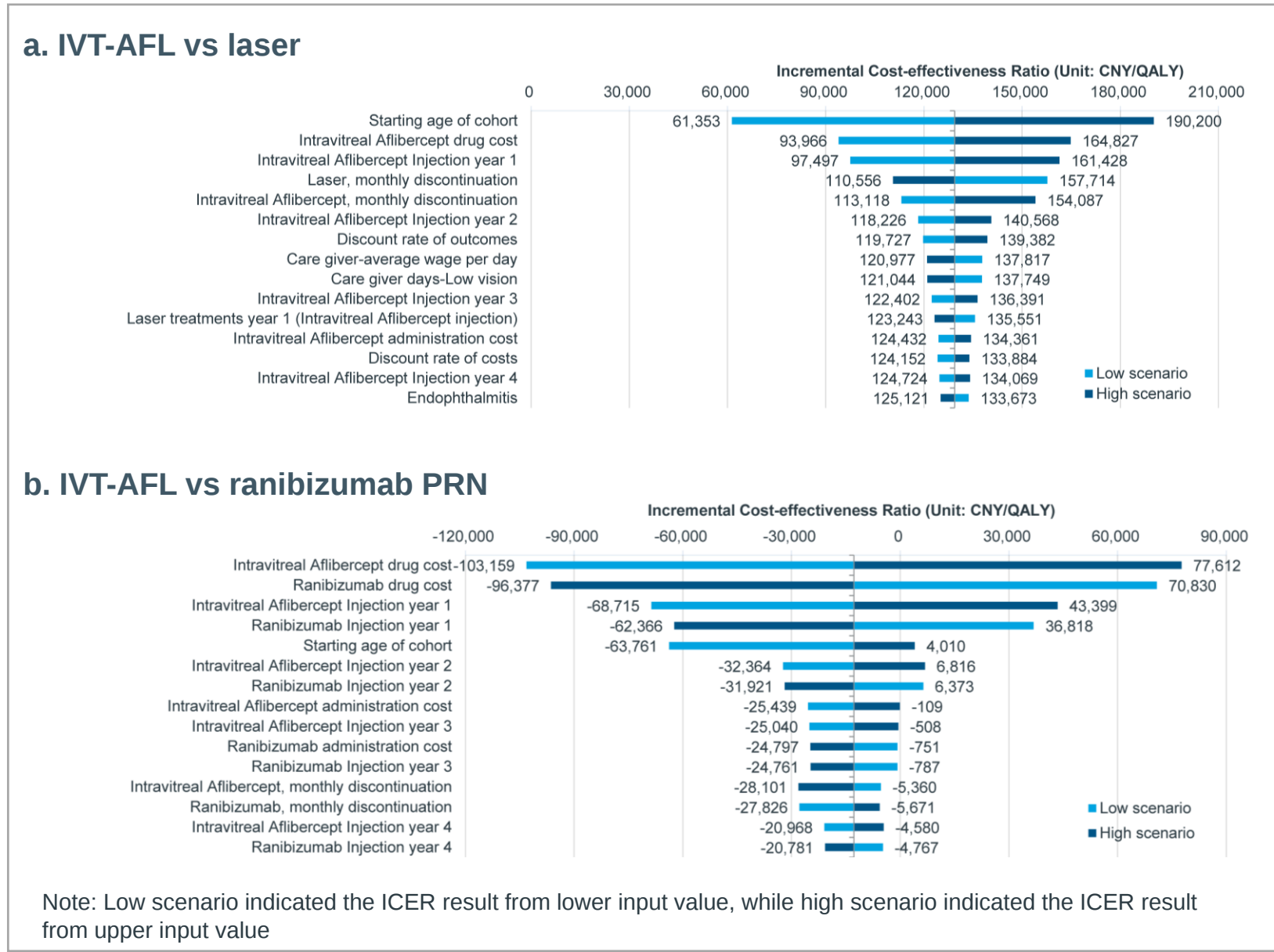
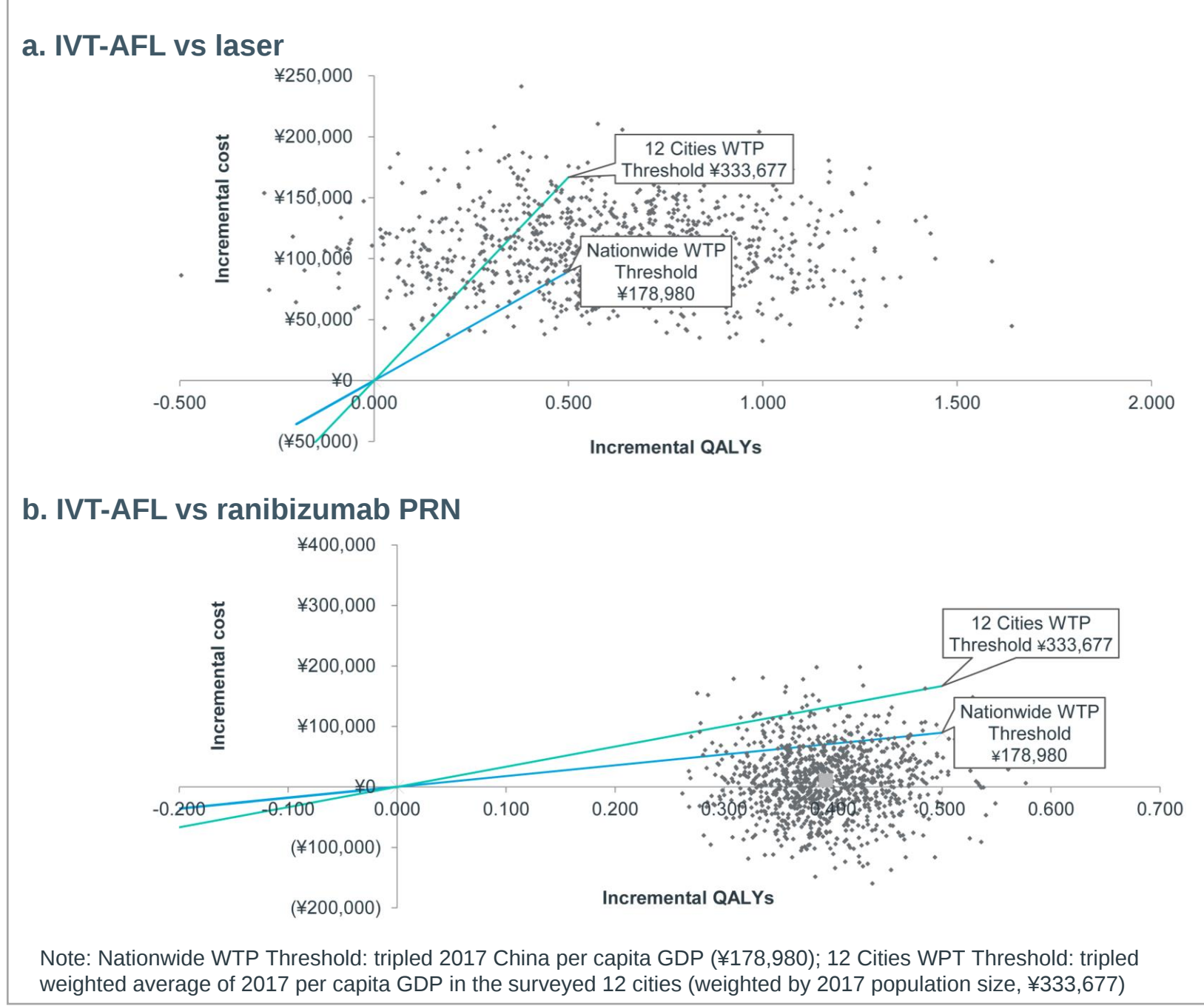


Figure 4. Scatter plot of probabilistic sensitivity analysis



Discussion and Conclusion

- The VIVID-EAST trial-based cost-effectiveness analysis comparison demonstrated that when compared with laser, IVT-AFL has the potential to be a cost-effective strategy in the treatment of visual impairment due to DME in China, providing more QALYs and further saving indirect costs. When compared with ranibizumab PRN, with the relative efficacy data derived from an NMA study, IVT-AFL would be considered as a dominant strategy. Results indicate a significant burden of indirect costs caused by visual impairment and blindness, which are consistent with previous disease burden studies¹¹.
- Our findings were consistent with most previous studies of comparing IVT-AFL with Ranibizumab. A US study based on the Diabetic Retinopathy Clinical Research Network Comparative Effectiveness Trial found that IVT-AFL was associated with higher QALY gain than Ranibizumab¹². Another study also found that IVT-AFL generated higher QALYs and reduced costs per patient per year compared to Ranibizumab at NHS list prices¹³.
- Our study strengths also include the adoption of societal perspective and the attempt in estimating the indirect costs based on the best available data.
- There are potential limitations in this study. Firstly, since there were no data available for efficacy and resources used in the subsequent years, we assumed no vision state changes for patients in the maintenance phases. Secondly, given limited empirical data were available for model testing, we tried to close the data gaps of resources use after year 1 by relying on physician surveys. Lastly, we used the allowance of blindness documented by the government as a surrogate for the cost of blindness since it is difficult to estimate the true cost.
- Despite any limitations, as the first study providing evidence on the cost-effectiveness of treatments for DME in China, this study may provide important economic evidence reference for clinical and reimbursement decision-making.

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