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Interferon-gamma release assay for tuberculosis screening of solid-organ transplant recipients is cost-effective

A. Kowada

General Affairs Department, Ota City Office, Tokyo, Japan

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SUMMARY

Objectives: Tuberculosis (TB) is a serious infectious disease with high mortality for solid-organ transplantation. Preventive therapy of latent tuberculosis infection (LTBI) has been considered to reduce TB risk and improve outcomes of transplantation. The aim of this study was to evaluate the cost-effectiveness of the interferon-gamma release assays (IGRAs); QuantiFERON®-TB Gold in-Tube (QFT) and T-SPOT®.TB (TSPOT)), for kidney, liver and lung transplant recipients in low TB incidence countries.

Methods: Decision trees and Markov models were developed for four strategies; QFT, TSPOT, the tuberculin skin test (TST) and no screening. Targeted populations were hypothetical cohorts of kidney, liver and lung transplant recipients aged 40 years using a societal perspective on a lifetime horizon. Per-person costs, effectiveness and incremental cost effectiveness ratios were calculated and compared.

Results: QFT was the most cost-effective (Kidney; US$ 5679, 3.026 QALYs, Liver; US$ 5914, 2.365 QALYs, Lung; US$ 6092, 3.761 QALYs). No screening was the least effective. Cost-effectiveness was not sensitive to BCG vaccination rate, and the costs of screening tests and treatment.

Conclusions: TB screening using IGRA with individualized TB risk assessment and follow-up monitoring of drug toxicity during LTBI treatment is recommended for solid organ transplantation, on the basis of the benefits and cost-effectiveness.

Introduction

Tuberculosis (TB) is a serious and important infectious disease with higher mortality and morbidity for transplantation.[1–6] Most TB is considered to cause by reactivation of latent tuberculosis infection (LTBI) among solid-organ transplant recipients.[2,3] For diagnosing LTBI, *Mycobacterium tuberculosis*-specific interferon-gamma release assays (IGRAs); QuantiFERON®-TB Gold In-Tube (QFT) [QIAGEN, Gaithersburg, USA, Australia] and T-SPOT®.TB (TSPOT) [Oxford Immunotec, Oxford, UK], are available as more accurate methods than the tuberculin skin test (TST).[7,8] IGRAs have no influence by Bacillus Calmette–Guérin (BCG) vaccination and superior specificity than that of TST in BCG vaccinated individuals, and have no booster phenomenon unlike TST. However, there is a weak point that none of IGRAs and TST differentiates active TB from LTBI.

TB screening using TST or IGRA testing with preventive LTBI treatment reduces the risk of TB reactivation and avoids active TB among solid-organ transplant recipients. Pre-transplant treatment of LTBI may be recommended to improve transplant outcomes in transplant recipients. TST and IGRAs have lower sensitivities and specificities of transplant recipients than those of the general population.[8] Currently, TST using nine months of isoniazid (9H) is the standard method among transplant recipients. The adverse hepatotoxic effects present a major difficulty to continue and complete LTBI treatment, especially liver transplant recipients.[2,9] For transplant recipients with diagnosing positive TST or/with IGRA, LTBI treatment is still controversial by the adverse hepatotoxic effects.

In this study, we assessed the cost effectiveness of IGRAs (QFT and TSPOT) and TST compared with no screening to evaluate the optimal TB screening with considering its benefits and hepatotoxicity among solid-organ transplant recipients in low TB incidence countries.

Methods

Model structure

Decision trees combined with Markov models were developed for four strategies; no screening, TST, QFT and TSPOT. (Fig. 1)

1. No screening.

Abbreviations: LTBI, latent tuberculosis infection; TB, tuberculosis; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; QFT, QuantiFERON®−TB Gold In-Tube; TSPOT, T-SPOT®.TB; TST, tuberculin skin test; 9H, 9 months of isoniazid; BCG, Bacillus Calmette-Guérin.

E-mail address: kowada-a7450@city.ota.tokyo.jp

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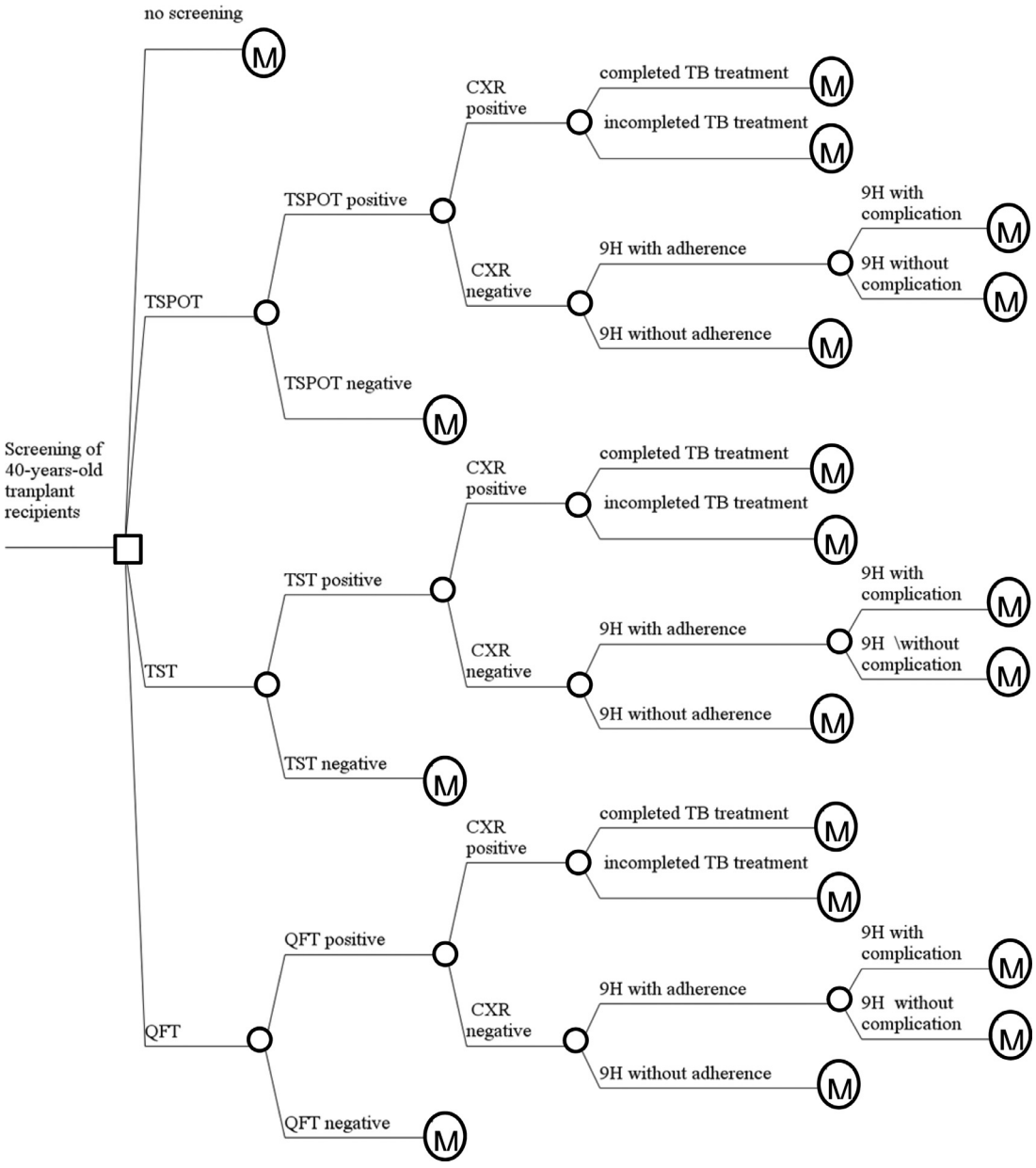


Fig. 1. Simplified decision trees for transplantation. QFT = QuantiFERON®-TB Gold in-Tube; TB = tuberculosis; TSPOT = T-SPOT®.TB; TST = tuberculin skin test; CXR = Chest X-ray examination; 9H = nine months of isoniazid. A square node represents the decision node. A circle node represents a chance node. Branches from a chance node represent possible outcomes. An Ⓜ node represents a Markov node.

2. TST strategy: A transplant recipient undergoes TST testing. If TST induration diameter (initial or after a booster effect) is ≥ 5 mm in those non BCG-vaccinated and ≥ 10 mm in those BCG-vaccinated, the recipient undergoes the chest x-ray examination (CXR). If active pulmonary TB is suspected based on CXR, and subsequent smears and cultures followed by drug sensitivity test of sputum examination are performed, and if extrapulmonary TB is suspected due to the presence of suggestive symptoms, signs and microbiologically confirmed cased on these clinical data, the recipient is treated per the standard 6-month protocol for TB treatment. If active TB is not detected, the recipient is treated per 9H. If the liver complication due to 9H occurs, 9H is discontinued. If TST induration diameter is < 5 mm in those without BCG vaccination and < 10 mm in those with BCG vaccination, the recipient has no need for CXR and follow-up. The percentage of TST testing and reading for the recipients is estimated to be 100%.
3. IGRA (QFT or TSPOT) strategy: A transplant recipient undergoes IGRA testing. If IGRA is positive, the recipient undergoes CXR. If active pulmonary TB is suspected based on CXR, and subsequent smears and cultures followed by drug sensitivity test of sputum examination are performed, and if extrapulmonary TB is suspected due to the presence of suggestive symptoms, signs and microbiologically confirmed cased on these clinical data, the recipient is treated per the standard 6-month protocol for TB treatment. If active TB is not detected, the recipient is treated per 9H. If the liver complication due to 9H occurs, 9H is discontinued. If IGRA is negative, the recipient has no need for CXR and follow-up.

The incremental cost effectiveness ratio of each screening arm was calculated and compared. The willingness-to-pay threshold is US$ 100,000/QALY in this study. Decision-analytical calculations were performed using Tree Age Pro 2012 (Tree Age Software Inc., Williamstown, MA, USA).

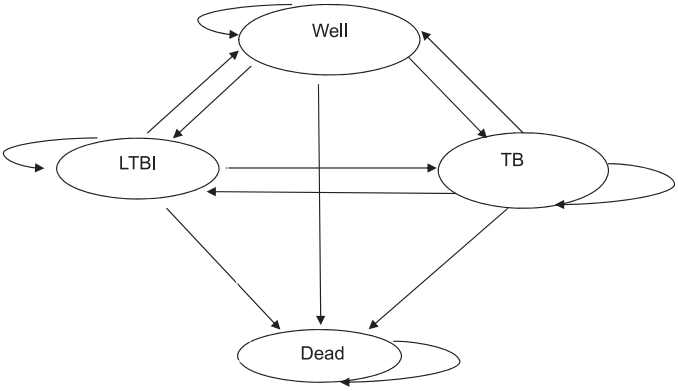


Fig. 2. Simplified Markov model diagram. Arrows indicate the direction in which a contact moves from one health state to another each year. LTBI = latent tuberculosis infection taking 9H with and without complication; TB = TB during and before treatment

As this was a modeling study with all inputs and parameters derived from published literature, ethics approval was not required.

Target population

Kidney, liver and lung transplant recipients aged 40 years were chosen as a hypothetical cohort on a lifetime horizon using a societal perspective.[1,5]

Markov models

The following six clinical states were included in this model to represent the possible clinical states in the target populations: (i) Well (no LTBI and no TB); (ii) LTBI; (iii) LTBI taking 9H without complication; (iv) LTBI taking 9H with liver dysfunction; (v) TB during and before treatment; (vi) Dead. (Fig. 2)[10–15] Each cycle length was one year.

Costs, effectiveness, probabilities, utilities and other assumptions

All data were collected using MEDLINE. A search of the literature published from 1980 to May 12, 2018 was undertaken to use incremental cost-effectiveness analysis.

The rates of LTBI and TB, the adherence rate of 9H, the completion rate of TB treatment, the probability of hepatotoxicity induced by 9H, the efficacy of 9H, the recurrence rate of TB after treatment, the mortality rate of TB and mortality rate due to the other causes were derived from published literatures.[1,4,6,16–24] The sensitivities and specificities of TST, QFT and TSPOT were assumed from the published literature.[8]

Cost data were collected using a societal perspective. All costs were adjusted to 2016 Japanese yen, using the medical care component of the Japanese consumer price index and were converted to US dollars, using the Organisation for Economic Co-operation and Development (OECD) purchasing power parity rate in 2016 (1US$ = \101.6).[25] The cost of TST screening included the TST reagent and the labor costs for a nurse in 2 visits and a physician in 2 visits. The cost of IGRA screening included the screening kit and the labor cost for a physician in 2 visits. The cost of CXR screening included the material cost of CXR and the labor cost for one physician visit. The costs of TB treatment, LTBI treatment and treatment of liver dysfunction caused by 9H were determined from national fee schedule in Japan.[26,27] (Table 1) The costs of smears, cultures and drug sensitivity tests of sputum examination were also considered.[26,27] All costs were discounted at a fixed annual rate of 3%.

The main outcome measure of effectiveness was quality-adjusted life-years (QALYs). Health state utilities were obtained from the literatures and were calculated by using a utility weight. (Table 1)[10–15] All clinical benefits were discounted at a fixed annual rate of 3%. Per-person QALYs were calculated for each strategy.

Incremental cost-effectiveness ratios (ICERs) were calculated by using incremental costs and incremental QALYs gained and were compared with the willingness-to-pay level of US$ 100,000/QALY.

Sensitivity analysis

One-way sensitivity analysis was performed to determine which strategy yielded the greatest benefits and costs, using the wide ranges of probabilities, costs and utilities. Probabilistic sensitivity analysis using the Monte-Carlo simulation was performed to assess the impact of the uncertainty of the key variables in the model on the base case estimates and recalculated expected values during 10,000 reiterations. The uncertainty in probability parameters was assumed to have a beta distribution, and the uncertainty in cost parameters was assumed to have a log-normal distribution (Table 1).

Results

In the base-case analysis, the total costs and QALYs assigned to QFT was US$ 5679 and 3.026 QALYs for kidney transplant recipients, US$ 5914 and 2.365 QALYs for liver transplant recipients, and US$ 6092 and 3.761 QALYs for lung transplant recipients [year 2016 values]. QFT was the most cost-effective for transplantation at the willingness-pay level of US$ 100,000/QALY gained (Tables 2 and 3).

Sensitivity analysis

Cost-effectiveness was not sensitive to BCG vaccination rate, the rates of LTBI and TB, and the costs of screening tests and treatment. Cost-effectiveness was sensitive to the sensitivities and specificities of QFT and TSPOT at a willingness-pay level of US$ 100,000/QALY gained. The TSPOT strategy was more cost-effective than the QFT strategy when QFT sensitivity was over 0.56, when QFT specificity was under 0.67, when TSPOT sensitivity was under 0.46, and when TSPOT specificity was over 0.69.

Probabilistic sensitivity analysis

According to the Monte Carlo simulations for 10,000 trials, QFT was the most cost-effective strategy for solid organ transplantation at a willingness to pay threshold of US$ 100,000/QALY.

At a willingness to pay threshold of US$ 100,000/QALY in BCG vaccinated transplant recipients, the probability of QFT was 62% versus 38% for TSPOT for kidney transplantation, and was 59% versus 41% for TSPOT for liver transplantation and 58% versus 42% for TSPOT for lung transplantation. At a willingness to pay threshold of US$ 100,000/QALY in non BCG vaccinated transplant recipients, the probability of QFT was 53% versus 36% for TSPOT and 11% for TST for kidney transplantation, and was 46% versus 31% for TSPOT and 23% for TST for liver transplantation, and was 50% versus 34% for TSPOT and 16% for TST for lung transplantation (Fig. 3).

Discussion

This study demonstrated that IGRA with preventive treatment was more cost-effective than TST and no screening in solid-organ transplant recipients. The superiority of IGRA specificities may be main cause of these results. This result may promote to make the decision for TB specialists and physicians of transplantation. Individualized TB risk assessment should be performed before transplantation. Follow-up monitoring of drug toxicity and careful drug

Table 1
Baseline estimates for selected variables.

	Base-case value	One-way sensitivity analysis range	Probabilistic sensitivity analysis distribution	References
Kidney transplantation				
Prevalence of LTBI	0.3	0.1–0.5	Beta	16
Prevalence of active TB	0.009	0.001–0.03	Beta	6
Adherence rate of 9H	0.47	0.3–0.7	Beta	17
Complication rate of 9H	0.05	0.02–0.1	Beta	17
Efficacy of 9H	0.8	0.6–0.9	Beta	18
TB recurrence rate	0.085	0.02–0.25	Beta	19
Completion rate of TB therapy	0.9	0.3–0.9	Beta	assumed
Mortality due to the other causes	0.25	0.2–0.5	Beta	20
Mortality due to TB efficacy of 9H	0.18	0.1–0.5	Beta	1
Utility				
Well	0.81	–	Fixed	10–13
LTBI	0.81	–	Fixed	10–13
LTBI taking LTBI treatment without complication	0.78	–	Fixed	10–13
LTBI taking LTBI treatment with liver dysfunction	0.69	–	Fixed	10–13
TB during and before treatment	0.65	–	Fixed	10–13
Death	0	–	Fixed	10–13
Liver transplantation				
Prevalence of LTBI	0.37	0.1–0.5	Beta	4
Prevalence of active TB	0.01	0.001–0.03	Beta	6
Adherence rate of 9H	0.65	0.3–0.7	Beta	21
Complication rate of 9H	0.06	0.02–0.1	Beta	4
Efficacy of 9H	0.8	0.6–0.9	Beta	18
TB recurrence rate	0.085	0.02–0.25	Beta	19
Completion rate of TB therapy	0.35	0.3–0.9	Beta	4
Mortality due to the other causes	0.31	0.2–0.5	Beta	4
Mortality due to TB	0.18	0.1–0.5	Beta	1
Utility				
Well	0.71	–	Fixed	10–12,14
LTBI	0.71	–	Fixed	10–12,14
LTBI taking LTBI treatment without complication	0.69	–	Fixed	10–12,14
LTBI taking LTBI treatment with liver dysfunction	0.60	–	Fixed	10–12,14
TB during and before treatment	0.57	–	Fixed	10–12,14
Death	0	–	Fixed	10–12,14
Lung transplantation				
Prevalence of LTBI	0.40	0.1–0.5	Beta	assumed
Prevalence of active TB	0.015	0.001–0.03	Beta	22
Adherence rate of 9H	0.69	0.3–0.7	Beta	23
Complication rate of 9H	0.027	0.02–0.1	Beta	23
Efficacy of 9H	0.8	0.6–0.9	Beta	17
TB recurrence rate	0.085	0.02–0.25	Beta	19
Completion rate of TB therapy	0.9	0.3–0.9	Beta	assumed
Mortality due to the other causes	0.2	0.2–0.5	Beta	24
Mortality due to TB	0.18	0.1–0.5	Beta	1
Utility				
Well	0.82	–	Fixed	10–12,15
LTBI	0.82	–	Fixed	10–12,15
LTBI taking LTBI treatment without complication	0.80	–	Fixed	10–12,15
LTBI taking LTBI treatment with liver dysfunction	0.70	–	Fixed	10–12,15
TB during and before treatment	0.66	–	Fixed	10–12,15
Death	0	–	Fixed	10–12,15
Accuracy				
Sensitivity of TST	0.31	0.26–0.36*	Beta	8
Specificity of TST in non-BCG vaccinated recipients	0.63	0.60–0.65*	Beta	
Specificity of TST in BCG vaccinated recipients	0.38	0.33–0.42	Beta	8, assumed
Sensitivity of QFT	0.53	0.46–0.59*	Beta	8
Specificity of QFT	0.69	0.65–0.72*	Beta	
Sensitivity of TSPOT	0.50	0.42–0.59*	Beta	
Specificity of TSPOT	0.67	0.61–0.73*	Beta	
Cost (US$ 2016 1$ = ¥101.6)				
QFT	62.0	31.0–124.0	Lognormal	26,27
TSPOT	62.0	31.0–124.0	Lognormal	26,27
TST	18.3	9.1–36.6	Lognormal	26,27
CXR	37.1	18.6–74.2	Fixed	26,27
Smears, cultures and drug sensitivity test of sputum examination	163.3	81.7–326.6	Fixed	26,27
LTBI treatment of 9H	1219.3	609.7–2438.6	Fixed	26,27
Treatment of drug-induced hepatitis by LTBI treatment	21,350	10675–42700	Fixed	26,27
Treatment of TB for 6 months	33,573	16787–67146	Fixed	26,27

LTBI = latent tuberculosis infection; TB = tuberculosis; 9H = nine months of isoniazid; TST = tuberculin skin test; CXR = chest X-ray examination; QFT = QuantiFERON®-TB Gold In-Tube; TSPOT = T-SPOT®.TB; * 95 % confidence interval.

Table 2
Cost-effectiveness of TB screening strategies for BCG vaccinated transplant recipients.

Strategy	Cost(US$ 2016)	Incremental cost(US$)	Effectiveness(QALYs)	Incremental effectiveness(QALYs)	ICER(US$/QALY)
Kidney transplantation					
no screening	1001	0	2.558	0	0
QFT	5679	4678	3.026	0.468	9990
TSPOT	5738	59	3.022	−0.005	Dominated
TST	8049	2370	2.951	−0.075	Dominated
Liver transplantation					
no screening	936	0	1.785	0	0
QFT	5914	4978	2.365	0.58	8583
TSPOT	5928	15	2.359	−0.006	Dominated
TST	7804	1891	2.294	−0.071	Dominated
Lung transplantation					
no screening	1559	0	3.232	0	0
TSPOT	6072	4513	3.756	0.523	8621
QFT	6092	4533	3.761	0.528	8580
TST	7981	1889	3.698	−0.062	Dominated

QFT = QuantiFERON®-TB Gold In-Tube; T-POT = T-SPOT®.TB; TST = tuberculin skin test; QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; BCG = Bacillus Calmette–Guérin.

Table 3
Cost-effectiveness of TB screening strategies for non-BCG vaccinated transplant recipients.

Strategy	Cost(US$ 2016)	Incremental cost(US$)	Effectiveness(QALYs)	Incremental effectiveness(QALYs)	ICER(US$/QALY)
Kidney transplantation					
no screening	1001	0	2.558	0	0
TST	5604	4603	3.005	0.447	10,293
QFT	5679	4678	3.026	0.468	9990
TSPOT	5738	59	3.022	−0.005	Dominated
Liver transplantation					
no screening	936	0	1.785	0	0
TST	5566	4630	2.350	0.565	8192
QFT	5914	348	2.365	0.015	23,566
TSPOT	5928	15	2.359	−0.006	Dominated
Lung transplantation					
no screening	1559	0	3.232	0	0
TST	5904	4345	3.743	0.511	8508
TSPOT	6072	168	3.756	0.013	13,172
QFT	6092	188	3.761	0.018	10,683

QFT = QuantiFERON®-TB Gold In-Tube; TSPOT = T-SPOT®.TB; TST = tuberculin skin test; QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; BCG = Bacillus Calmette–Guérin.

administration are also required during LTBI treatment for each transplant recipient.

The studies of the superior cost-effectiveness of IGRAs were previously reported on TB screening for immunosuppressive patients with diseases such as rheumatoid arthritis, human immunodeficiency virus infection and those on hemodialysis and the older people in low TB incidence countries.[28–31] The similar results were obtained in this study.

To the best of our knowledge, this study is the first cost-effectiveness analysis of IGRAs for transplantation using Markov models.

The World Health Organization (WHO) strongly recommends that systematic risk assessment, testing and treatment of LTBI should be performed in people preparing for organ or hematological transplantation.[32] Recommendations for the diagnosis and treatment of LTBI and active TB in organ transplant recipients are based on consensus guidelines formulated by experts in this field. An individual risk-driven approach based on targeting people for preventive therapy is needed. The risk factors and epidemiologic factors of transplant recipients for LTBI treatment should be individually evaluated with benefits of treatment before the start of treatment with systematic risk assessment.[5,33] The standard LTBI treatment for transplantation is isoniazid daily for 9 months. The evidence of the efficacy of LTBI treatment for preventing active TB in transplant recipients is still quite limited in several observational studies, prospective studies and randomized controlled trials.[34–36] Current guidelines for transplantation recommend that all recipients be routinely screened for LTBI prior to transplantation when transplant recipient with a positive TST and /or IGRA be treated.[33,37,38] Pre-transplant prevention with LTBI treatment should be considered to improve transplant outcomes and avoid the complications associated with post-transplant diagnosis and treatment of active TB. Treating lung transplant recipients appears to be more important for preventing pulmonary tuberculosis from the grafts. The low completion rate of LTBI treatment decreases its efficacy among transplant recipients. Especially, LTBI treatment for liver transplantation has the potential complexity of severe hepatotoxicity. Closely monitoring of the adverse events of hepatotoxicity is needed throughout LTBI treatment. 126,670 solid organs reported to be transplanted in 2015 worldwide.[39] Health care leaders should be aware that about 40,000 recipients of kidney, liver and lung transplantation may need LTBI treatment in one year.

There are several limitations. First, there is the limited scarce data of diagnostic accuracies of IGRAs and TST in solid-organ transplant recipients.[40] The sensitivities and specificities of LTBI screening kits, IGRAs and TST, were obtained from meta-analysis for hemodialysis patients and estimated in this study.[16] There may be more likely false positive, false negative and indeterminate results of IGRAs in transplant recipients. Further research of more accurate immunodiagnostic tests that can even distinguish between LTBI and active TB. Those tests will be able to select the recipients or donors with the risk to progress active TB in the recent fu-

ture. Second, the completion of LTBI treatment has a difficulty due to the adverse effects, the interactions with immunosuppressive drugs and the immunocompromised states of transplant recipients. Three months of rifapentine plus isoniazid with directly observed treatment may improve adherence and treatment completion in transplant recipients and be considered in the future. The short-course treatment regimen is effective as 9H and has the lower rate of severe hepatotoxicity than that of 9H.[21,23,41,42] Further research for clinical trials and well-controlled prospective studies with short course LTBI treatment regimens in transplant recipients is needed to assess their efficacy, safety, hepatotoxicity, adherence and completion of treatment for solid-organ transplantation. Third, the risk of donor-derived TB infection is not considered in this study. Living donors; such as TB contacts and the individuals who were born or lived for a significant period of time in TB endemic countries; present a higher rate of having LTBI. Donor-derived TB after transplantation is associated with significant morbidity and mortality.[2] Further cost-effectiveness study for TB screening of living transplant donors will be needed. Fourth, there is no complete tuberculosis data on what is happening in the world in human cell, tissue and organ transplantation. Global knowledge base on transplantation (GKT) has an important role to providing open access to data on activities in cell, tissue and organ transplantation at the global level, identifying whether countries have cornea or other tissue activities and whether there is a practice of allogeneic bone marrow transplantation.[43] Fifth, the cost of education and the cost of maintaining IGRAs and labor were not calculated in the models. Sixth, tuberculosis risk factors; history of tuberculosis, tuberculosis exposures, human immunodeficiency virus infection, country of origin, higher intensity immunosuppression, diabetes mellitus and increased recipient age; were not considered in the models. Finally, there are different costs and medical systems in each country. Further cost-effectiveness studies for transplantation by the variance of each country will be needed not only in low-incidence countries but also in high-endemic countries.

In conclusion, TB screening using IGRA is the most cost effective to improve outcomes for solid organ transplantation on the basis of cost-effectiveness. Individualized TB risk assessment and follow-up

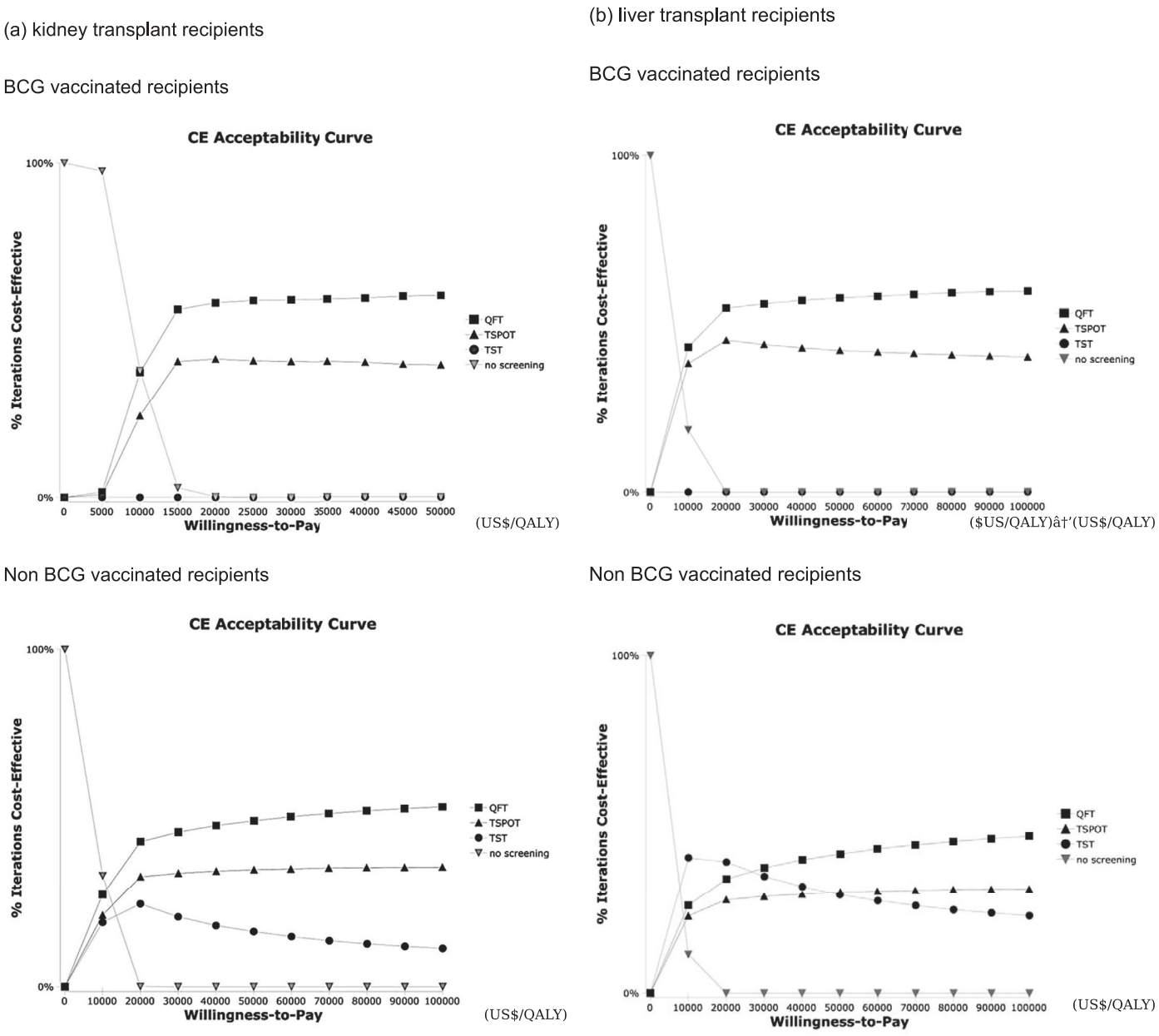
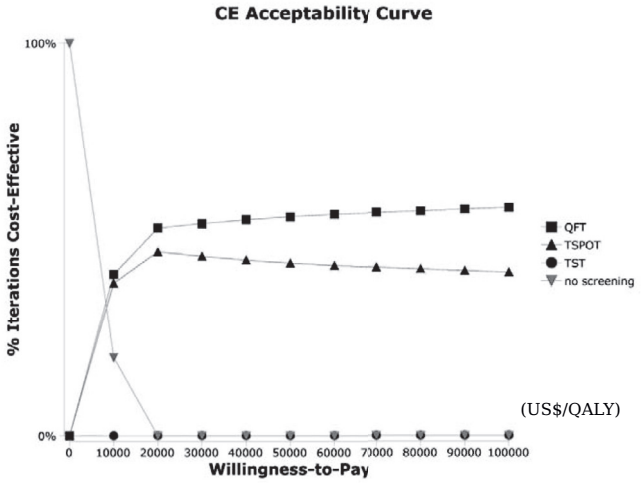


Fig. 3. Cost-effectiveness acceptability curve. QFT = QuantiFERON®-TB Gold In-Tube; TSPOT = T-SPOT®.TB; TST = tuberculin skin test.

(c) lung transplant recipients

BCG vaccinated recipients



Non BCG vaccinated recipients

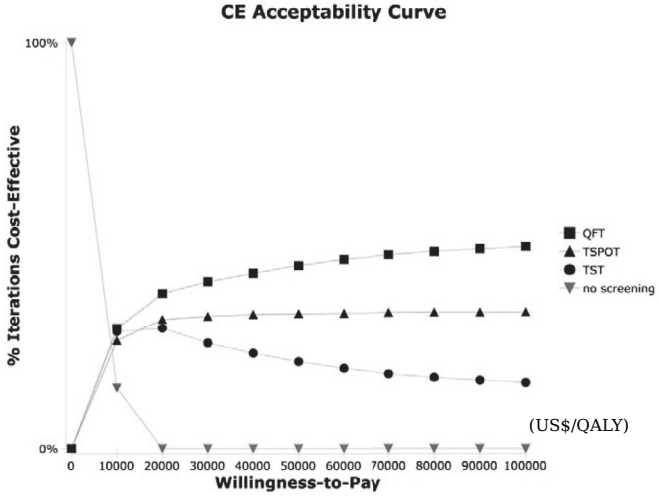


Fig. 3. Continued

monitoring of drug toxicity during LTBI treatment should be performed for each transplant recipient. Further research of more accurate immunodiagnostic screening method and preventive therapy with higher adherence and lower hepatotoxicity is needed for solid organ transplantation.

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Competing interests statement

The author reports no conflicts of interest that are directly relevant to the content of this study. The author has no financial disclosures.

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