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Cost-effectiveness analysis of genotyping for *HLA-B*15:02* in Indonesian patients with epilepsy using a generic model

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Conflicts of Interests

The authors declare no conflict of interest regarding the information presented in this manuscript.

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Abstract

Carbamazepine (CBZ)-induced Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are strongly associated with the *HLA-B*15:02* allele. Screening *HLA-B*15:02* before CBZ administration might prevent CBZ-induced SJS/TEN by enabling clinicians to prescribe alternative therapy for positive patients. Similar to other Southeastern Asian countries, *HLA-B*15:02* is highly prevalent in Indonesia. Therefore, we assessed the economic value of *HLA-B*15:02* screening before CBZ prescription to patients with epilepsy in Indonesia. A generic cost-effectiveness model and decision support tool, developed to enable users to perform an initial cost-effectiveness analysis from a healthcare provider/payer perspective, were used to assess the value of *HLA-B*15:02* genotyping. The incremental cost-effectiveness ratio of adopting universal *HLA-B*15:02* screening was 656 444 671 Indonesian Rupiah (IDR)/quality-adjusted life year (QALY) gained for patients compared with 2 634 975 574 IDR/QALY gained for providing valproic acid (alternative drug) without screening. Thus, neither *HLA-B*15:02* screening nor substitution with VPA meets the Indonesian threshold for cost effectiveness. However, the improved outcomes with this test in other Asian countries may inform the desirability of implementation in Indonesia even with suboptimal cost-effectiveness.

Keywords

cost utility analysis; SJS/TEN; *HLA-B*15:02* ; Indonesian population; generic model

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening acute inflammatory skin conditions that are among the most severe adverse drug reactions (ADRs) [1,2]. Approximately 80% of SJS/TEN cases are caused by medications, with the remainder caused by chemical exposure, mycoplasma pneumonia, viral infection, or immunization [3,4]. The clinical presentation of SJS/TEN includes a rash with target-like lesions and mucositis involving ocular, oropharyngeal, and genital surfaces. Patients are systemically unwell and experience fever and malaise [5]. The mortality rate of patients with SJS/TEN is 5%–50%, and 30%–70% of surviving patients suffer from long-term sequelae such as severe dry eye syndrome and trichiasis [2,6,7].

Carbamazepine (CBZ), a drug prescribed for the treatment of seizure disorders, bipolar disorder, trigeminal neuralgia, and chronic pain, is one of the drugs most frequently linked to SJS/TEN and other cutaneous eruptions including maculopapular exanthema (MPE) and Drug Rash with Eosinophilia and Systemic Symptoms Syndrome (DRESS Syndrome) [8–13]. Previous studies have shown that the development of SJS/TEN induced by CBZ also has a genetic basis [11], and a strong association has been identified between the *HLA-B*15:02* allele and risk for CBZ-induced SJS/TEN among Han Chinese [13–14]

and in Southeast Asian countries, including Thailand [15], India [16], and Malaysia [17]. However, the allele is rare in populations of European descent [11]. Evidence for the association between *HLA-B*15:02* and MPE was observed in the Thai population [12], but subsequent studies have disputed the association. DRESS does not appear to be associated with *HLA-B*15:02*, but is associated with another allele, *HLA-B*58:01* [13].

Screening for *HLA-B*15:02* in individuals with Southeast Asian ancestry before initiating CBZ treatment was found to decrease the incidence of SJS/TEN in Taiwan [18], Thailand [19], and Singapore [20]. This practice is also recommended by drug regulatory agencies such as the U.S. Food and Drug Administration [21], UK Medicines and Healthcare Products Regulatory Agency [22], and the European Medicines Agency [23]. However, it has not been implemented in most Asian countries owing to limited data regarding the contribution of *HLA-B*15:02* to drug-induced SJS/TEN and the cost effectiveness of genotype-guided approaches, especially across Southeast Asian countries.

Indonesia is among the Southeast Asian countries that has not adopted *HLA-B*15:02* screening. Previously, we described the high frequency of the *HLA-B*15:02* allele in healthy Javanese and Sundanese populations [24,25]. Additionally, our recent study revealed a significant association between the *HLA-B*15:02* allele and the risk of CBZ-induced SJS/TEN in the Javanese–Sundanese population in Indonesia [26]. These data suggest that the Indonesian population may especially benefit from genetic screening prior to CBZ treatment by identifying the risk of developing SJS/TEN.

In Indonesia, CBZ is the first-line drug for the treatment of psychiatric and neurologic diseases owing to its affordability and efficacy. However, owing to concerns regarding the development of SJS/TEN, some clinicians prefer to prescribe alternative drugs, such as valproic acid (VPA). The implementation of *HLA-B*15:02* screening for patients with newly diagnosed epilepsy and neuropathic pain would allow the prescription of alternative medications (e.g., VPA) to patients testing positive for the allele and CBZ for those with a negative result. However, the cost effectiveness of implementing *HLA-B*15:02* screening prior to CBZ treatment should be analyzed relative to the current practice of prescribing CBZ universally without screening or the prescription of VPA or other drugs universally without screening to influence Indonesia health care policy decisions, especially the Indonesian Ministry of Health decisions. The present study was performed to analyze the cost effectiveness of screening adult patients newly diagnosed with epilepsy for *HLA-B*15:02* to prevent CBZ-induced SJS/TEN.

Materials and Methods

Model structure

We utilized a generic cost-effectiveness model and a decision support tool developed to enable users to perform an initial cost-effectiveness analysis from a healthcare provider/payer perspective (only direct medical costs were used) to assess the value of *HLA-B*15:02* genotyping for adult patients newly diagnosed with epilepsy to prevent CBZ-induced SJS/TEN [27]. We enrolled adult patients (aged 40 years or older, based on the model assumption of the average age of epilepsy onset = 40 years and life expectancy = 60 years

[28]) with newly diagnosed epilepsy in Indonesia for whom CBZ was considered suitable as first-line therapy, by providing requested input values that are specific to Indonesia. The model assumed that VPA has efficacy and safety profiles comparable with those of CBZ but without the risk of SJS/TEN [29]. The model also assumed that neither CBZ nor VPA induces other ADRs; that the probability of VPA-induced SJS/TEN is zero; and that the probability of CBZ-induced SJS/TEN in an *HLA-B*15:02* negative population is zero [27]. The lifetime was defined as a length of 1 year. The primary outcomes were lifetime costs, quality-adjusted life-years (QALYs) gained, and incremental cost-effectiveness ratio (ICER) in Indonesian Rupiah (IDR) per QALY gained.

The decision tree for the generic model (Fig. 1) consisted of three potential strategies for patients requiring epilepsy treatment: first, administering CBZ to all patients without *HLA-B*15:02* screening (reflecting the current practice in Indonesia) and second, testing patients for the *HLA-B*15:02* allele and prescribing VPA for those that tested positive and CBZ for those that tested negative. The latter group was further divided into patients with a true negative and a false negative result. A false negative result of the *HLA-B*15:02* screening test indicates that a patient does not have the allele while in fact, the patient possesses the allele. In the third strategy, patients did not undergo *HLA-B*15:02* screening and were treated with VPA. There were two potential initial outcomes for all patients: developed or did not develop SJS/TEN.

A Markov model (Fig. 2) was used to generate the estimates of the lifetime effect of CBZ or VPA. There were three potential outcomes for patients that developed SJS/TEN and were hospitalized for treatment: (a) recovery; (b) recovery with long-term sequelae; or (c) death (Fig. 2a). The remaining patients did not develop SJS/TEN (Fig. 2b) and died from other causes. The parameters used in the analysis are presented in Table 1 and are discussed in detail below.

Model parameters

Table 1 shows the input parameters requested in the generic model. A complete list of parameters, including default parameter values, are documented in the generic model presented in supplementary materials PHG500725sm_1.docx, Appendix A [27].

Predictive value of *HLA-B*15:02* screening

The prevalence of *HLA-B*15:02* carriers in the study population was 20.8% [24]. This was estimated from 237 unrelated individuals of Javanese or Sundanese–Javanese ethnicity from the general population in the western part of Java Island, Indonesia. Subjects were interviewed to derive their ethnics background, dating back three generations. The probability of CBZ-induced SJS/TEN in *HLA-B*15:02*-positive patients in Indonesia was assumed to be 1.1% [26, 30, 31].

Costs and utilities

We calculated the direct medical costs incurred by patients for the treatment of CBZ-induced SJS/TEN based on information provided by experts and the Indonesia Case Base Groups (INA-CBGs) system, a prospective payment system formulated by the Social Security

Institution of Health that sets the diagnosis and procedure grouping, without considering its type and the amount of health service provided. INA-CBGs data are representative of all Indonesians. The price per unit of the antiepileptic drug in 2015 was obtained from the INA-CBGs data. All costs are reported in IDR in 2015.

Cost-effectiveness analysis

Cost effectiveness was determined as an incremental cost per QALY gained for *HLA-B*15:02* screening versus no *HLA-B*15:02* screening before CBZ administration. The total costs and QALYs associated with each treatment strategy were calculated over the span of a lifetime.

Sensitivity analysis

A probabilistic sensitivity analysis was carried out to estimate the impact of the uncertainty using probability distributions relative to base-case values for some parameters to determine the ICER. A cost-effectiveness ceiling threshold of 150 000 000 IDR per QALY gained was used.

Results

Base-case cost-effectiveness analysis

Table 2 shows the base-case cost effectiveness of *HLA-B*15:02* screening, presented in IDR and QALYs. Compared with the current practice of “no screening” and the prescription of CBZ, *HLA-B*15:02* screening and the prescription of VPA to patients tested positive for the allele resulted in an improvement in QALYs by 0.011 at a marginal increase in cost of IDR 6 951 845. Using these estimates, the ICER was identified as IDR 656 444 671 per QALY gained. Further, the prescription of VPA for all patients who were not screened was dominated by the testing arm as it yielded the same QALYs as the screening strategy but at a higher cost of IDR 49 610 785.

Sensitivity analysis

For the sensitivity analysis, we calculated the probability that the three treatment strategies were cost effective at different ceiling ratios (Fig. 3). As a result, the Indonesian cost-effectiveness threshold (estimated as three times gross domestic product per capita = IDR 150 000 000) was derived. Compared with *HLA-B*15:02* screening and VPA treatment, the current practice of treating patients with CBZ had the highest probability of being cost effective. In fact, a negative correlation was found for the probability of cost effectiveness for the current practice and the threshold value. As the cost-effectiveness probability of the screening strategy was positively correlated with the ceiling threshold, it was more likely to be cost effective than “no screening” and the prescription of either CBZ or VPA above a threshold value of IDR 500 000 000.

The cost effectiveness of universal *HLA- B*15:02* screening was sensitive to the probability of CBZ-induced SJS/TEN occurring in a patient that tested positive for *HLA-B*15:02*. Thus, a threshold analysis was carried out to determine the ICER for the range of CBZ-induced SJS/TEN prevalence in the Indonesian population. The probabilistic sensitivity

analysis revealed that screening with genetic testing increased costs and QALY in all the iterations. Furthermore, an analysis of the number needed to screen revealed that 423 patients with epilepsy should be screened for the *HLA-B*15:02* allele to prevent one case of SJS/TEN.

Discussion

Pharmacogenomics plays an increasingly important role in identifying genetic markers of drug response, including the risk for drug hypersensitivity. Pharmacogenomics seeks to enable healthcare systems to deliver optimal evidence-based and efficient therapy and avoid adverse events in patients. Policies for the adoption of a pharmacogenomic test should thus rely on rigorously validated evidence of a relationship between genotype and drug response (i.e., clinical validity). Additionally, a clear course of action should be derived for disease treatment based on genotype results [32].

Previous studies have consistently demonstrated that the development of CBZ-induced SJS/TEN is influenced by genetics [11]. Additionally, a strong association was identified between the *HLA-B*15:02* allele and the risk for CBZ-induced SJS/TEN among Han Chinese [13–14] and in Southeast Asian countries, including Thailand [15], India [16], and Malaysia [17]. Similar results were also found in an Indonesian study [26]. It was recently reported that *HLA-B*15:02* allele was not specific for carbamazepine-induced SJS/TEN only, but was also significantly associated with carbamazepine-induced MPE in the Thai population [12]. However, no association of *HLA-B*15:02* with MPE was observed in several other studies [13, 33, 34, 35]. In contrast to SJS/TENS, data for the model parameters is lacking for MPE. Prior models have not included MPE, and the generic model used also did not include this condition. Therefore, MPE was not included in the analysis. Further study is needed to confirm the relationship between MPE and *HLA-B*15:02* in other populations and to develop the parameters needed to perform an analysis using the model.

With the increasing cost of health care, it has become increasingly important to weigh the cost versus benefit of genotyping to guide therapeutic decisions. Cost utility and decision analyses are required not only to guide clinicians in health care decisions but also to facilitate the safe and efficient delivery of health care. As a result, costs and the allocation of resources can play a major role in clinician decision making. In this study, we used a previously validated generic model populated with values based on country-specific data (i.e. carrier prevalence, costs of care, and the probability of adverse events in *HLA-B*15:02* positive patients) and using evidence-based assumptions that reflect the Indonesian perspective. We observed that screening for the CBZ-induced SJS/TEN susceptibility allele, *HLA-B*15:02*, or the prescribing of alternative drugs, such as VPA, for all patients decreased the number of CBZ-induced SJS/TEN cases, but with a cost effectiveness that exceeds the current societal thresholds. Comparing the two alternative strategies, *HLA-B*15:02* screening was identified to be the preferred choice relative to alternative drug treatment as it was less expensive, despite the similar health outcomes achieved with both the strategies. The use of a generic model significantly reduces the time and expertise needed to perform the analysis. There are other alternatives to CBZ besides

VPA for the Indonesian population; however, because the model employed in this study used VPA for the analysis, we opted to collect information regarding VPA alone. Moreover, because the model assumed equivalent efficacy and zero adverse events, more expensive medications than VPA would be less cost effective in clinical practice.

A recent study in Indonesia [26] and the Philippines [36] revealed that the B75 serotype plays an important role in these populations. The HLA-B75 serotype includes *HLA-B*15:02, HLA-B*15:08, HLA-B*15:11, HLA-B*15:15, HLA-B*15:21*, and *HLA-B*15:31* [37]. The B-75 serotype allele has been reported in the populations of several Asian countries; these include *HLA-B*15:11* in Japan [38]; *HLA-B*15:08* in India [36]; and *HLA-B*15:21* in Thailand [15], Indonesia [26], and the Philippines [36]. As the B75 serotype allele was observed in several populations, Yuliwulandari et al (2017) [26] suggested assessing the performance of a B75 serotype allele screening in Asian countries, in addition to *HLA-B*15:02* screening. However, the currently available data are insufficiently robust to inform assumptions for the model; therefore, the analysis was restricted to *HLA-B*15:02*. As more data accumulate, a further study should be conducted to derive and evaluate a model for the cost effectiveness of B75 although, given the results of the sensitivity analysis, it is unlikely to result in the cost effectiveness of the intervention. In this study, a previously developed and validated cost-effectiveness model was used. Changing model parameters would have necessitated the reconstruction of the model. The current generic model could be repurposed for such a study, avoiding the effort to create a model *de novo*. However, it is important to recognize that in scenarios where evidence is accumulating rapidly, models cannot remain static, as was highlighted in a decision-analysis to inform a Lynch screening implementation program [39].

This study had some limitations. First, as SJS/TEN is a rare condition in the Indonesian population, very few patients with SJS/TEN were enrolled, which may affect the accuracy of the cost and the utility estimates. Second, as an active surveillance system was not implemented to measure the prevalence of CBZ-induced SJS/TEN in the Indonesian population, we assumed that it would be similar to that reported in other countries, especially in the case of data reported from the Thai population [19]. Therefore, the availability of prevalence data from Indonesia may improve the parameter estimates used in the model. The sensitivity analysis shows that the model is relatively insensitive to population prevalence, in so far as achieving a cost-effectiveness threshold is concerned. Other severe cutaneous adverse events, such as drug-induced hypersensitivity syndrome (DiHS or DRESS), can occur and could potentially affect the model. Based on informal communication with authors of previously published work, it appears that DiHS was implicitly included in prior models; therefore, it is not expected to affect the results. The model also assumes no adverse events in non-carriers of *HLA-B *15:02* and in those treated with VPA. While the risk is likely not zero, published evidence is sufficient to indicate that the risk in these populations is extremely low, such that the use of zero in the assumption should not unduly bias the result. Any value greater than zero would shift the result to even less favorable cost-effectiveness, and therefore, the conclusion would not be altered. These limitations can be mitigated via a sensitivity analysis, which enables analysis over a wide range of cost and utility estimates.

Collectively, our findings suggest that from the Indonesian societal perspective, it is not cost effective to carry out *HLA-B *15:02* screening for patients who would often be administered CBZ. However, these findings could demonstrate to policymakers, such as the Ministry of Health, the effect of implementing a pharmacogenomic-guided medical intervention in the Indonesian population. Such implementation could reduce the economic impact of this adverse drug reaction and would be similar to the genome-guided warfarin treatment in Croatia, which involves the reimbursement of pharmacogenomic testing costs [40]. Additionally, given the improvements in clinical outcomes with *HLA-B*15:02* screening in Taiwan [18], Thailand [19], and Singapore [20] and the availability of more effective alternative drugs, implementing *HLA-B*15:02* testing to predict the risk for CBZ-induced SJS/TEN may become an effective and desirable strategy in Indonesia even if cost-effectiveness is less than the predicted value.

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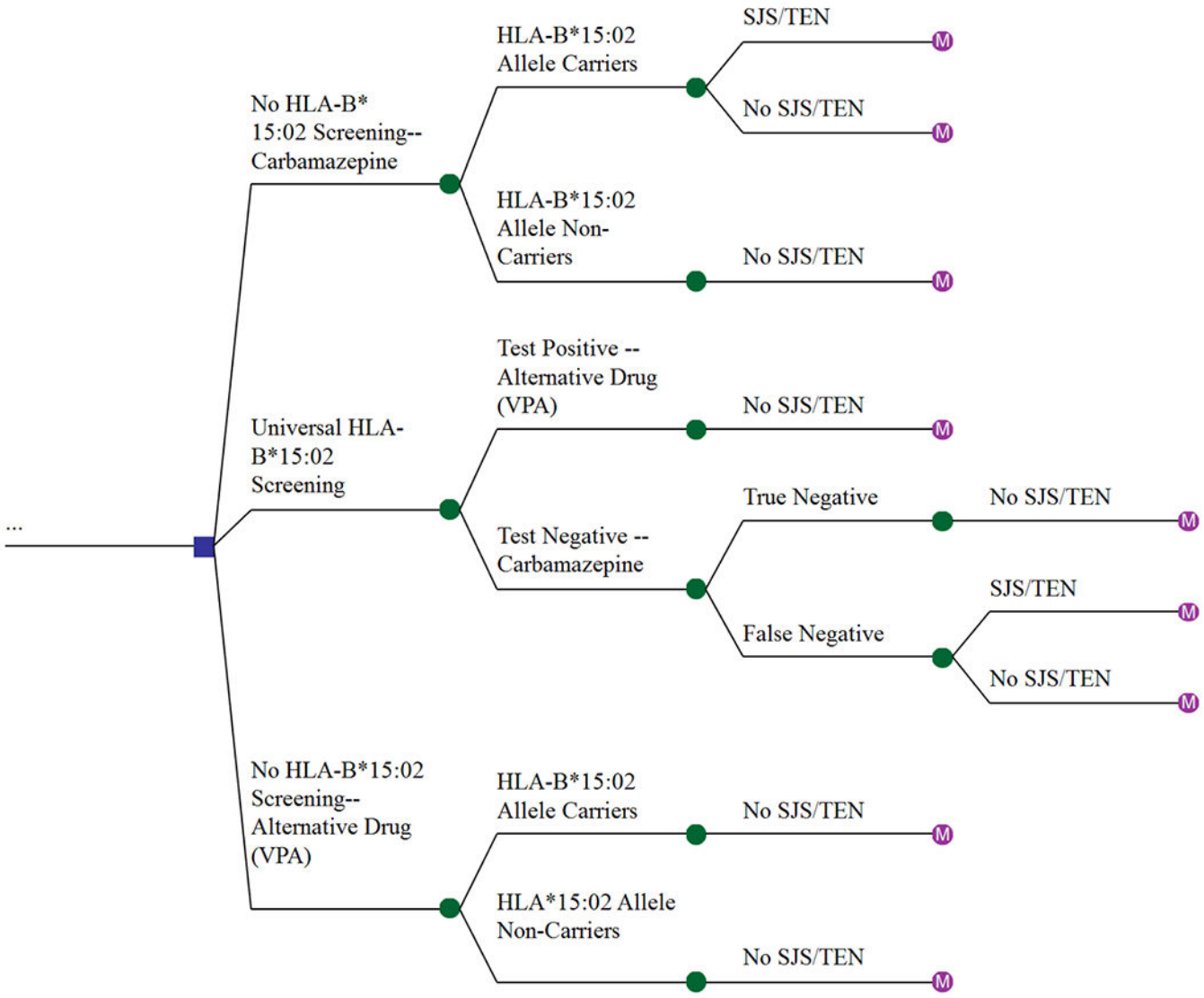

Fig 1.

Decision tree model showing the three potential strategies for the treatment of patients with epilepsy.

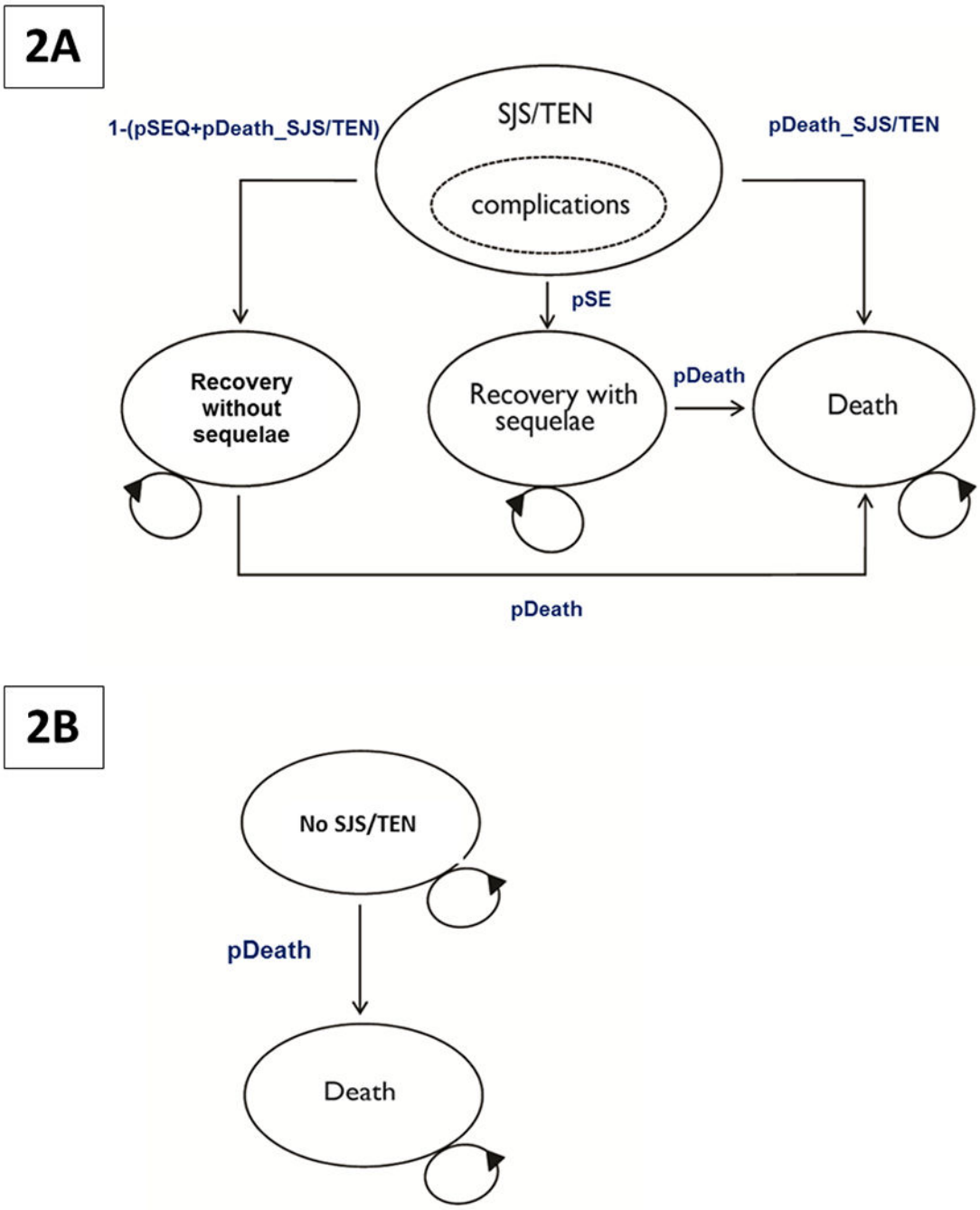

Fig 2. Markov model showing the three potential outcomes for patients treated with CBZ or VPA

A. Patients that developed SJS/TEN following CBZ treatment

B. Patients that did not develop SJS/TEN following treatment with CBZ or VPA

Abbreviations: SJS: Steven–Johnson Syndrome; TEN: toxic epidermal necrolysis; CBZ: carbamazepine; VPA: valproic acid.

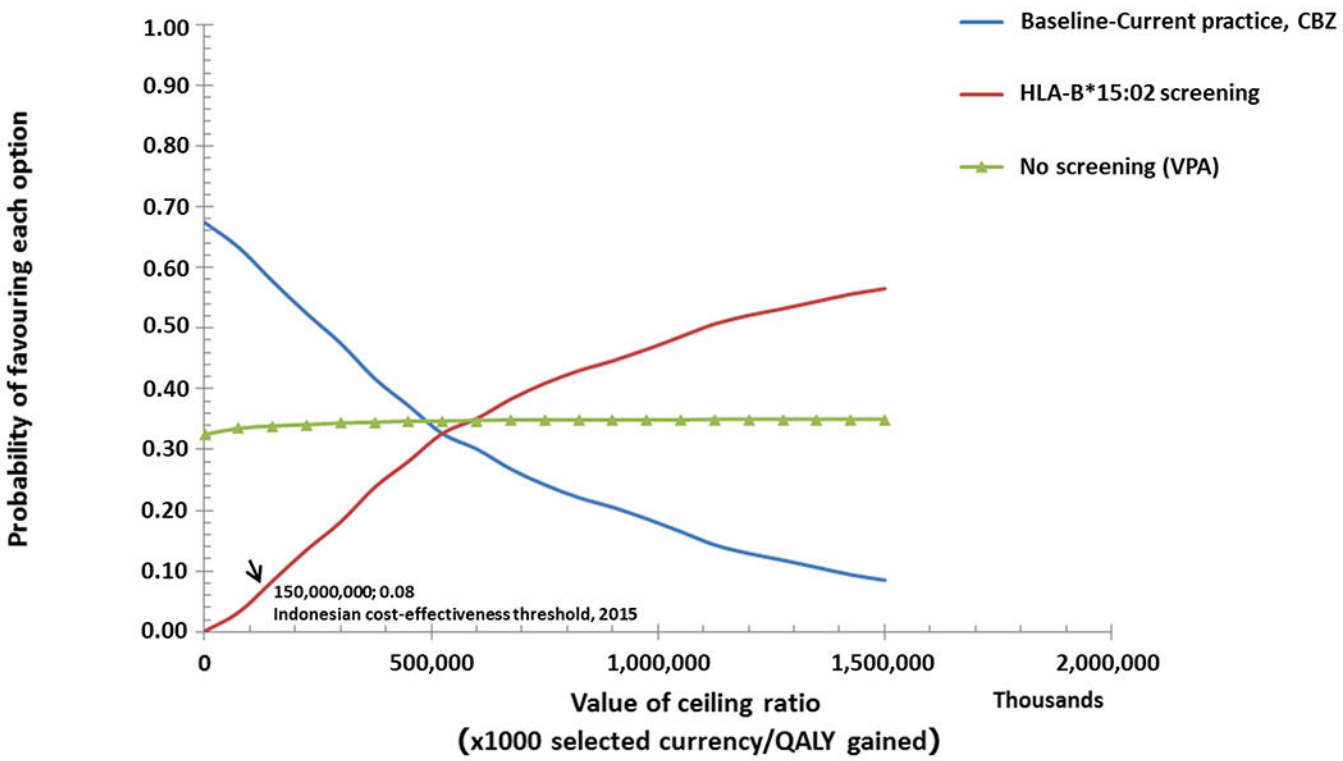

Fig 3.

Cost-effectiveness acceptability curves: the likelihood that each strategy will be acceptable to a decision maker, ultimately influencing their willingness to pay.

Table 1:

Input parameters used in the generic model analysis

Variable	Distribution	Mean	Reference
Required input variable			
pHLA (Prevalence of *HLA-B*15:02* allele (carrier status) in population)	Beta	0.208	[24]
pSTpos (Probability of CBZ-induced SJS/TEN in HLA-B*15:02-positive patients)	Beta	0.01139	[26, 30,31]
Cost parameters (2015 Indonesian Rupiah (IDR) values)			
cHLA-B (Cost of HLA-B*1502 screening test (includes all costs related to test))	Gamma	1,000,000	Input by user
DC_SJS (Annual direct medical cost of CBZ-induced SJS/TEN)	Gamma	5,026,302	Input by user
DC_SEQ (Annual direct medical cost of sequelae (base-case value assumes dry eye syndrome))	Gamma	4,425,000	Input by user
DC_Epi (Annual direct medical cost of epilepsy treatment with CBZ)	Gamma	1,064,909	Input by user
DC_Alt_Epi (Annual direct medical cost of epilepsy treatment with VPA)	Gamma	2,457,384	Input by user
Optional input variables			
uSEQ (Utility score of patients who experience SJS/TEN sequelae (assumes dry eye syndrome))	Beta	0.68	[27]
uEpi (Utility score of patients with epilepsy)	Beta	0.85	[27]
Epi_Trt_duration (Treatment duration of epilepsy)	Uniform	30	[27]
cDC (Discount Rate for costs)		0.3	[27]
cDO (Discount Rate for outcomes)		0.3	[27]

Table 2:

Cost-effectiveness of three strategies for patients with epilepsy treated by CBZ in Indonesia (base-case) *

Strategy	Cost (IDR)	Incremental cost (IDR)	QALYs	Incremental QALYs	ICER (IDR/QALY gained)
Current practice of no *HLA-B*15:02* screening and CBZ treatment	21,678,072	0	16.98	0	0
*HLA-B*15:02* screening, with positive and negative patients treated with VPA and CBZ, respectively	28,629,918	6,951,845	16.99	0.011	656,444,671
No *HLA-B*15:02* screening and VPA treatment	49,610,785	27,932,713	16.99	0.011	2,634,975,574

IDR, Indonesia Rupiah 2015 value; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

* Values are rounded to the nearest whole number.