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ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness and Value of Information Analyses of Caplacizumab for the Treatment of Thrombotic Thrombocytopenic Purpura in Brazil

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Abstract

Objectives The objective was to evaluate the cost effectiveness of caplacizumab for the treatment of patients with acquired immune thrombocytopenic thrombotic purpura (iTTP) compared to standard of care from the perspective of the Brazilian Unified Health System (SUS).

Methods A decision tree followed by a Markov model with a lifetime horizon was developed. Patients entered the model with an acute iTTP event. All patients were assumed to be admitted to hospital where they either respond to treatment or die. The model offered three health states: remission, relapse or death. Input data were obtained from literature searches with the data on efficacy of caplacizumab based on the HERCULES trial. The incremental cost-effectiveness ratio (ICER) was compared to the willingness-to-pay threshold for rare diseases of Brazilian reais (R$)120,000/quality-adjusted life years (QALYs). In addition to various sensitivity analyses, a value of information (VOI) analysis was conducted.

Results In the base case, caplacizumab resulted in 0.70 QALYs gained, and cost R$1,333,601 more, with an ICER of R$1,901,729/QALY. The cost of the caplacizumab vial was the most influential parameter. Probabilistic analysis showed that caplacizumab was not cost effective in any iterations for the threshold of the rare disease. The expected value of perfect information per year is R$0.

Conclusion Although caplacizumab results in incremental QALYs, based on the proposed cost, caplacizumab is not cost effective from the SUS perspective, and VOI results indicate that further research would not be worthwhile.

Key Points for Decision Makers

Caplacizumab improves health-related quality of life for patients with thrombotic thrombocytopenic purpura, but the high costs of caplacizumab might hinder its adoption.

The clinical benefit of caplacizumab is highly dependent on its effect on acute mortality, which is currently uncertain for the Brazilian setting.

Caplacizumab is not cost effective from the perspective of Brazilian Unified Healthcare System (SUS).

Further investment in research to decide if caplacizumab should be added to the SUS benefit list would not be worthwhile.

1 Introduction

Acquired immune thrombotic thrombocytopenic purpura (iTTP) is a rare autoimmune thrombotic microangiopathy characterized by hemolytic anemia and thrombocytopenia [1]. Patients with iTTP suffer ischemic organ manifestations, caused by a severe deficiency of ADAMTS13, a von Willebrand factor cleavage enzyme, which leads to the consumption of platelets in von Willebrand factor-platelet aggregates and culminates in microvascular thrombosis. In a systematic review of iTTP prevalence, the strongest estimate identified for the incidence of iTTP is 33 per million yearly, based in a retrospective study from Denmark [2]. Without treatment, iTTP leads to thromboembolic events and is fatal [3].

When early treatment is initiated, the lethality of iTTP can be considerably reduced [4]. Treatment of an acute

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presentation consists of therapeutic plasma exchange (TPE) with the aim of replacing functional ADAMTS13 and removing von Willebrand factor-platelet aggregates and autoantibodies. To suppress anti-ADAMTS13 autoantibodies, patients receive immunosuppressive therapy with glucocorticoids and rituximab [1].

Patients with iTTP have substantial clinical burden resulting in increased readmission rates and high hospital expenditures. In a retrospective claims database study in the USA, the median inpatient cost to the hospital throughout the index admission was US$33,221, with a median length of stay of 11.5 days [5]. Moreover, delayed treatment of thromboembolic events may lead to irreversible neurological deficits and long-term consequences such as depression and high blood pressure, increasing the burden of disease [3].

Caplacizumab is an innovative treatment. It is the first drug to act on the pathophysiology of iTTP [6]. In the HERCULES trial, a double-blind randomized clinical study with 145 patients, caplacizumab led to faster platelet count normalization compared to placebo; the platelet count normalization rate ratio was 1.55, favoring caplacizumab (95% confidence interval [CI] from 1.09 to 2.19; $p = 0.01$) [7]. Furthermore, the secondary composite endpoint of iTTP-related death, iTTP recurrence, or thromboembolic event during the treatment period was 74% lower with caplacizumab than with placebo (12% vs 49%, $p < 0.001$) [7]. Due to this growing evidence of the clinical benefit, the International Society of Thrombosis and Homeostasis conditionally recommends starting caplacizumab promptly upon acute presentation of iTTP [8].

In Brazil, caplacizumab entered the market in 2021 as a new treatment for iTTP [9]. In an expanded Brazilian access program, which included five patients with iTTP who were treated with caplacizumab, all five achieved clinical response and clinical remission, with a good safety profile [10]. However, the inclusion of caplacizumab in the benefit list for patients with iTTP within the Unified Healthcare system (SUS) has not been assessed by the National Commission for the Incorporation of Technologies (CONITEC).

Due to the high price of caplacizumab, the objective of this analysis was to assess the cost effectiveness of caplacizumab compared to the current standard of care from the SUS perspective. In addition, we aimed to conduct a value of information (VOI) analysis to investigate if investment in future research would be worthwhile from the SUS perspective.

2 Methods

The cost-effectiveness model used TreeAge Pro 2024 (TreeAge Software, Williamstown, MA) and was conducted according to the methodological guidelines of the Brazilian Ministry of Health and reported in accordance with international guidelines for health economic evaluations [11, 12]. A CHEERS VOI checklist was submitted for peer review [13]. Because iTTP requires follow-up and relapses can occur throughout the patient's lifetime, the base-case analysis adopted a lifetime horizon. To reflect the outpatient follow-up in the remission phase, model cycles were defined at three months.

The study population comprised adults aged ≥ 18 years, diagnosed with iTTP based on clinical presentation, that is, patients who presented thrombocytopenia, microangiopathic hemolytic anemia and symptoms of ischemia (the most common symptoms being neurological, renal, cardiac or mesenteric). In line with the HERCULES study, on which the analysis was based, it was considered that patients had a mean age of 46 years and 69% of patients were female [7].

The two strategies to be compared were based on iTTP treatment guidelines [8, 14, 15].

1. Timely initiated standard of care, i.e., TPE and corticosteroids, in less than 24 hours from suspected diagnosis. In addition, according to international therapeutic guidelines, rituximab should be started promptly upon symptom presentation [8, 14, 15]. However, due to limited availability in Brazil, rituximab was only considered for patients who presented an unfavorable clinical course (exacerbation or refractoriness to treatment) [10, 16].
2. Caplacizumab added to standard of care.

2.1 Model Structure

Patients entered a decision tree model at the time of the acute phase of iTTP. At the beginning of the model, all patients were assumed to be admitted to hospital. In the state 'acute iTTP', patients were treated according to one of the compared strategies. During the acute phase, patients may or may not have suffered an 'exacerbation', defined as a new drop in platelet count after an initial response (platelet count above 150 thousand $\times 10^9$ L) with the need to restart treatment with plasmapheresis in less than 30 days [15]. Patients who survived the acute phase of the disease entered a Markov model in the 'remission' state. Patients in remission may remain in this health state, relapse, or die. Patients who relapse may return to remission or die.

To reflect the long-term morbidity of iTTP in the 'remission' state, we considered patients might have depressive symptoms and/or neurocognitive symptoms. This choice was made because these are the most frequent and quality of life (QoL)–affecting long-term sequelae [3]. The structure of the model is shown in Figure 1.

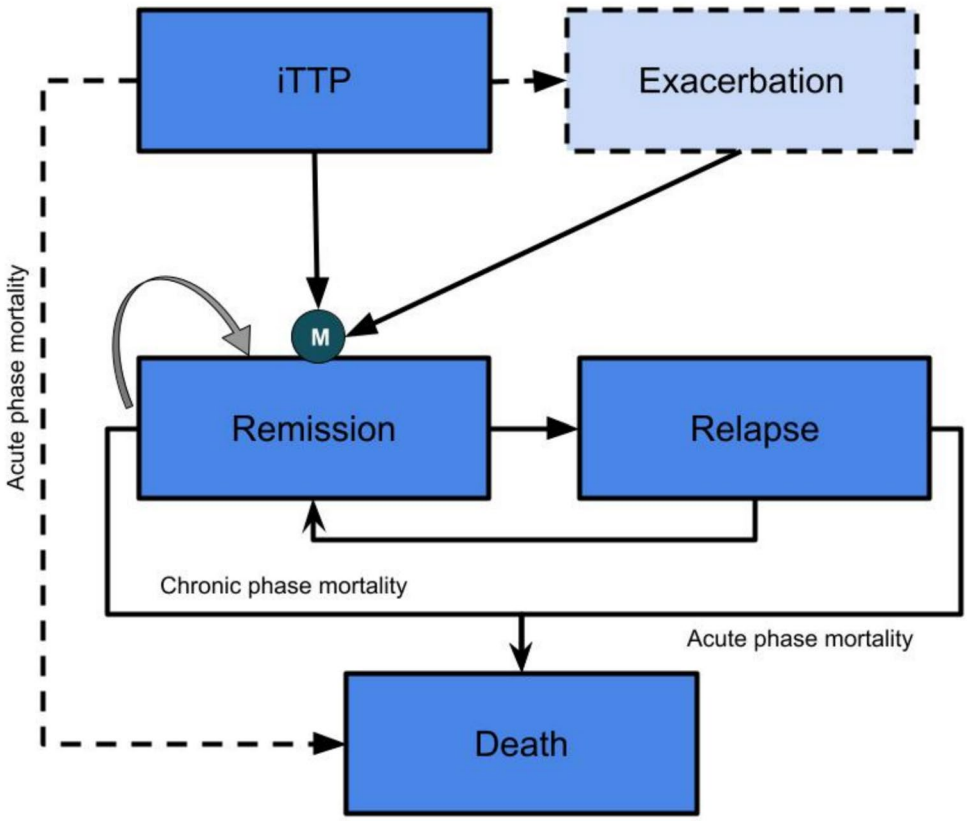

Fig. 1 Decision tree and Markov model structure.M stands for the Markov model start. *iTTP* immune thrombotic thrombocytopenic purpura

2.2 Input Parameters

We carried out several literature reviews to identify the appropriate parameters for the model. Studies to inform input parameters were selected based on the best available evidence (i.e., studies with lower risk of bias and those that were most applicable to the study population and modelling context, considering time to iTTP diagnosis, severity of disease, secular trend, and differential rituximab utilization). Probabilities and utilities applied to the model are shown in Table 1.

2.2.1 Probabilities

The probability of exacerbation was taken from the HERCULES trial [7]. Compared to the placebo group, patients in the caplacizumab group had a 67% lower incidence of exacerbation ($p < 0.001$) [7]. The probability of relapse was obtained from the long-term follow-up post-HERCULES study [17]. With regard to the probability of relapse, caplacizumab was assumed to have no expected effect on the underlying immunopathology of the disease. This is in line with two recent meta-analyses (including randomized trials and observational studies) [18, 19] and with the statistical nonsignificant (post hoc) difference in the post-HERCULES trial [17].

For acute mortality in the standard-of-care group, we applied mortality data derived from a meta-analysis of observational studies targeting iTTP patients only. Retrospective data reflecting mortality data for the Brazilian population (indirect evidence including other thrombotic microangiopathy patients) [16, 20], and mortality rates from randomized trials, which might not be reflective of the real world setting, were investigated in scenario analyses. We applied the mortality hazard from a meta-analysis from randomized controlled trials (RCTs) showing non-significant effect of caplacizumab [HR: 0.29 (95% CI: 0.05–1.73)] [19].

The survival curves of the model cohorts for both the base case and scenario analyses are presented in online resource, Figure A1.

Finally, the general mortality of the Brazilian population per each age group was taken from national databases (online resource, Table A1).

2.2.2 Health-Related Quality of Life

The utilities of the acute phase combined various sources using the multiplicative method, and an age-dependent population utility baseline was incorporated based on Brazilian EQ-5D data (online resource, Table A2). Due to the lack of specific utility data for iTTP in the acute phase, utilities for this state were obtained from a study that evaluated the loss

Table 1 Probabilities and utilities included in the model

Parameter	Input value	Source
Probabilities	*Probability per cycle (SD)*	
Exacerbation		
Caplacizumab	0.042 (0.020)	HERCULES [7]
Standard of care	0.384 (0.050)	HERCULES [7]
Relapse		
Caplacizumab	0.028 (0.020)	Post-HERCULES [17]
Standard of care	0.102 (0.050)	Post-HERCULES [17]
Acute-phase mortality		
Standard of care	0.062 (0.104)	Neupane et al. [19]
Risk ratio	*Mean (SD)*	
Acute mortality hazard with caplacizumab	0.29 (0.56)	Neupane et al. [19]
Utilities	*Utility value (SD)*	
Age-dependent population utility at baseline	0.80	Santos et al. [25]
Hospitalization multiplier	0.64 (0.060)	Pappas et al. [21]
Remission multiplier applied in the model	0.93 (0.031	Burns et al. [22]
Depression multiplier	0.80 (0.004)	Ascef et al. [24]
Neurocognitive symptom multiplier	0.73 (0.004)	Ascef et al. [24]

CI confidence interval, *SD* standard deviation

of QoL during an episode of hospitalization due to ischemic or hemorrhagic stroke [21]. The study reported utilities collected at different points of hospitalization to capture the gradual improvement during hospitalization [21], which is usual for an acute episode of iTTP.

The utility of the 'remission' state was obtained from the study by Burns et al. [22] and was collected from 72 patients with iTTP from the Oklahoma registry. In that study, a SF-36 questionnaire was mapped to EuroQol 5 Dimension (EQ-5D) utility values using a linear regression model [22]. For the 'remission' health state, 49% of patients were assumed to have long-term neurocognitive symptoms and 14% had depression [23]. The disutilities for patients with depression and neurocognitive symptoms were obtained from a Brazilian study with 8374 patients, which used the EQ-5D method to elicit utilities of patients treated in the primary care [24]. It was assumed that disutility due to neurocognitive symptoms is comparable to that of patients who suffered a cerebrovascular event and have minimal sequelae.

2.2.3 Costs and Resources Used

The resources used in the acute phase of treatment reflect diagnostic laboratory and imaging tests, red blood cell transfusion, the passage of a central venous catheter, plasmapheresis with fresh frozen plasma (FFP), medication costs (i.e., caplacizumab, methylprednisolone, prednisone and rituximab) and daily ward and intensive care unit (ICU) costs.

The resource consumption related to length of in-hospital stay, the length of stay in the ICU and the number of TPE in each group described in Table 2.

A micro-costing study was conducted with access to real-world data from the SUS Hospital Information System (SUS-HIS). The SUS-HIS contains data from hospitals from all Brazilian regions and is updated every 6 months. We used the R package micro datasus to fetch and process raw data from DATASUS from June 2023 to June 2024. In order to identify the cost per day of in-hospital stay and the ICU-related costs, we filtered all in-hospital admissions associated with the ICD code M31.1 (referring to thrombotic microangiopathy). The complete R code can be found in the online resource Table A3.

According to that data set, there were 366 adult patients admitted with iTTP. The mean costs per in-patient stay and ICU stay are presented in Table 2. The procedure code 0303060247 (treatment of other vaculopathies) was associated with the in-hospital stay 293 times (80% of all in-hospital stays). The second most frequent procedure code associated was 0303040149 (treatment of acute stroke—ischemic or hemorrhagic), which was associated with 4.3% of all in-hospital stays.

To calculate the costs associated with TPE, a micro-costing study was conducted considering the SIGTAP codes—reported in detail in online resource, Table A4.

All costs refer to 2024 Brazilian reais (R$). Unitary costs for outpatient procedures were taken from the SUS table of procedures and medications. To estimate total public spending, costs of laboratory and imaging tests were multiplied by 2.8 (as empirical data demonstrated that the table of procedures covers about one-third of total spending, with the rest being the responsibility of the state and of municipalities)

Table 2 Resources used and costs with hospitalization and plasmapheresis

Parameter		Source
Resource use data	*Average (median) in days*	
Length of hospital stay		
Caplacizumab	9.9 (9.0)	HERCULES [7]
Usual treatment	14.4 (12)	HERCULES [7]
ICU length of stay		
Caplacizumab	3.4 (3.0)	HERCULES [7]
Usual treatment	9.7 (5.0)	HERCULES [7]
Plasmapheresis time		
Caplacizumab	5.8 (5.0)	HERCULES [7]
Usual treatment	9.4 (7.0)	HERCULES [7]
Cost data	*Mean (SD)*	
Hospitalization costs		
Emergency admission, average length of stay	R$124.11 (1.5 days)	HIS [26] via *micro datasus*
Adult ICU stay (per day)	R$3862.85 (1648)	HIS [26] via *micro datasus*
Hospital stay (clinical ward) average cost (per day)	R$166.14 (323)	HIS [26] via *micro datasus*
TPE costs		
Cost of 1 bag of fresh frozen plasma (200 mL)	R$157.28	Micro-costing based on SIGTAP procedure codes[a]
Cost TPE (per day)	R$2201.92	Micro-costing based on SIGTAP procedure codes[a]

HIS Hospital Information System, *ICU* intensive care unit, *R$* Brazilian reais, *SD* standard deviation, *TPE* therapeutic plasma exchange

[a]The micro-costing is reported in online resource Table A4

[27]. The costs of diagnostic assessments and initial patient management are detailed in online resource, Table A5.

The costs of medication were taken from reference price list, referring to legally established maximum sales price to the government (PMVG for the acronym in Portuguese, 0%) [28]. The cost per caplacizumab vial applied to the analysis R$22,487.55, the cost per day of prednisone treatment was R$5.51 and the cost of 3-day treatment with methylprednisolone was R$485.16 (online resource, table A6). To quantify the use of resources, the following treatment protocols based on international guidelines [14, 15] and expert opinion in the acute phase were considered:

- *Caplacizumab* The first dose of caplacizumab (10 mg) must be administered intravenously (IV) before the first TPE. After each TPE, caplacizumab 10 mg/day should be administered subcutaneously (SC) for the duration of TPE. After the end of TPE, caplacizumab (10 mg) should be administered SC for another 30 days and at the end of this period, if there are still signs of active underlying disease, it should be continued until the patient has sustained normalization of ADAMTS13 activity.
- *Therapeutic plasma exchange* TPE should preferably be performed with FFP and ideally, should be started within 4 h of clinical diagnosis, but no later than 24 h and maintained for two days after platelet normalization (defined as platelets above $150{,}000 \times 10^9$ L). The recommended dose is 40 mL/kg, and an FFP bag contains 200 mL. Micro-costing of TPE is detailed on online resource, Table A5.
- *Corticosteroids* Patients received IV methylprednisolone 1000 mg/day on Day 1 for 3 days, followed by orally administered prednisone 1 mg/kg/day. Patients continued to receive prednisone 1 mg/kg for 14 days after stopping TPE, followed by progressive weaning over the next 4 weeks until complete suspension. An average weight of 70 kg was assumed.
- *Rituximab* Rituximab was used for patients who did not achieve platelet normalization after 4 days of TPE, and those who presented an exacerbation, at the dosage of 375 mg/m^2/week, for 4 weeks. A mean weight of 70 kg was assumed, and we assumed there would be no vial sharing.

In case of relapse, costs are the same as for acute phase treatment. The costs of the remission phase include costs for follow-up with a specialist and laboratory tests (online resource, Table A7). For the first two years after the acute phase, the frequency of outpatient visits was four times a year for two years, and annually thereafter.

2.3 Analyses

We calculated the incremental cost-effectiveness ratio (ICER), expressed as the cost per quality-adjusted life year (QALY) gained, as recommended in the methodological

guidelines of the Brazilian Ministry of Health [11]. To assess the value of the intervention from the SUS perspective, the cost per QALY was compared with the willingness-to-pay threshold of R$120,000 [29]. According to the recommendations of the Brazilian Ministry of Health, the applicable threshold for rare diseases is 3 times that of standard willingness-to-pay threshold (R$40,000) [29]. Health costs and outcomes were discounted at a rate of 5% per year, as recommended by the methodological guidelines from Brazilian Ministry of Health [11].

2.3.1 Sensitivity Analysis and Scenario Analyses

Deterministic sensitivity analyses were conducted by varying each of the parameters included within their CIs and assessing the impact of each parameter on the ICER. Larger ranges were established for the cost of caplacizumab in the deterministic sensitivity analysis to assess the impact on ICER of potential caplacizumab price reductions.

Probabilistic sensitivity analyses with 10,000 iterations were conducted to evaluate the robustness of the results, in which all parameters were varied simultaneously within a pre-established distribution. The beta distribution was applied to probabilities and utilities, gamma distribution was applied to costs and resource use [30]. The lognormal distribution for hazard ratio of mortality was adjusted based on the equations from Barendregt et al. [31]. The parameter ranges, standard deviations, and distributions are presented in online resource, Table A8.

Because of the uncertainty in data on acute mortality in the standard-of-care group, we tested two scenario analyses: (i) applying higher mortality rates taken from Brazilian retrospective cohorts (indirect evidence including other thrombotic microangiopathy patients) [16, 20] and (ii) applying lower mortality rates from two randomized trials [19]. In addition, we tested a scenario assuming no mortality difference.

2.3.2 Value of Information (VOI) Analysis

A VOI analysis was conducted to estimate the value of conducting additional research to increase certainty about the input parameters and therefore reduce the uncertainty of the analysis [32]. The expected value of perfect information (EVPI) assesses if the cost of conducting new research is a reasonable application of SUS financial resources [32]. These values represent the cost of making the decision based on current (uncertain) evidence and set the maximum amount that should be applied into additional research to reduce uncertainty of the analysis. If a high EVPI is identified, the expected value of perfect partial information (EVPPI) can be calculated to quantify how much each individual input parameter contributes to decision uncertainty [32].

The EVPI and the EVPPI were calculated based on the results of 10,000 iterations from the PSA using the Sheffield Accelerated Value of Information (SAVI) tool [33]. In detail, the EVPI was calculated by averaging the maximum net monetary benefit (NMB) over the joint distribution of all the parameters in the model. The EVPPI was then calculated by fitting a regression based on the Generalized Additive Model (GAM) between the incremental net benefit and the parameters of interest. Accuracy checks were performed by calculating the standard deviation. The EVPI was calculated for all the 22 parameters that entered the PSA analysis and for the following sets of parameters: (i) number of TPE days with caplacizumab and with standard of care, (ii) number of ICU days with caplacizumab and with standard of care, (iii) length of hospital stay with caplacizumab and with standard of care. These sets of parameters were chosen because, although they were uncorrelated in the model, a correlation might exist. Based on Briggs et al. (2006), all resource use parameters were parametrized to a gamma distribution using mean values and standard deviations. The expected value of sample information (EVSI) was not calculated.

To calculate the number of patients affected by the decision, we considered the incidence of iTTP is 2.7×10^5 yearly, based on a systematic review of iTTP epidemiology [2, 34]. In this review, an incidence of 3.3×10^5 was identified when considering cases with suspected iTTP diagnosis and a platelet count $< 100{,}000 \times 10^9$ L, and an incidence of 2.7×10^5 when considering only cases presenting with $< 50{,}000 \times 10^9$ L, and the latter was chosen for being more specific [2, 34]. By applying this incidence rate to the total Brazilian population, 5335 patients with iTTP were estimated per year. We considered the time horizon for the decision relevance of 10 years.

2.3.3 Model Validation

To build the model, some assumptions were adopted due to unavailability of data or for simplification purposes when an impact on the results was not expected. The main assumptions adopted, and their justifications, are shown in the online resource, Table A8. To validate the model and its assumptions, clinical experts were consulted (*face validity*) and comparisons were made with other similar models (*cross validity*).

3 Results

The base-case results are shown in Table 3. In the base case, the cost of treatment with caplacizumab was R$1,803,267 and usual treatment was R$469,667, resulting in an

Table 3 Base-case results

Strategy	Cost (R$)	Incremental cost (R$)	Effectiveness (QALY)	Incremental effectiveness (QALY)	ICER (R$ per QALY)
Standard of care	469,667		8.99		
Caplacizumab	1,803,267	1,333,601	9.69	0.70	1,901,729

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life years, *R$* Brazilian reais

additional cost of R$1,333,601. Treatment with caplacizumab was more effective, resulting in 0.70 additional QALYs. The ICER was R$1,901,729 per QALY gained.

3.1 Sensitivity Analyses

The most impactful parameter in the ICER was the mortality hazard of caplacizumab. Assuming the lower bound of the mortality hazard (i.e., caplacizumab leading to a robust mortality reduction), caplacizumab would still lead to higher costs (R$1,349,432) but result in 0.91 QALYs gained (R$1,475,364 per QALY). Assuming the upper bound of the CI, caplacizumab would be more costly and lead to loss of QALYs (Fig. 2 and online resource, Fig. A2). Assuming no mortality difference, caplacizumab would lead to incremental costs (R$1,269,131), and 0.01 incremental QALYs, and an ICER of over R$90 million per QALY (online resource, Table A10).

Assessing potential price reductions for caplacizumab, a price reduction of 80% would be needed to reach the Brazilian willingness-to-pay threshold established for rare diseases (R$120,000).

The probabilistic sensitivity analysis demonstrated that 95% of the iterations fell in the upper right quadrant, that is, caplacizumab is more effective, but leads to additional cost from the SUS perspective (online resource, Fig. A3). For a cost-effectiveness threshold of R$120,000 per QALY, there is 0% probability of caplacizumab being cost effective.

In scenario analyses, varying the source of acute mortality in the standard of care group, we obtained different results. Considering data from Brazilian cohorts, caplacizumab would cost R$1,318,056 and lead to a QALY gain of 1.69, with an ICER of R$781,615 per QALY. In contrast,

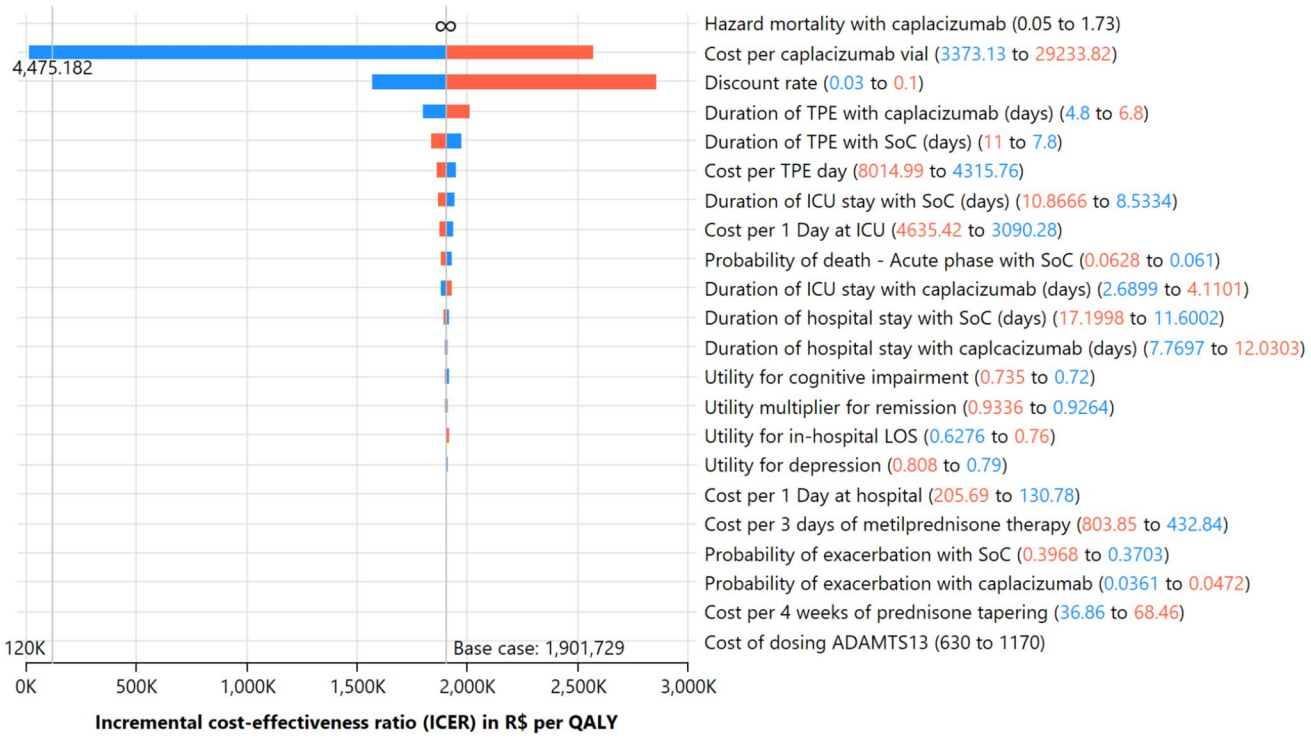

Fig. 2 Results of deterministic sensitivity analysis in the incremental cost-effectiveness plan Infinity symbol represents that the range exceeds the figure limits. *ICU* intensive care unit, *LOS* length of stay, *QALYs* quality-adjusted life years, *R$* Brazilian reais, *SoC* standard of care, *TPE* therapeutic plasma exchange, *WTP* willingness-to-pay

lower mortality rates in the standard of care group, as those reported in RCTs lead to smaller QALY gains (0.48 QALY) and an extreme ICER value (R$2,741,298 per QALY). Results from scenario analyses are presented in online resource, Table A10.

3.2 VOI Results

The overall EVPI per year is R$0 for Brazil, assuming 5335 patients annually and a willingness-to-pay threshold of R$120,000 per QALY. The overall EVPI depends on the willingness-to-pay threshold. As shown in Fig. 3, accepting higher threshold values would lead to a higher overall EVPI value.

3.3 Validation

Cross validation corroborates that the structure of our model and model outputs are comparable to previously published economic evaluations [35–37]. Additional model validation efforts are reported according to the AdViSHE (A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users) tool, provided in the online resource, Table A11.

4 Discussion

For Brazilian patients with iTTP, caplacizumab resulted in additional health benefits (0.70 QALY gained) compared to standard of care. However, the health benefits did not offset the high acquisition cost of caplacizumab, resulting in an unfavorable ICER (R$1,901,729 per QALY gained), which

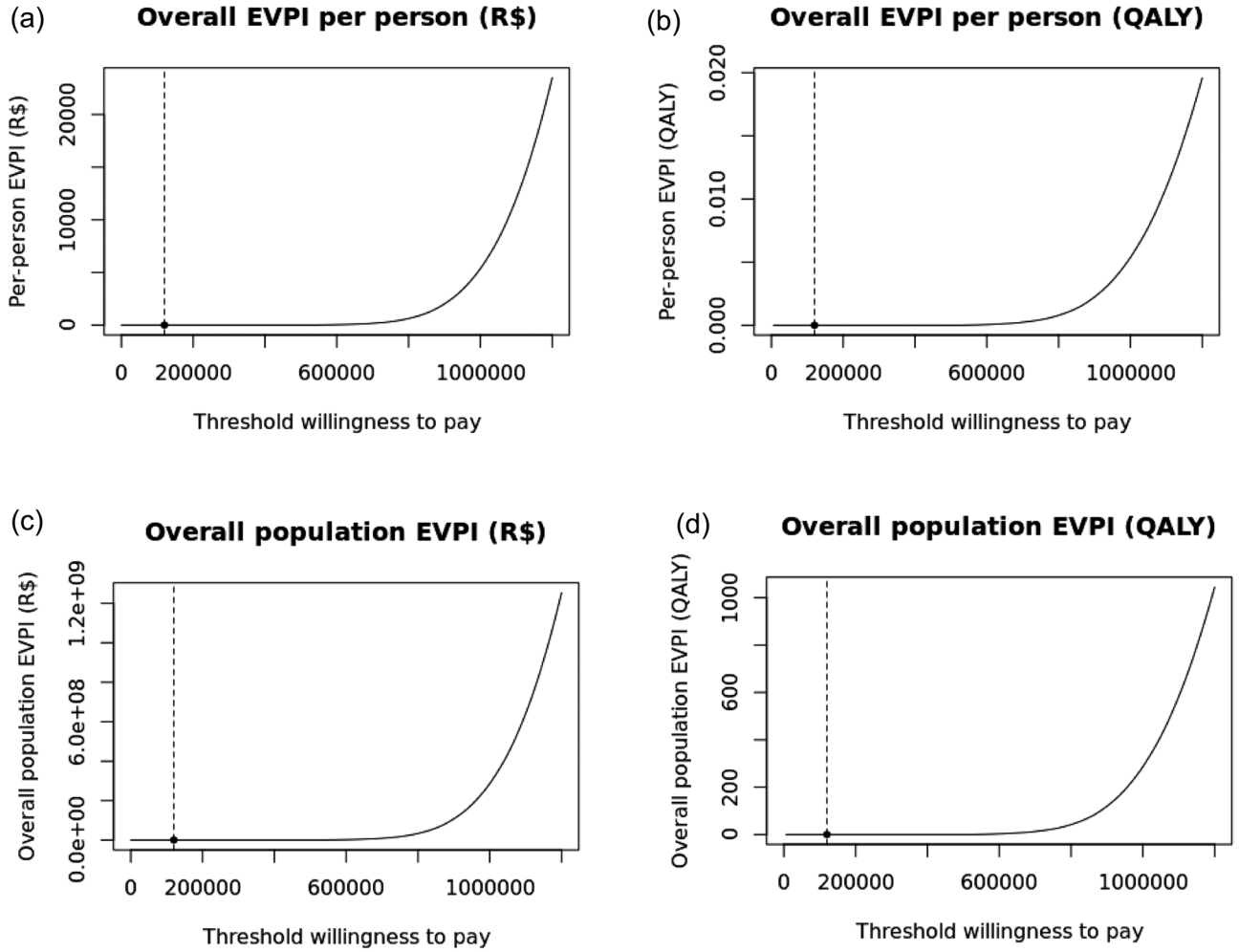

Fig. 3 Per-person and population EVPI for Brazil for varying WTP values; **a** overall EVPI per person (R$); **b** overall EVPI per person (QALY); **c** overall population EVPI (R$); **d** overall population EVPI (QALY). Threshold WTP in R$ per QALY. *EVPI* expected value of perfect information, *QALY* quality-adjusted life year, *R$* Brazilian reais, *WTP* willingness to pay

is approximately 16 times the willingness-to-pay threshold in force in Brazil. In sensitivity analysis, we showed that a price reduction of 80% would be needed in order to reach the maximum willingness-to-pay established in Brazil for rare diseases.

The probabilistic analysis showed that there is no probability of caplacizumab being cost effective for the threshold for rare diseases in Brazil. We further explored uncertainty using VOI analysis. The EVPI quantifies the return from investment in research, that is, the health gains (valued in monetary terms) and cost savings expected of enabling a reassessment of the cost-effectiveness decision of caplacizumab versus standard of care in light of less uncertainty. In other words, null EVPI means that research or data collection efforts would be considered inefficient application of financial resources, because it would have no return in terms of resolving uncertainty of the cost-effective analysis. As a result, a recommendation for caplacizumab is not dependent on efforts for purchasing additional data.

Even though the value of further research is limited, it is important to highlight that real world data from DATASUS seems to be unrepresentative for iTTP. We attempted to fetch data for the ICD for iTTP (M31.1) using the R package *micro datasus*, and we found only 357 inpatient stays associated with this diagnosis from June 2023 to June 2024, while the expected number of patients per year based on disease incidence in Brazil is ~ 5000 patients. We hypothesize that (because the initial symptoms are unspecific) most patients are misdiagnosed or miscoded at admission. It is plausible that these patients admitted under the ICD M31.1 in fact have presented a relapse, thus the probability of an iTTP diagnosis would rise considerably, and physicians would be more prone to use this ICD code upon admission. In contrast, fetching in-hospital admissions under more generic ICD codes (such as D55.9—hemolytic anemia) may result in an overestimated number of patients.

The results of the deterministic sensitivity analysis revealed the acute mortality reduction and the cost of caplacizumab as the most sensitive parameters. Assuming no mortality difference between caplacizumab and standard of care group, the QALY gains would be negligible, leading to an unreasonable ICER. Although there is parameter uncertainty related to the effect of caplacizumab in acute mortality, it was not captured in the VOI analysis as driver to decision uncertainty. The explanation for this phenomenon is that VOI analysis explores decision uncertainty by varying all model parameters simultaneously based on the standard deviation [32]. In our model, even for the iterations in which caplacizumab lead to acute mortality reduction (and QALYs gained), the incremental NMB is negative due to the high incremental costs of caplacizumab. In other words, even assuming there is mortality reduction, for the willingness-to-pay threshold set for the VOI analysis (R$120,000 per QALY), caplacizumab is not cost effective. Thus, VOI analysis allows an in-depth exploration of decision uncertainty in cost-effectiveness analyses.

A VOI analysis is conditional to the establishment of a willingness-to-pay threshold. In Brazil, recommendations for the use of willingness-to-pay thresholds have been in force since 2022. The standard threshold was established at R$40,000 per QALY, and for rare diseases R$120,000 per QALY [29]. Because iTTP is a serious and potentially fatal disease with a prevalence less than 1/50,000 inhabitants [38], it is also classified as an ultra-rare disease with no willingness-to-pay threshold established as yet [29]. For the purposes of VOI analysis, we applied the threshold for rare diseases and presented the EVPI variation for alternative willingness-to-pay threshold values. Although VOI analysis is briefly mentioned in the Brazilian methodological guidelines for health economic evaluations, this methodology is not yet applied in submissions to CONITEC [39]. To the best of our knowledge, this is the first time VOI has been executed in a health economic assessment from the SUS perspective and sets out an example of application in the context of rare diseases.

The structure of our model is comparable to previously published economic evaluations [35–37]. In the cost-effectiveness study made by the National Institute for Health and Care Excellence (NICE), it was assumed (based on expert opinion) that patients who received caplacizumab would have an improvement in QoL due to a lower long-term incidence of cognitive symptoms and depression [36]. However, data on the long-term follow-up of the HERCULES study demonstrated that there was no clinically relevant difference in cognitive symptoms between patients treated with or without caplacizumab [17]. An Italian study with 39 patients followed for 8 years published after the appraisal from NICE demonstrated that the caplacizumab group did not have a lower incidence of long-term neurological symptoms [40]. Therefore, in our model the long-term effects of caplacizumab were dismissed.

Although the average yearly cost of treatment would be GBP270,000, NICE issued a positive recommendation to add caplacizumab into the National Health Service (NHS) benefit list [36]. In contrast, Canada's Drug Agency issued a negative appraisal, justified by the lack of cost effectiveness of caplacizumab [35]. In addition, the Australian PBAC also issued a negative appraisal [41].

For our study, some limitations have to be acknowledged. First, adverse events associated with caplacizumab were not explicitly accounted for. The most common adverse events reported are gingival bleeding and epistaxis, which usually do not require additional treatment [7]. Because a recent meta-analysis showed a non-significant increase in major bleeding (relative risk [RR]:

2.08, 95% CI; 0.56–7.51, 4 studies, 215 patients) in the caplacizumab group compared to standard of care [19], for both groups we assumed the costs to be covered by the inpatient costs and the disutilities due to longer length of stay due to treatment-emergent complications.

Second, in line with previous cost-effectiveness analyses the utility values for the acute phase were taken from the literature considering proxy diseases that have similar clinical courses. In the case of data on utility for iTTP, which is a common shortcoming in most cost-effectiveness analyses in this field [42], the value was taken from a conference abstract. To underpin the input data on utility for the model, all assumptions made were validated by clinical experts.

Third, one important limitation of this analysis is the difficulty of picturing the actual care being practiced for iTTP in Brazil, which might be associated with higher mortality rates than the scenarios in which caplacizumab has been studied. Previous studies reflecting the Brazilian context indicated that diagnostic delays are a major factor leading to high mortality rates in patients with thrombotic microangiopathy [16, 20]. Although the present VOI analysis was designed to capture the value of additional investment in research related to a narrow decision problem (i.e., is caplacizumab cost effective?), is it important to highlight that literature indicates that further investment toward improving time to diagnosis and prompt treatment initiation is key to improving patient outcomes in iTTP.

In the absence of reliable Brazilian data, the acute-phase mortality applied to the model corresponds to aggregated data from several observational cohorts from other countries [19]. The effect of higher acute mortality in the standard-of-care group was explored in sensitivity analyses that result in a more favorable cost-effectiveness ratio. However, effectiveness of caplacizumab was not studied in the context of delayed diagnosis, and the application of these higher mortality rates to the standard-of-care group to our model—combined with mortality hazard from RCTs—might lead to an overestimation of the effect of caplacizumab.

In fact, the incremental effectiveness of caplacizumab depends heavily on its association with reduced acute mortality, which was not yet confirmed in recent meta-analyses of RCTs [8, 19]. In another study with aggregate data from observational studies, acute mortality in the caplacizumab group was half that observed for standard of care, corresponding to a relative risk reduction of 59% and a number-needed-to-treat of 35 [43].

5 Conclusion

Caplacizumab leads to gains in QALYs, but its high cost does not offset the health gains from a SUS perspective, resulting in an unfavorable ICER. Based on the proposed cost, caplacizumab is not cost effective from a SUS perspective. The VOI results indicate that further research would not be worthwhile.

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Declarations

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Ethics approval This research was conducted based on publicly available data and therefore no ethical approval is required.

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Data availability Data used in the development of this model is publicly available. The model file in Trex format can be made available upon inquiry to the corresponding author.

Code availability The Trex model used in this study was provided to the journal's peer reviewers for their reference when reviewing the manuscript.

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