ECONOMIC IMPACT OF THE PREDICT-ITP TOOL FOR THE DIAGNOSIS AND TREATMENT OF IMMUNE THROMBOCYTOPENIA

ECONOMIC IMPACT OF THE PREDICT-ITP TOOL FOR THE DIAGNOSIS AND TREATMENT OF IMMUNE THROMBOCYTOPENIA

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Lay Abstract

Platelets help to stop bleeding. Immune thrombocytopenia (ITP) is a disease characterized by decreased platelet counts in the blood. This condition may cause symptoms such as recurring gums and nosebleeds, effortless bruising, and potential life-threatening bleeding. There is no specific test to identify ITP, and its diagnosis is based on excluding other causes of low platelet counts. As a result, an incorrect diagnosis is common in the clinic, resulting in unnecessary testing, wrong treatment, decreased quality of life, and increased costs.

To identify the probability of a patient having ITP at the initial hematology consultation, McMaster researchers developed a clinical prediction model. The objectives of this study protocol were to determine the cost savings of the prediction model compared to the standard of care. I have designed an economic analysis that will accompany a randomized trial, comparing the use of the prediction model vs. no model (the current standard of care). The primary outcome of the economic analysis will be to demonstrate the clinical prediction model's cost-effectiveness. Secondary outcomes are the difference in costs between the prediction model and current ITP care, resource utilization, and life quality.

Abstract

Immune thrombocytopenia (ITP) is an autoimmune disease characterized by reduced production and augmented destruction of platelets. Adults with ITP have platelet blood counts less than $100x10^9$/L. Ranging from mild to severe, bleeding symptoms may include epistaxis, gingival, petechiae, mucosal, gastrointestinal, vaginal, or intracranial bleeding. ITP can be primary or secondary to other medical conditions. Three phases categorize primary ITP based on the onset and persistence of symptoms: newly diagnosed, persistent, or chronic (1-4).

An ITP diagnosis includes a complete blood count, blood film, and viral and autoimmune testing. Depending on patients' comorbidities, the type and number of examinations may vary (3). Diagnosis may also depend on the platelet count response to medications or treatment of secondary causes. There is the need to streamline ITP diagnosis. The time-consuming and high-cost approaches to ruling out other thrombocytopenic conditions, have led Michael G. DeGroote Centre for Transfusion Research (MCTR) researchers to optimize ITP care by developing the Predict-ITP Tool to identify patients with ITP during the initial hematology consultation. The clinical prediction model incorporates data such as platelet count variability, maximum mean platelet volume (MPV), lowest platelet count value, and a history of severe bleeding at any time (5).

Improving diagnostic accuracy may improve the quality of life and help reduce expensive, unnecessary, and potentially harmful treatments. Overall, this project

aims to determine the cost savings of the Predict-ITP tool when implemented in practice, compared to current ITP diagnostic practices. To achieve this goal, in this thesis, we will first estimate the current cost of ITP care and design a health economic evaluation to accompany a randomized controlled trial (RCT) comparing the quality of life and economic impact of the Predict-ITP tool versus current ITP care

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List of abbreviations

ACA	Anti-Cardiolipin Antibodies
ANA	Antinuclear Antibody
CAD	Canadian Dollar
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CIHI	Canadian Institute for Health Information
CPM	Clinical Prediction Model
CRT	Cluster Randomized Trial
CUA	Cost-Utility Analysis
DAT	Direct Antiglobulin Test
ED	Emergency Department
HIREB	Hamilton Integrated Research Ethics Board
HRQoL	Health-Related Quality of Life
ICUR	Incremental Cost-Utility Ratio
ITP	Immune Thrombocytopenia
IVIG	Intravenous Immunoglobulin
MPV	Mean Platelet Volume
NSI	Nonspecific Inhibitor
PRO	Patient-Reported Outcome
QALY	Quality-Adjusted Life Year
RCT	Randomized Controlled Trial
TPO-RA	Thrombopoietin Receptor Agonist
TSH	Thyroid-Stimulating Hormone or thyrotropin

CHAPTER I: Project introduction

Platelets, or thrombocytes, assist in wound healing and prevent bleeding. In adults, blood platelet counts of <150,000/μL or <150 x 10^9/L define thrombocytopenia. Treatment depends on the etiology and disease severity. Thrombocytopenia-triggering mechanisms involve reduced platelet production, increased platelet sequestration, and increased platelet destruction or consumption. Varied clinical conditions may cause thrombocytopenia, including bone marrow disorders like aplastic anemia, leukemia, and myelodysplastic syndromes. Chemotherapy and liver-spleen-related conditions, like chronic liver diseases and hypersplenism, may also result in thrombocytopenia. Blood clotting disorders, including disseminated intravascular coagulation (DIC), can produce low blood platelet counts. In addition, immune mechanisms, including drug-induced thrombocytopenia, thrombotic thrombocytopenia, and immune thrombocytopenia, can also manifest thrombocytopenia. Other causes of thrombocytopenia include systemic disorders, nutritional deficiencies, inherited diseases, and infections (5-9).

IMMUNE THROMBOCYTOPENIA AND PROJECT OUTLINE

Hippocrates and Galen defined purpura as a reddish-purple skin lesion originated by bleeding in the dermis or subcutaneous tissues. Purpura comes from the Ancient Greek word porphyra, meaning purple in Latin. Historically, there have been scholars who have made efforts to define this condition. In 1025, Avicena

described the illness as immunological thrombocytopenia (ITP) (6). In the 16th century, Amatus Lusitanus of Portugal thought purpura to be a clinical illness that might recover on its own. The progress made in microscopy through the 19th century, helped identify the platelet as a leading agent for the thrombocytopenic component of ITP. Advances made during the 20th and 21st centuries led to comprehend the pathophysiology and autoimmune components of this condition (7).

ITP can occur due to malignancies, infections, medications, and in the context of systemic autoimmune diseases. Based on the onset and persistence of symptoms, ITP is classified as newly diagnosed (0–3 months after diagnosis), persistent (more than 3–12 months after diagnosis), or chronic (more than 12 months after diagnosis) (3,8). Acute ITP is more common among children, and a viral infection may precede its presentation. Infants may not need treatment; up to 85% of cases recover without medical intervention within three months. Chronic ITP might affect adults and is more common in females than males (3:1 ratio). This epidemiology might be due to the increased prevalence of autoimmune diseases in women (8,9).

ITP is an autoimmune disease that causes impaired production and/or destruction of platelets. ITP affects around 3.3 per 100,000 adults per year, with a prevalence of 1 per 8,000 per year, and it is characterized by platelet counts $<100x10^9$/L in adults (4,10). This condition also has a gradual onset and may include bruises, conjunctival hemorrhage, oral hemorrhage, epistaxis, gastrointestinal and

abnormal gynecological bleeding, and hematuria (9). In adults with ITP, major bleeding and intracerebral hemorrhage affect approximately 9.6% (4.1–17.1%, with 95% confidence interval [CI]) and 1.4% (0.9–2.1%, 95% CI) of cases, respectively (11). Furthermore, ITP may negatively impact patients' quality of life by producing fatigue, anxiety, and depression, interfering with their daily activities (12).

ITP diagnosis

Establishing a certain ITP diagnosis has been challenging for clinicians, leading to diagnostic errors and delays in the process. The time to diagnosis differs widely depending on the approach studied. In the Immune thrombocytopenia (ITP) World Impact Survey (iWISH), patients reported a median time of 0.5 months (IQR 0.1-1.0 month) between the initial health care provider visit and ITP diagnosis. In addition, 12% of patients needed more than 6 months to get an ITP diagnosis. Physicians attributed the time to diagnose ITP to several factors, including ruling out other causes of thrombocytopenia (68%), time waiting for a specialist consultation (58%), diagnostic examination (55%), and misdiagnoses of other conditions (53%). In contrast, when validating a clinical prediction model, Li et al. estimated a median time of 3.1 years (IQR 0.8–5.0 years) for patients to achieve a correct ITP diagnosis. A period of 0.8 years (IQR 0–2.5 years) was the average time for establishing a non-definite ITP diagnosis (5,13).

Specific ITP tests are currently lacking in clinical practice. ITP is a platelet blood count of less than $100x10^9$/L, with other causes of thrombocytopenia excluded. Additional criteria can help identify ITP among patients with thrombocytopenia from other causes. The first criterion is a platelet count nadir of less than $20x10^9$/L. The second is a platelet count response of $30x10^9$/L or greater, after corticosteroids treatment, intravenous immunoglobulin (IVIG), or the treatment of an underlying condition for patients with secondary ITP (14).

Investigations often used to exclude other causes of thrombocytopenia in patients suspected of ITP include a serial complete blood count, bone marrow examination, viral panel (particularly hepatitis C virus (HCV) and human immunodeficiency virus (HIV)), and autoimmune testing. Imaging and additional laboratory parameters may be useful in some circumstances. For instance, other tests available to rule out secondary causes of ITP may include abdominal ultrasound, hepatitis B virus, and Helicobacter pylori (15). Other not widely used investigations involve antiplatelet antibody testing, P-selectin expression, and immature platelet fraction, which may help distinguish the underlying causes of thrombocytopenia (16).

Therefore, the 2019 American Hematology Society (ASH) guidelines state that, in the absence of a gold standard test to diagnose ITP, clinicians should rely on both laboratory and clinical parameters. Additionally, diagnosis may depend on the platelet count response to medications, such as corticosteroids, intravenous

immunoglobulin (IVIG), or treatment of secondary causes. The type and number of examinations may vary according to the patients´ condition (3, 17).

ITP treatment

The treatment of ITP depends on the severity of thrombocytopenia and the presence of active bleeding. The ASH panel recommends commonly used corticosteroids as first-line treatment (e.g., dexamethasone or prednisone) for up to 6 weeks and intravenous immunoglobulin (IVIG) or anti-D immunoglobulin when a rapid platelet count increase is needed or if corticosteroids are contraindicated (3,18).

Second-line therapies are available for patients with more than 3 months of disease who do not respond to corticosteroid therapy or who are dependent on corticosteroids. Second-line strategies include rituximab, splenectomy, and thrombopoietin receptor agonist (TPO-RA) agents—either eltrombopag or romiplostim. Other medications available include immunosuppressants (azathioprine, cyclophosphamide, cyclosporine, danazol, dapsone, and mycophenolate mofetil). The selection of the most appropriate second-line therapy is mainly based on the patient's characteristics, preferences, and disease course (3). Furthermore, the sequence of second-line treatments lacks consensus and depends on factors such as the frequency of bleeding episodes requiring hospitalizations, use of rescue medications, comorbidities, duration of ITP, patient age, medication compliance, patient preferences, availability of social/medical support networks, and costs (19,20).

Cost of ITP care

The costs of primary ITP depend on factors such as the disease stage, investigations, bleeding events, need for rescue therapy, and hospitalizations. Currently, limited and fragmented evidence on cost is available, particularly for the diagnostic component of ITP. The following provincial agencies, boards, and associations were the cost sources for this project and for the cost data used in Chapter II: Ontario´s schedules of benefits, the Canadian Institute for Health Information (CIHI), Ontario drug formulary, Ontario exceptional access program product prices, Canadian blood services, the Ontario Regional Board Coordinating Network, and the Ontario Nurses Association. Based on this information, to follow we provide a current cost scenario per patient going through an ITP diagnostic and therapeutic journey. The costs listed are in 2024 Canadian dollars (CAD). The Bank of Canada Inflation Calculator helped to inflate prices for any services that are not available in 2024.

Patients suspected of having primary ITP can incur several investigations to exclude other causes of thrombocytopenia. Depending on the individual clinical context and the group treatment approach, patients may need different tests to arrive at the diagnosis of ITP. Nonetheless, the American Society of Hematology guidelines recommend a complete blood count ($3.98), blood film ($5.70), and a viral panel, which includes HIV, HBV, and HCV ($31.81). The International Consensus Report also includes additional tests such as Helicobacter pylori

detection ($6.20), direct antiglobulin (DAT) ($6.81), blood group (Rh) ($6.81), quantitative immunoglobulins ($5.22), and bone marrow investigation ($164.00) to rule out other causes of thrombocytopenia.

The McMaster researchers included tests such as anticardiolipin antibodies-ACA ($2.34), lupus anticoagulant ($5.17), antinuclear antibodies-ANA ($6.42), abdominal ultrasound ($37.6), creatinine ($1.28), electrolytes (sodium, potassium, and chloride) ($3.60), thyrotropin ($3.58), liver enzymes (alanine aminotransferase-ALT and aspartate aminotransferase-AST) ($2.56), and serum protein electrophoresis ($17.58). The approximate total cost of testing a patient suspected of ITP is $310.66 for an individual undergoing all of the above-mentioned investigations. Nonetheless, additional tests may be necessary (17,21).

The treatment of chronic primary ITP includes first- and second-line therapies. First-line treatments consist of corticosteroids (e.g., dexamethasone, prednisone), intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Newly diagnosed patients should take corticosteroids for up to six weeks. A cycle of 3 months of corticosteroids—dexamethasone (40 mg/day for 4 days) or prednisone (1.0 mg/kg/day with taper)—may cost up to $73.20 for dexamethasone and $27.72 for prednisone in a 70 kg individual. Patients with corticosteroid contraindications or who need a more rapid platelet count increase are candidates for IVIG or anti-D immunoglobulin treatment. In a 70 kg person, for instance, a cycle dose of IVIG

(1.0 g/kg) or anti-D immunoglobulin (50µg/kg) may cost up to $4,316.90 for IVIG and $1,028.38 for anti-D (22,23).

Second-line therapy may include rituximab, thrombopoietin receptor agonist agents (e.g., eltrombopag, romiplostim), and splenectomy. In a 70 kg and 1.7 m person, a month of treatment with rituximab (375 mg/m^2 intravenously every week for 4 weeks) can cost up to $8,316. The monthly cost for thrombopoietin agent users is $3,900 for eltrombopag (50 mg per day) and $11,564 for romiplostim (700 mg subcutaneously every week for 4 weeks). Splenectomy is $14,725.67. A specific second-line treatment order lacks consensus. Other medications with limited evidence, utilization, and experts' discussion are: azathioprine (50 to 200 mg per day), which costs $1.27 per 50 mg tablet; cyclosporine A (up to 200 mg per day), $6.46 per 100 mg capsule; danazol (200 to 800 mg per day), $2.45 per 200 mg capsule; dapsone (50 to 100 mg per day), $0.70 per 100 mg tablet; and mycophenolate mofetil (500 to 2000 mg per day), $0.74 per 500 mg tablet (3,23-25).

Blood component preparation, administration, and materials costs per unit/event include: red cell concentrate (RCC) $424.00; RCC preparation and dispensing (e.g., electronic crossmatch) $42.85; platelet concentrate pooled-buffy coat $184.00; platelet preparation and dispensing (e.g., medical laboratory assistant) $42.85; nursing hour (hourly rate plus benefits and vacation) $56.66; and infusion materials (burethrol, infusion tubing, and jelco) $15.01 (24-26). Further ITP care

expenses are: initial hematology consultation ($172), follow-up visits ($44.43 average per visit), and hospitalizations ($1,269 average per day), which may vary depending on the patient's clinical state, comorbidities, and bleeding episodes (29,30). The chapter II supplementary material categorizes the costs of the enrolled patients at the McMaster University Medical Centre suspected of ITP during 2018.

The McMaster ITP Registry

The McMaster ITP registry, operating since 2010, is a prospective, longitudinal registry of consecutive patients with thrombocytopenia (platelet count <150 x 10^9/L) aged 18 or older referred to the hematology clinic at McMaster University Medical Centre. The registry consists of a comprehensive record of investigations and clinical information collected during their care process, from the baseline hematology consultation and every six-month visit (1). The Hamilton Integrated Research Ethics Board (HIREB) approved the McMaster ITP registry (REB#15703).

Strengths of the ITP registry:

1. Patients with thrombocytopenia are enrolled consecutively, reflecting real-world practice, making the results more applicable to broader populations.
2. Two hematology specialists validate several clinical activities, including the initial diagnosis, re-evaluation of diagnosis, and assessment of bleeding.
3. The registry collects detailed data, from diagnostic to treatment procedures, to better classify patients with thrombocytopenia according to their clinical and investigational parameters (1).

Limitations of the ITP registry**:**

1. The single-centre approach may limit the generalizability of results.
2. Referral bias may be present because those patients referred to the McMaster University Medical Centre can exhibit a more severe ITP.
3. Recall bias may occur when referred patients to the McMaster hematologic clinic do not accurately remember details when reporting a past experience or event (1).

A clinical prediction model (CPM) for ITP – the Predict-ITP tool

Diagnosing ITP is challenging because there is no specific diagnostic test. Hence, it is necessary to exclude other thrombocytopenic conditions first. The Michael G. DeGroote Centre for Transfusion Research (MCTR) experts used clinical and laboratory parameters from the McMaster ITP registry to devise the Predict-ITP tool. This clinical prediction model plans to fulfill the need for a reliable and timely method for diagnosing ITP. The tool estimates the patient's likelihood of having ITP during the initial hematology consultation. The tool utilizes a logistic regression analysis that considers factors such as platelet count variability, lowest platelet count value, maximum mean platelet volume (MPV), and the history of major bleeding at any point in time. The Predict-ITP tool score ranges from 0 (indicating a low likelihood of ITP) to 1 (indicating a high likelihood of ITP). Depending on the cut-off threshold score, it can classify patients as having ITP. Researchers found that the Predict-ITP tool would have accurately identified 83.5% of individuals with ITP as ITP cases (sensitivity) and 74.8% of patients without ITP as not having ITP (specificity) at their initial visit. Applying the Predict-ITP tool at the first hematology visit may result in a 53.42% reduction of ITP treatments in patients *without definite ITP* and 10.53% in those *with definite ITP* (5).

THESIS RATIONALE AND IMPORTANCE OF TOPIC

ITP is an autoimmune disease characterized by a low blood platelet count that may increase the risk of bleeding. Lacking a definitive diagnostic test, ITP is a heterogeneous syndrome with varying clinical presentations and responses to treatment. Misdiagnosis is present in up to 12% of primary ITP cases in clinical practice, leading to unnecessary testing, inappropriate management, decreased quality of life for patients, and increased costs to the health care system (Figure 1) (1,20).

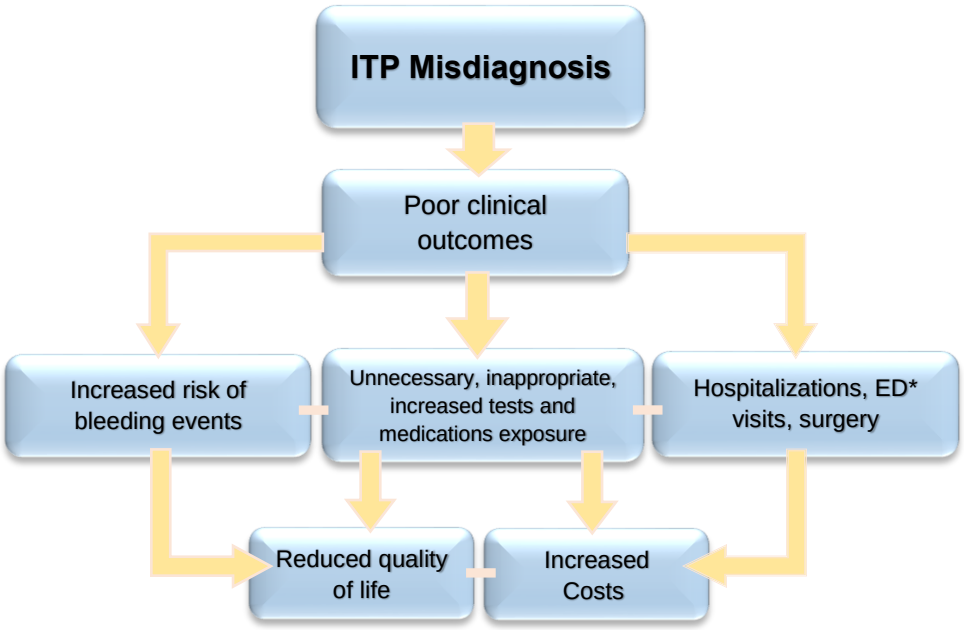

Figure 1. Consequences of misdiagnosing ITP patients – individual and health care system perceptions included. * ED: "Emergency Department".

Diagnosing ITP is challenging. However, initiating timely and appropriate treatment is critical to mitigating complications. ITP diagnosis usually requires routine laboratory testing, the physician's experience, and clinical judgment.

Depending on the patient´s co-morbidities and clinical condition, additional tests may be required to rule out other causes of thrombocytopenia or to screen for potential complications of ITP (3,17).

The development of an innovative clinical prediction model (the Predict-ITP tool) represents a practical path toward achieving ITP's diagnostic precision. By combining different laboratory and clinical parameters, the Predict-ITP tool produces the probability of ITP, helping clinicians ease the diagnostic process. The clinical prediction model demonstrated promising diagnostic accuracy during internal validation in the McMaster ITP registry, correctly identifying ITP patients in over 80% of cases (5). However, its economic implications need a full assessment.

Implementing the Predict-ITP tool for ITP diagnosis may impact and have implications on the following components:

- Health care costs: expenses incurred by individuals, providers, or health care systems to maintain or recover ITP patients´ health. It includes laboratories, imaging, medications, consultations, follow-up visits, emergency department (ED) visits, interventions, and hospitalizations.
- Health outcomes: the impact of diagnosing ITP using the Predict-ITP tool may be assessed by measuring its health effects, such as time to diagnosis, time to treatment initiation, quality of life, and adverse events (31,32).
- Cost-effectiveness: the comparison of benefits and costs between the groups of patients who used the Predict-ITP tool versus those who did not. This analysis

helps policymakers and decision-makers to decide if the benefits of improved health outcomes and resource utilization outweigh the potential costs of deploying the Predict-ITP tool.

- Health care service use: the Predict-ITP tool has the potential to reduce unnecessary health care service utilization, such as repeated laboratory tests, specialist consultations, medication overuse, ED visits, surgical interventions, and hospital admissions.
- Resource allocation: healthcare systems have finite budgets. Thus, identifying and managing resources in a thoughtful manner is crucial to distributing them among programs, populations, and individuals. Identifying those health outcomes and potential economic savings will help decision-makers distribute the healthcare system´s funds efficiently and fairly.

Thus, this thesis will estimate the current cost of ITP care and design both a health economic evaluation and a randomized controlled trial (RCT). The study will compare the quality of life and economic impact of using the Predict-ITP tool versus current ITP care without the tool for the diagnosis and management of ITP. It may provide valuable insights for patients, clinicians, scientists, health care decision-makers, and policymakers regarding the implementation of the Predict-ITP tool in routine clinical practice. This project has the potential to highlight health improvements that could optimize the management of ITP patients and deliver a basis for resource allocation schemes, which may lead to a more efficient use of health care expenditure and better health outcomes.

THESIS PROJECT

Overview

There are two objectives for this project. The first is to explore the associated cost of current clinical care for patients with thrombocytopenia using data from the ITP registry. The second is to design a health-economic evaluation to accompany a randomized control trial that tests the use of the Predict-ITP tool compared with no tool.

The thesis project question: What are the current care costs, and what will be the design of a health economic evaluation alongside a randomized controlled trial to evaluate the impact on health-related quality of life and healthcare costs in patients suspected of having ITP over a two-year follow-up period?

Hypothesis

The Predict-ITP tool will enhance quality of life and produce cost savings in diagnosing and treating patients suspected of ITP compared to the current care.

Study components

This study consisted of three parts: Part A was to estimate the costs associated with current clinical diagnosis and care for patients with thrombocytopenia enrolled at the McMaster ITP registry. Part B was to design a randomized controlled trial. Part C was to propose an economic analysis that will evaluate the health-economic impact of the Predict-ITP tool. Table 1 describes key design components of the project.

	Part A - Determining the Cost of Current ITP care	**Part B – Designing a randomized control trial (RCT) for the Predict-ITP tool**	**Part C – Designing a health economic evaluation for the Predict-ITP tool trial**
Objective	Estimate the costs associated with current clinical diagnosis and care for patients with thrombocytopenia - without the use of the Predict-ITP tool	Evaluate Predict-ITP tool's impact on HRQoL compared to current care.	Estimate the cost-effectiveness testing the new clinical prediction model – the Predict-ITP tool – compared to no tool (current ITP care)
Methods	**Study characteristics**: Quantitative, retrospective – Cost estimation using data from the McMaster ITP Registry	**Study characteristics**: design of a RCT – comparing Predict-ITP with current care, two-arm design over two-year follow-up at seven hematology centres across Canada.	**Study characteristics**: design of a cost-utility analysis, comparing the costs and benefits between the Predict-ITP and current care.
	Participants: Consecutive patients enrolled at the McMaster ITP Registry during 2018	**Participants**: patients referred to the specialized hematology centres with platelet count of $<100 \times 10^9$/L.	**Participants**: RCT participants in Part B.
Data collection	• Imaging • Laboratory investigations • Clinic visits • First and second lines ITP treatments • Hospitalizations / Interventions	Clinical information and health-related quality of life (HRQoL) metrics using the EQ-5D-5L tool	QALYs, cost data, and healthcare utilization records.
Outcomes of interest	• Costs of each component of current ITP care • Total cost of ITP care for the studied cohort	**Primary**: Health related quality of life **Secondary**: • Corticosteroids exposure • ITP bleeding–related episodes • Treatment-related side effects record	**Primary**: Incremental cost-effectiveness ratio (ICER) **Secondary**: • Cost comparisons • Budget impact

Table 1. Components of the thesis project with characteristics.

GLOSSARY OF HEALTH ECONOMICS TERMS

Types of costs

There are direct, indirect, and intangible types of health-related costs. Direct costs correspond to patients' care. These expenses include medical (e.g., consultations, medications, laboratory tests, hospitalizations) and non-medical costs (e.g., caregiver time, transportation). Indirect costs include lost productivity (e.g., absenteeism). The intangible costs are the monetary value of the pain, damage, or suffering caused by health issues (31-33).

Discount rate

The discount rate helps determine the present value of costs and benefits across different periods of time. It is not an inflation adjustment. Health authorities and regulatory organizations often apply a 1.5-3% discount rate each year when doing health economic analysis. When assessing the plausibility of health interventions over extended periods of time, the discount rate is relevant (31).

Perspective

The perspective refers to the analytical viewpoint when evaluating costs and consequences. There are three main perspectives: patient, society, and payer. The patient perspective studies disease consequences and their impact on patients and families. In terms of cost elicitation, it may be either out-of-pocket or co-payment expenditures. The social perspective includes all health care-related costs,

covering both direct and indirect. The payer perspective refers to the costs incurred by a specific organization; they can be public (e.g., health care systems, state/provincial, or federal governments) or private payers (e.g., insurance companies), which covers direct costs and may also indirect expenditures (e.g., reimbursement or disability pensions) (32,33).

The present research investigated the perspective of a public payer (e.g., the Ministry of Health of Ontario) and included direct medical costs of ITP care.

Health Economic Evaluations

A health economic evaluation is the systematic and comparative analysis of two or more courses of action in terms of their costs and health outcomes. Identifying the most efficient option among a set of alternatives is the objective. Figure 2 illustrates the health-economic evaluation of the Predict-ITP tool (31,32).

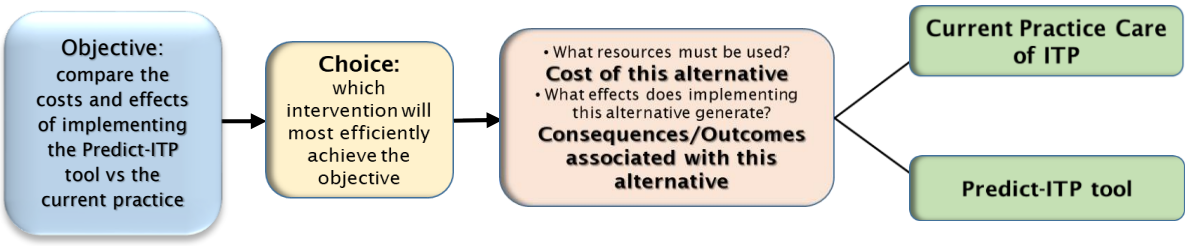

Figure 2. Health economic evaluation for the Predict-ITP tool. Modified from Hurley, Chapter 4 – Methods of economic Evaluation (31).

The concept of resource constraints is important in an economic evaluation. Scarcity of time, health professionals, equipment, and facilities are major concerns

for health care systems around the globe. Therefore, decision-makers, within a unified framework, must conduct a systematic analysis to determine the most efficient option through quantifying the resources and health benefits of each alternative. Thus, it is key to adopt a perspective or viewpoint (e.g., public payer, specific institution) to assess costs and consequences.

Health economic evaluations often adopt one of the following methods:

- Cost-effectiveness analysis: monetary units (e.g., Canadian dollars) and natural units (e.g., ITP cases detected) measure costs and consequences, respectively. Interventions share a similar, common health outcome. However, it is disease-specific. The goal is to decide which interventions are the most effective, or whether an intervention is effective. Its outcome measures include the incremental cost-effectiveness ratio, the cost per life year gained, and the cost per case averted.
- Cost-utility analysis: values costs in monetary units and consequences in quality-adjusted life years (QALYs). This analysis is useful to choose between different types of health outcomes (e.g., myocardial infarction mortality vs. disability-caused bleeding-related episodes in ITP patients). In other words, the outcome is measured using generic scale, allowing comparison across diseases and treatments. The economic summary measure is the cost per quality-adjusted life year.

- Cost-benefit analysis: this method values both costs and consequences in monetary units. Willingness to pay is normally the method for assigning the monetary value to health. This approach is suitable to decide between health outcomes and other types of outcomes (e.g., health vs. education). The outcome measures are the net monetary benefit or cost-to-benefit ratio (31,32).

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CHAPTER II: Part A – Determining the cost of current ITP care

BACKGROUND

Determining the current ITP care costs through the valuation of health care expenditures is essential for helping decision-makers formulate health care policies. Cost components included in the evaluation were medications, images, consultations, ED visits, hospitalizations, interventions, and laboratory tests. Therefore, this analysis plays an important role in informing resource allocation, ensuring the accountability and financial sustainability of the health care system.

Currently, there is limited information on the economic impact of ITP care. The cost estimation for ITP care is important for patients, clinicians, and scientists. Those costs are building blocks for cost effectiveness analysis aimed at optimizing financial health care spending. ITP has diverse diagnosis approaches based on individuals' characteristics. Hence, using a real-world data source such as the McMaster ITP registry can reflect current ITP care parameters and costs for this analysis.

LITERATURE REVIEW

ITP care involves several investigations and treatments, depending on the individual's characteristics and needs. Several studies have explored the economic impact of ITP (see Appendix 1 for the search strategy for ITP care costs). Some researchers have focused on treatments, principally second-line therapies, which are often the newest and most expensive management options. In addition, others have analyzed the costs of hospital length of stay, emergency department (ED) visits, ITP bleeding events, and ITP treatment-related adverse events.

Studies of treatment costs and resource utilization have found that IVIG is a major cost driver for ITP (1-3). In addition, a study found that thrombopoietin receptor agonists (TPO-RA) drugs appeared to be less expensive than rituximab or observation and rescue approaches (4).

A second-line treatment approach has been the focus of some researchers. They conducted studies comparing three treatments for patients with ITP: splenectomy, rituximab, and TPO-RAs. Researchers have concentrated their interest on finding an appropriate sequential order of those three ITP therapy options (5-9).

Real-world evidence-based studies have evaluated the overall economic impact of ITP treatment, bleeding, and adverse event (AE) costs (10-12). Weycker et al. used a U.S. private health care claims database to evaluate the overall economic impact of ITP treatment. Each year, approximately 20,000 children and adults in the United

States receive a new diagnosis of ITP. During the first 12 months of diagnosis, the medical burden was close to $400 million (2016 US dollars) for this population (10).

Similarly, Donga et al. conducted a claim-based analysis to evaluate the cost burden of AE associated with ITP treatment (11). Rituximab was the most frequent ITP treatment related to adverse events; anti-D therapy showed lower numbers. Urinary tract infection was the most costly adverse event, independent of treatment. Lin et al. also evaluated the costs of bleeding events in patients with ITP. They found that the mean total reimbursement per bleeding-related episode was $6,022 adjusted to 2015 US dollars, with a remarkable difference between settings: outpatient ($2,150) and inpatient ($45,114) (12).

ITP hospitalizations were longer, with an increased mortality risk and higher costs than other US discharged populations. The mortality rate, major bleeding events, and admission rates increased with age and were higher among women than men. Overall, the cost was higher for men than women (13-15). Bauer et al. found a direct relationship between ITP duration and cost (16), and Saleh et al. showed that ED visits and hospitalizations accounted for the majority of ITP care-related expenditure (17).

STUDY DESIGN

This study aimed to estimate the costs of diagnosis and treatment of patients suspected of ITP through a retrospective analysis of data from patients consecutively enrolled at the McMaster ITP registry during 2018. It was possible to obtain information about laboratory investigations, imaging, clinic visits, first- and second-line ITP treatments, ED visits, hospitalizations, and interventions. The main purpose of using consecutive sampling to obtain this data source was to mitigate selection bias by distributing the characteristics of patients within the group.

This study component involved collecting investigations and treatments costs of patients suspected of ITP referred to the McMaster University Medical Centre and enrolled in the ITP registry. This registry is a data source for extracting service usage frequency. Cost estimates are based on service utilization and the cost per unit of service (18). Sources of data on unit costs included the Ontario Schedule of Benefits Lab, effective July 24, 2023; Ontario Schedule of Benefits Physician Services, effective April 1, 2024; the Canadian Institute for Health Information (CIHI); Ontario Drug Formulary; Ontario Exceptional Access Program product prices; Canadian Blood Services; Ontario Nurses Association; and Hamilton Regional Laboratory Medicine Program direct communication.

METHODS

This study used a quantitative approach to assess the costs of ITP care. We collected data retrospectively using the McMaster ITP registry.

Inclusion criteria: consecutive individuals under investigation for thrombocytopenia—platelet count <150 × 10^9/L—attending to the McMaster University Medical Centre in Hamilton, Canada—individuals enrolled in the McMaster ITP Registry—between January 1 and December 31 of 2018.

Exclusion criteria: individuals with co-enrollment in a distinct clinical trial.

Data collection methods and sampling: the McMaster ITP Registry was used to collect clinical information regarding investigations and treatments. Convenience sampling with a consecutive approach was performed to collect information according to the ITP registry and inclusion criteria. All the screened patients were de-identified.

Ethics and informed consent: no relevant ethical issues were recognized in the implementation of this project component. The selection process did not favor any particular gender, religion, or socio-economic group. ITP registry participants signed the informed written consent. The Hamilton Research Ethics Board approved the McMaster ITP registry project (Project ID: 16461).

Cost components

Cost elicitation involves the collection of data on the health resources used and the valuation of the resources in monetary units. These monetary units, expressed in 2024 Canadian dollars (CAD), valued the cost of ITP care. Adjustments to unit costs take into account inflation or wage association agreements from the base year to 2024 with a one-year cost collection period. Therefore, the discount rate does not apply.

The scope of this research component was to assess the current direct medical costs for ITP care from a public payer perspective (e.g., the Ontario Ministry of Health). The health care services for ITP included the following categories (see Appendix 2 for details):

- Laboratory examinations: serum chemistry and hematology.
- Haematopathology investigations: bone marrow investigations.
- Imaging: ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) of spleen.
- Medications: first- and second-line treatment.
- IVIG infusion: immunoglobulin with infusion materials and staff.
- Blood components.
- Registration, follow-ups, ED visits, and hospitalizations.
- Splenectomy.

RESULTS

In this project component, we included 75 consecutive ITP-registry patients—31 females (41.3%) and 44 males (58.7%)—referred to McMaster University Medical Centre in 2018 for diagnosis and treatment of thrombocytopenia. Among the population, 38 patients had a definite diagnosis of ITP, and 37 individuals had diagnoses different from ITP. The patients' mean age at consent was 55.8 years. The median (IQR) minimum platelet count was 82 x 10^9/L (36, 124.5). More details are available in Table 1.

Study population characteristics
31 Females (41.33%) vs. 44 Males (58.67%)
38 (50.67%) definite ITP vs. 37 (49.33%) different from ITP
Mean age at consent 55.8 years
Median (IQR) age at consent 58 years (40.5, 71)
Mean initial platelet count: 113.8
Median (IQR) initial platelet count: 101 (63, 150.5)
Mean minimum platelet count: 91.7
Median (IQR) minimum platelet count: 82 (36, 124.5)

Table 1. Study population characteristics

Health services: costs and frequency estimates

Current ITP care practices include a variety of tests, medications, and interventions based on the patient's needs. According to the available data, we listed the investigations and therapies used in ITP care. We calculated the frequencies and valued the cost of investigating and treating each patient enrolled at the McMaster ITP registry between January 1 and December 31 of 2018. The costs described henceforth are in 2024 Canadian dollars (CAD). The Bank of Canada Inflation Calculator will help to inflate prices for any services that are not available in 2024.

The average cost per patient was $4,181.84 over 1 year ($6,176.16 for patients with definite ITP and $2,133.61 for those with diagnoses different from ITP), with a total cohort cost of $313,637.84 for those included in the ITP registry during 2018. The following tables contain the appraised variables, as well as their costs and frequency of use.

Laboratory examinations

Service	Units	Units used	Cost per unit (CAD)	Total cost (CAD)
Complete Blood Count	per test	352	3.98	**1,400.96**
Creatinine	per test	194	1.28	**248.32**
Total bilirubin	per test	193	1.28	**247.04**
Alanine aminotransferase - SGPT (ALT)	per test	186	1.28	**238.08**
Aspartate aminotransferase - SGOT (AST)	per test	178	1.28	**227.84**
Potassium	per test	129	1.16	**149.64**
Sodium	per test	128	1.16	**148.48**
Quantitative immunoglobulins	per test	108	5.22	**563.76**
Thyrotropin	per test	92	3.58	**329.36**
Antinuclear antibody (ANA screen)	per test	85	6.42	**545.7**
Lactate dehydrogenase	per test	80	1.28	**102.4**
HBV Serology	per test	74	10.25	**758.5**
Activated partial thromboplastin time	per test	72	2.66	**191.52**
Prothrombin time (PT) in INR (international normalized ratio)	per test	71	2.66	**188.86**
HCV Serology	per test	71	10.25	**727.75**
Lupus anticoagulant. anti-cardiolipin antibodies	per test	70	7.51	**525.7**
Albumin electrophoresis	per test	69	17.58	**1,213.02**
Blood film examination	per test	46	5.7	**262.2**
Albumin	per test	23	1.28	**29.44**
Direct Antiglobulin Test (DAT)	per test	10	6.81	**68.1**
HIV Serology	per test	9	11.31	**101.79**
Serum Protein Electrophoresis	per test	8	17.58	**140.64**
Subtotal				**$8,409.1**
Mean +/- SD			**$5.52 +/- $1.09**	**$382.23 +/- $77.69**
Median. IQR			**$3.78 . 6.92**	**$242.56 . 403.70**

Table 2. Laboratory examinations

Laboratory tests involved hematology, serum chemistry, and other blood tests. Costs ranged from $1.16 to $17.58. The mean laboratory test cost was $5.52, and

the standard deviation (SD) was +/- $1.09. The most frequent laboratory examination was the complete blood count with 352 tests, whereas the least used was the serum protein electrophoresis with only 8 tests (19).

Haematopathology

Service	Units	Units used	Cost per unit (CAD)	Total cost (CAD)
Bone marrow interpretation (Romanowsky stain)	per test	10	62.75	**627.5**
Bone Marrow Biopsy	per test	8	101.25	**810**
Bone Marrow Aspirate	per test	7	101.25	**708.75**
Subtotal				**$2,146.25**
Mean +/- SD			**$88.42 +/- $12.83**	**$715.42 +/- $52.79**
Median. IQR			**$101.25 . 38.5**	**$708.75 . 182.5**

Table 3. Haematopathology services

Haematopathology investigations included bone marrow biopsies and bone marrow aspirates, which cost $101.25 each, while interpretation was $62.75.

Imaging

Service	Units	Units used	Cost per unit (CAD)	Total cost (CAD)
Ultrasound – Abdominal (Average)*****	per test	17	37.6	**639.2**
Computed Tomography (CT) – Abdominal	per test	7	86.6	**606.2**
Magnetic Resonance Imaging (MRI) – Abdominal	per test	1	73.35	**73.35**
Subtotal				**$1,318.75**
Mean +/- SD			**$65.85 +/- $14.63**	**$439.58 +/- $183.36**
Median. IQR			**$73.35 . 49.0**	**$606.2 . 565.85**

***** H (Hospitalization) $48.75 and P (Outpatient) $26.45

Table 4. Imaging services

The ITP diagnostic process included spleen images using ultrasound, CT, and MRI, which ranged from $37.6 to $86.6; mean $65.85 SD +/- $14.63. Spleen ultrasound was the most demanded image, 18 in total, followed by 7 CTs and 1 MRI (20). The average cost for investigating a patient suspected of ITP in the McMaster ITP registry during 2018 was $158.82.

IVIG infusion

Service	Units	Units used	Cost per unit (CAD)	Total cost (CAD)
Immunoglobulin	per gram	670	61.67	41,318.9
Nursing time [a]	per hour	14	56.66	793.25
Physician visit (Average)	per event	14	44.43	622.02
Preparation and dispensing fee [b]	per event	14	42.85	599.9
Infusion materials (Burethrol. infusion tubing. and jelco)	per package	14	15.01	210.14
Subtotal				**$43,544.21**
Mean +/- SD			**$44.12 +/- $8.11**	**$8,708.84 +/- $8,153.07**
Median. IQR			**$44.43 . 30.24**	**$622.02 . 20,651.05**

[a] Nursing time 13% is added for benefits and 4.8% for vacation pay. Total hourly cost is estimated to be $56.66. Based on the Ontario Wages for RN – Ontario Nurses Association – Term: April 1, 2023 to March 31, 2025 document, available in https://www.ona.org/wp-content/uploads/2023-hospital-central-contract-highlights.pdf
[b] E.g. performed by Medical Laboratory Assistant. If performed by Medical Laboratory Technologist $58.54.

Table 5. IVIG infusion

Treatment plans vary from patient to patient, and therefore costs differ. The cost per unit of medication ranged from $0.022 to $2,066.07, with a mean of $557.66 and SD +/- $259.47 for the studied population (21,22). In terms of first-lines, for instance, the cost of administering intravenous immunoglobulin (IVIG) includes the biologic, physician and nursing time, preparation and dispensing costs, and infusion materials (18). IVIG cost $61.67 per gram, whereas its administration was $158.95 per event per patient (23).

Medications

Service	Units	Units used	Cost per unit (CAD)	Total cost (CAD)
Mycophenolate Mofetil (Cellcept) 500mg	per dose	368	0.74	272.32
Prednisone 5mg	per dose	314	0.022	6.91
Eltrombopag (Revolade) 50mg	per dose	292	130.00	37,960.00
Cyclosporine (Neoral) 100mg	per dose	124	6.46	801.04
Dexamethasone 4mg	per dose	120	0.61	73.2
Romiplostim (Nplate) 250mg	per dose	37	1,033.02	38,221.74
Romiplostim (Nplate) 500mg	per dose	37	2,066.07	76,444.59
Rituximab 100mg	per dose	10	297.00	2,970.00
Rituximab 500mg	per dose	5	1,485.00	7,425.00
Subtotal				**$16,4174.80**
Mean +/- SD			**$557.66 +/- $259.47**	**$18,241.64 +/- $8,987.25**
Median. IQR			**$130 . 1,258.34**	**$2,970 . 37,918.11**

Table 6. Medications

Surgical intervention

Service	Units	Units used	Cost per unit (CAD)	Total cost (CAD)
Splenectomy	per intervention	1	14,725.67	**14,725.67**

Table 7. Surgical intervention

Second-line options included thrombopoietin receptor agonist (TPO-RA) agents—eltrombopag and romiplostim—rituximab, immunosuppressants, and splenectomy. Of these, only one patient had the splenectomy, which cost $14,725.67. Total second-line costs fluctuate between $272.32 for mycophenolate mofetil and $114,666.33 for romiplostim (24). The average cost of first- and second-line treatment with administration was $2,967.07 per patient.

Blood components

Service	Units	Units used	Cost per unit (CAD)	Total cost (CAD)
Red cell concentrate (RCC)	per unit	1	424.00	**424.00**
Platelet concentrate pooled-buffy coat	per unit	1	184.00	**184.00**
RCC preparation and dispensing [a]	per event	1	42.85	**42.85**
Platelet preparation and dispensing (Medical Laboratory Assistant)	per event	1	42.85	**42.85**
Subtotal				**$693.7**
Mean ± SD			**$173.43 +/- $89.91**	**$173.43 +/- $89.91**

[a] E.g. electronic crossmatch. If it is full serological crossmatch is $117,08 per event.

Table 8. Blood components

Blood products needed in two patients were $608.00 for red cell concentrate and platelet units; $42.85 cost the administration per event per patient.

Registration, follow-ups, ED visits, and hospitalizations

Service	Units	Units used	Cost per unit (CAD)	Total cost (CAD)
Hospitalizations	per day	45	1,269.00	**57,105.00**
Registration	per episode	75	172.00	**12,900.00**
Follow-ups (Average)	per episode	72	44.43	**3,198.96**
ED visits	per episode	15	358.92	**5,383.8**
Subtotal				**$78,587.76**
Mean +/- SD			**$461.09 +/- $276.94**	**$19,646.94 +/- $12,657.67**
Median. IQR			**$265.46 . 965.16**	**$9,141.9 . 42,308.58**

Table 9. Registration, follow-ups, ED visits, and hospitalizations

The average cost of follow-up visits was $44.43, and registration visits were $172 (20). The cost per visit to the ED was $358.92, and the estimated cost per day of hospitalization was $1,269 (24,25).

Cost drivers

Patients required different investigations and therapies depending on their specific needs. The average cost per patient enrolled in the ITP registry over 1 year was $4,181.84. The treatment approaches mainly determined the differences in ITP care costs among patients. First-line treatment included corticosteroids (prednisone, dexamethasone) and IVIG. Second-line therapies were TPO-RA agents (e.g., eltrombopag, romiplostim), rituximab, and splenectomy. Other second-line medications included cyclosporine and mycophenolate mofetil.

Treatment of ITP depends on the degree of thrombocytopenia, duration of disease, patient age and comorbidities, and other factors that may affect bleeding risk (26). Based on these characteristics, the cost of medications, the need for hospitalization, and the use of rescue therapy (particularly IVIG) are considered drivers of immune thrombocytopenia care costs (27). Consistent with this, we found that romiplostim ($114,666.33), hospitalization ($57,105.00), and IVIG ($41,318.90) were the top three cost drivers in the 2018 ITP-registry, accounting for 67.94% of the total expenditure of the cohort.

Costs by subgroups and categories

Subgroup	N (Number of patients)	Category	Units used	Total cost (CAD)
Overall cohort	**75**			
Sex	**75**			
Females	31	Laboratory examinations	1066	3,972.34
		Haematopathology	11	959.75
		Imaging	8	398.80
		IVIG (biologic agent)	670	41,318.90
		Medications	958	39,060.71
		Surgical intervention	1	14,725.67
		Hospitalization (days)	14	17,766.00
		ED visits (events)	8	2,871.36
		Blood products (Red cells and platelets concentrates)	2	608.00
		Initial hematology consultation	31	5,332.00
		Follow-up visits	39	1,732.77
Males	44	Laboratory examinations	1182	4,436.76
		Haematopathology	14	1,186.50
		Imaging	18	957.55
		IVIG biologic agent	0	0
		Medications	349	125,114.09
		Surgical intervention	0	0
		Hospitalization (days)	31	39,339.00
		ED visits (events)	7	2,512.44
		Blood products	0	0
		Initial hematology consultation	44	7,568.00
		Follow-up visits	33	1,466.19
Diagnosis	**75**			
Definite ITP diagnosis	38	Laboratory examinations	1343	4,946.42
		Haematopathology	12	1,022.50
		Imaging	14	820.40
		IVIG biologic agent	670	41,318.90
		Medications	1168	152,978.76
		Surgical intervention	0	0
		Hospitalization (days)	17	21,573.00
		ED visits (events)	2	717.84
		Blood products (Red cells concentrate)	1	424.00
		Initial hematology consultation	38	6,536.00
		Follow-up visits	47	2,088.21
Different from ITP diagnosis	37	Laboratory examinations	905	3,462.68
		Haematopathology	13	1,123.75
		Imaging	12	535.95
		IVIG biologic agent	0	0
		Medications	139	11,196.04
		Surgical intervention	1	14,725.67
		Hospitalization (days)	28	35,532.00
		ED visits (events)	13	4,665.96
		Blood products (Platelet concentrate)	1	184.00
		Initial hematology consultation	37	6,364.00
		Follow-up visits	25	1,110.75

Table 10. Costs by subgroups and categories. Patients enrolled at the McMaster ITP registry during 2018

Sex: the mean cost of ITP care showed minimal difference between sexes; females (N = 31) incurred a slightly higher mean cost of $4,227.66 compared to $4,149.56 for males (N=44).

ITP diagnosis: each patient with a definite ITP diagnosis (N = 38) cost $6,176.16, whereas an individual with a diagnosis different from ITP (N = 37) cost $2,133.61. The difference in cost mainly accounts for the type of treatment offered and the hospitalization need.

First-line treatment: patients on dexamethasone (N = 2) cost $73.20, whereas those on prednisone (N = 2) were $6.91. Two individuals underwent IVIG; it cost $41,318.90, with an additional infusion charge (nursing and physician time, preparation and dispensing, and infusion materials) of $2,225.31. The total first-line treatment cost across the population studied was $43,624.32.

Second-line treatment: elevated costs associated with thrombopoietin receptor agonists (TPO-RAs). Over one-year, treatment with romiplostim (N = 1) cost $114,666.33, while eltrombopag (N = 1) was $37,960.00. A splenectomy (N = 1) cost $14,725.67, and rituximab (N = 1) therapy cost $10,395.00. Together, these second-line treatments reached $177,747.00. Additional second-line medications included cyclosporine (N = 1) at $801.04 and mycophenolate mofetil at $272.32, ending in a total second-line treatment expenditure of $178,820.36**.**

Emergency Department (ED) visits and hospitalizations: in the studied cohort, there were 15 ED visits that cost $5,383.80. Hospitalization stays accounted for 45 days at a cost of $57,105.00. Notably, two male patients had the longest hospital stays, lasting 10 and 21 days, which aligned with evidence indicating that males generally have longer hospital stays and higher associated costs (15). Overall, acute care expenditure cost $62,488.80.

Registration and follow-up visits: initial registration and follow-up visits for specialized care also contributed to the overall costs. The initial hematology visit (N = 75) cost was $12,900, and follow-up visits (N = 72) reached $3,198.96. Together, these specialized visits totaled $16,098.96.

Discussion

This analysis reveals distinct cost patterns in managing patients with a definite ITP diagnosis compared to those without this diagnosis based on current clinical practice. It reflects an important variation across different treatment modalities, but in this case, a small difference in cost between male and female patients. Individuals with a definite ITP diagnosis showed increased health expenditure compared to those without this condition. First-line options represent a relatively inexpensive alternative for ITP patients, with the exception of IVIG, which increases markedly the ITP management expenditure. Additionally, second-line treatments, in particular Romiplostim, imposed a substantial financial burden on the population studied. Outpatient visits contribute marginally to the cost of managing ITP.

Nonetheless, inpatient and acute medical care for ITP increase considerably the disease's overall economic burden.

This cost analysis offers several strengths, including a detailed cost breakdown by category and service, population-specific insights through cost segmentation by subgroups, and practical value for prospective health economic analyses. It will support researchers and policymakers in conducting comparative analyses and improving quality and cost efficiency.

On the other hand, the small sample size (N = 75) of this analysis may limit the precision in cost estimation and generalizability of findings. Additionally, the varied patient management and clinical background, treatment assumptions, and baseline platelet counts may limit accuracy in an economic evaluation. We will discuss the limitations in detail in Chapter V of this document.

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Chapter II – Supplementary materials

Appendix 1

Search strategy for ITP care cost

#	Searches	Results
1	Purpura, Thrombocytopenic, Idiopathic/	7923
2	(((idiopathic* or immune* or autoimmune* or auto-immune*) adj (thrombocytopenia* or thrombocytopenic purpura*)) or (werlhof* adj disease*)).ti,ab,kf,kw.	13496
3	1 or 2	14871
4	limit 3 to yr="2009-Current"	7547
5	limit 4 to (humans and english)	5171
6	limit 5 to "all adult (19 plus years)"	2542
7	Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/	20015
8	exp "Cost"/	270282
9	(cost or costs or costing or costly).ti.	137726
10	or/7-9	321878
11	6 and 10	29

Appendix 2

List of services used for ITP care at the McMaster University Medical Centre.

Categories	Services
Laboratory examinations (Hematology, serum chemistry and others)	
	Activated partial thromboplastin time
	Alanine aminotransferase - SGPT (ALT)
	Albumin
	Albumin electrophoresis
	Antinuclear antibody (ANA screen)
	Aspartate aminotransferase - SGOT (AST)
	Blood film examination
	Complete Blood Count
	Creatinine
	Direct Antiglobulin Test (DAT)
	HBV Serology
	HCV Serology
	HIV Serology
	Lactate dehydrogenase
	Lupus anticoagulant, anti-cardiolipin antibodies
	Potassium
	Prothrombin time (PT) in INR (international normalized ratio)

	Quantitative immunoglobulins
	Serum Protein Electrophoresis
	Sodium
	Thyrotropin
	Total bilirubin
Haematopathology	
	Bone Marrow Aspirate
	Bone Marrow Biopsy
	Bone Marrow interpretation (Romanowsky stain)
Imaging	
	Spleen Imaging – Computed tomography (CT)
	Spleen Imaging – Magnetic resonance imaging (MRI)
	Spleen Imaging – Ultrasound
Medications	
	Azathioprine (Imuran) 50mg
	Cyclosporine (Neoral) 100mg
	Dexamethasone 4mg
	Eltrombopag (Revolade) 50mg
	Mycophenolate mofetil 500mg
	Prednisone 5mg Tab
	Rituximab 100mg
	Rituximab 500mg
	Romiplostim (Nplate) 250mcg/0,5ml
	Romiplostim (Nplate) 500mcg/1 mL
IVIG infusion	
	Immunoglobulin
	Nursing time
	Physician visit
	Preparation and dispensing
	Infusion materials (Burethrol, infusion tubing, and jelco)
Blood components	
	Red cell concentrate (RCC)
	Platelet concentrate pooled-buffy coat
	RCC preparation and dispensing (e.g. electronic crossmatch)
	Platelet preparation and dispensing (Medical Laboratory Assistant)
Registration, follow-ups, ED visits, and hospitalizations	
	Hospitalizations
	Emergency Department (ED) visits
	Follow-ups
	Registration
Splenectomy	
	Splenectomy

CHAPTER III: Part B – Designing a randomized controlled trial for the Predict-ITP tool – The Predict-ITP HRQoL trial

BACKGROUND

Immune thrombocytopenia (ITP) is an autoimmune disease characterized by impaired production and/or destruction of platelets that affects 1 in 8,000 people per year. The platelet blood count in ITP is less than $100x10^9$/L with other causes of thrombocytopenia excluded. Based on disease duration, ITP can be classified as newly diagnosed (0–3 months), persistent (>3–12 months), or chronic (>12 months). ITP symptoms can occur gradually and vary from mild to severe. Patients with ITP may have bruises, mucocutaneous lesions, conjunctival hemorrhages, epistaxis, gastrointestinal or abnormal gynecological bleeding, hematuria, or intracerebral hemorrhage (1-4).

However, a lack and underestimation of ITP non-bleeding consequences may be present in literature (5). Derived from ITP treatment, adverse events may impact patients. Corticosteroids exposure in ITP, for instance, is considered one of the most common potential issues. ITP may impact patients' quality of life by producing fatigue, anxiety, and depression, negatively affecting their daily activities, including work productivity and social life (6,7).

LITERATURE REVIEW

The variable presentation of ITP can make disease progression difficult to predict. Currently, ITP care lacks specific and conclusive diagnostic criteria. This issue can lead to spending unnecessary time and resources, affecting not only health care systems' funds but also patients' quality of life. Adopting a clinical prediction model into practice to establish the likelihood of a patient having ITP will probably reduce patients' anxiety about the unknown (8). Enhancing the certainty of diagnosis will allow practitioners to go beyond laboratory tests and clinical findings. This reliability will increase patients' confidence and clinician accuracy in making an individualized treatment strategy (9). A precise and timely diagnosis may also alleviate unnecessary medication exposure and reduce adverse events in patients with ITP. These sensitive needs have become even more important in recent years. Appendix 1 describes the search strategy used.

Researchers have used a variety of tools to assess the quality of life of adults with ITP. For example, Al-Samkari et al. found both generic and specific tools. Some generic instruments used for assessing quality of life in ITP patients include: the Medical Outcomes Study Short Form 36 (SF-36v2), the Motivation and Energy Inventory (MEI-SF), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), the Functional Assessment of Cancer Therapy-Thrombocytopenia subset (FACT-Th6), and the EQ-5D. They found in this review the Immune

Thrombocytopenic Purpura Patient Questionnaire (ITP-PAQ) as the unique instrument valuing quality of life specifically in ITP patients (5).

Another relatively recent tool is the ITP Life Quality Index (ILQI). It is a 10-item, patient-reported outcome measure that has an integrative view of patients and physicians regarding aspects of ITP. Data collected from 1507 patients with ITP across 13 countries in the ITP World Impact Survey (I-WISh) validated this instrument. The I-WISh showed patients' interests in aspects such as increasing energy levels in 41%, preventing episodes of ITP from deteriorating in 44%, and achieving healthy platelet counts in 64% of cases (8).

Undesirable clinical outcomes related to treatment are also a concern for clinicians when managing ITP patients. Corticosteroids remain a common component of first-line ITP treatment. These medications have high initial response rates, are relatively well tolerated, and are low in cost. However, a prolonged and repeated course could be associated with toxicity (10). Among corticosteroid toxicity, there are several manifestations, including the most frequent, such as gastrointestinal toxicities (e.g., peptic ulcer, diarrhea, nausea) (6%), hyperglycemia (6%), weight gain (5%), insomnia or fatigue (3%), and hypertension (3%) (10,11).

EVALUATING HEALTH-RELATED QUALITY OF LIFE (HRQoL)

Health-related quality of life encompasses the physical, emotional, psychological, and social aspects of individuals affected by a health condition or medical interventions. HRQoL measures included generic instruments such as the Medical Outcomes Study Short Form 36 (SF-36v2), the EQ5D, or disease-specific tools including the Immune Thrombocytopenic Purpura Patient Questionnaire (ITP-PAQ) and the ITP Life Quality Index (ILQI). HRQoL is the most commonly evaluated patient-reported outcome measure that connects with the valuation of an individual´s health (5,12,13).

The *patient reported outcomes (PRO)* are attributes reported by patients about their own symptoms, functioning, health status, or health-related quality of life. PROs collect patients' perceptions directly through structured questionnaires. They are important for patient-centered care research (13).

A *health state* denotes patients' judgment about their own health. It is a set of characteristics that describe an individual's health at a given point in time. They can be ordinal (ranking) or cardinal (strength-based). Cardinal values are useful for determining the patient's health state preference over another. A *health state preference* represents individuals´ or populations´ subjective valuations or desirability of different health states (13,14).

The *health utilities* use cardinal values to quantify the strength of health state preferences. Their range is on a scale anchored at 0 (death) and 1 (full health). It is possible to have negative values for those health states considered worse than death (14).

In other words, health states are numerical values assigned to different health states based on a health utility index or value set according to the health state preferences of the general population in a specific region or country. These health utility values are generated through different utility elicitation approaches, including standard gamble (SG), time trade off (TTO), and discrete choice experiment (DCE) (15).

The measurement of health utilities involves:

1. Define health states.
2. Derive health state preference data from patients' perceptions to value their health states.
3. Calculate utility values, assigning a numerical value from a country/region-specific utility value set to the collected health states.

The EQ-5D tool

The EQ-5D is a standardized generic instrument that measures health-related quality of life and provides data for economic appraisal (14). The EuroQol Group has developed different versions of the tool for both children and adults. The instruments for adults are the EQ-5D-3L and EQ-5D-5L (14).

The EQ-5D-3L consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive component of the instrument will evaluate patients in five dimensions, including mobility, self-care, usual activities, pain and discomfort, and anxiety/depression. Each dimension will assess three levels of severity: no problems, some problems, and extreme problems (14).

The EQ-5D-5L tool is also a standardized generic instrument that provides data for economic evaluations (14). It also has two major components, the descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive component of the instrument evaluates patients in the same five dimensions. However, each dimension of the EQ-5D-5L will validate five levels of severity: no problems, slight problems, moderate problems, severe problems, and extreme problems. With more severity levels compared to the EQ-5D-3L, the EQ-5D-5L offers more sensitivity and may improve the accuracy of utility values in HRQoL assessments (16). For this project, we will use the EQ-5D-5L tool. In Appendix 2 of the supplementary material of this chapter, a sample version of both descriptive and VAS components is available.

When answering the instrument, the patient selects the box next to the most suitable level statement; a one-digit number will result for each of the five dimensions. Therefore, the resulting EQ-5D-5L health state will provide a 5-digit code that describes the patient's condition in five dimensions and five levels of severity. In total, 3125 health states are possible with combinations of dimensions and severity levels (14). For example, if a patient has moderate problems walking about, no problems washing or dressing, slight problems doing usual activities, severe pain or discomfort, and is slightly anxious or depressed, the 5-digit code is 31242. Another patient in a full health state is 11111.

A health index can be calculated for each EQ-5D-5L health state. The health utility values reflect the preferences of the general population and can be used for the quality-adjusted life years' calculation (14). In this project, health state preferences will be Canada-specific.

The EQ-5D second component, the visual analogue scale (EQ VAS), registers endpoints as *"The best health you can imagine"* and *"The worst health you can imagine"* in a vertical visual record. Health outcomes, measured through the VAS, will reveal the individual's health judgment on a scale numbered from 0 to 100. The patient will write the marked number on the vertical scale in the box named *"Your health today"* (14).

The Canadian population norms for the EQ-5D-5L

The Canadian EQ-5D-5L utilities or the Canadian population norms for the EQ-5D-5L describe the HRQoL of the general population (15). Researchers can use them to compare health status and quality of life across specific groups and demographics. The Canadian EQ-5D-5L valuation study (N = 1207) showed the mean EQ-5D-5L utility was 0.864 and standard deviation (SD) 0.121, and the mean EQ VAS for the general population was 82.3 and SD 14.23. The EQ-5D-5L utility mean was the highest for people aged 25-34 years, which was 0.881, and the lowest for people aged 55-64 years, which was 0.839. Furthermore, those patients with any self-reported chronic health condition (e.g., asthma, arthritis, high blood pressure, migraine headaches, etc.) had a mean of 0.836 and SD of 0.136. The EQ-5D-5L utility assigned values ranged from -0.148 for a health state of 55555 to 0.949 for a health state reported of 11111 (15).

The use of EQ-5D-5L in ITP patients

For ITP patients, previous studies evaluating HRQoL have reported different findings according to disease stage and therapy exposure. A study estimating the cost-utility and value of intravenous immunoglobulin, estimated a utility value for relapsing or refractory ITP patients at 0.76 (17). Another publication compared ITP patients (N = 247) with varied platelet counts and disease-stages, with the general population in Norway. The EQ-5D-3L index score was significantly lower in ITP

patients compared to the general population [mean (SD) = 0.790 (0.23) vs. 0.830 (0.041); p-value 0.007] (18).

In a report from Canada´s Drug Agency (CDA), formerly the Canadian Agency of Drugs and Technologies in Health (CADTH), evaluating the treatment of adults with immune thrombocytopenia after failure of first-line therapies, clinical experts categorized patients with EQ-5D index scores according to platelet blood counts, from 0.75 in patients with less than $10x10^9$L to 0.82 in those ranging 50 – 99 $x10^9$L (19).

STUDY DESIGN

The objective is to design a randomized controlled trial. An RCT denotes an effective approach to validate causality and objectively compare the quality of life of patients using the Predict-ITP tool vs. the current practice of ITP care. The primary purpose of a random method is to mitigate selection bias by allowing for an even distribution of patients' characteristics (prognostic factors) between the two randomization groups. The randomization to either the control or experimental groups will be computer-generated. Therefore, the similarities and differences can account only for individuals' needs, characteristics, and clinical background.

The research coordinators will randomly allocate the Predict-ITP tool at the first hematology consultation. Depending on each patient´s requirements, additional investigations may be necessary, no matter which arm. We will blind the patients during the baseline consultation and follow-up. We will also blind the adjudication committee, laboratory staff, and statisticians.

The use of the Predict-ITP tool requires a baseline complete blood count along with at least two previous platelet count values to establish the platelet variability index (PVI), and other variables included in the clinical prediction model to calculate the probability of ITP in a suspected patient (20,21).

The Predict-ITP tool trial will have the following two arms for patients suspected of ITP:

Arm 1: the Predict-ITP tool (Intervention arm)

Patients will receive care guided by the Predict-ITP tool. The clinical prediction model will mainly assist the hematology specialists in decision-making about investigations, treatment initiation, or alternative management strategies depending on the instrument results measuring the likelihood of ITP.

Arm 2: current ITP care (Control arm)

Patients will obtain habitual care. Hematology specialists will follow current clinical evidence protocols, clinical judgment, and existing diagnostic methods, without the influence of the Predict-ITP tool.

The difference between the study groups is that only the intervention arm uses the Predict-ITP tool. Regarding the final therapy decisions, it is important to note that they are at the discretion of the treating specialist. Additionally, we will monitor patients' symptoms and adverse events. To establish treatment response, we will also assess platelet counts regularly. To compare health outcomes and healthcare costs between the intervention and control groups, we will collect HRQoL data in the same manner for both arms. We will record corticosteroid exposure, medication use, emergency department visits, and hospitalizations to provide a complete picture of the impact of the Predict-ITP tool.

Alternative Study Designs

Alternative designs to the RCT may include case-control studies and cohort studies. Nonetheless, biases would occur, influencing conclusions. Case-control and cohort studies, which use observational methods, are descriptive, but they do not typically allow for group blinding. In case-control research, we may compare patients diagnosed with ITP (cases) to those who do not have the clinical condition (controls) to evaluate the accuracy of the Predict-ITP tool. Nevertheless, this design is susceptible to sampling bias. A retrospective cohort study is less time-consuming and less costly than a randomized controlled trial. However, it provides the researchers with minimum information on causality.

METHODS

Inclusion criteria: consecutive adults under investigation for thrombocytopenia referred to seven specialized hematology centres in Canada, including the McMaster University Medical Centre, with a platelet count of less than $100x10^9$/L, between January 1, 2025, and August 31, 2025, and willing to accept a follow-up period of two years.

Exclusion criteria: adults previously diagnosed with a hematological disorder or started any related treatment. Individuals with previous spleen surgery will be excluded. Also, patients on corticosteroid or immunosuppressive therapy for any other reason will be excluded.

Recruitment: convenience sampling with a consecutive approach will be performed for the initial recruitment of patients. Patients suspected of ITP referred to the hematology specialist will be screened and informed about the project. If agreed, patients will be contacted by a research coordinator in each centre regarding the inclusion and exclusion criteria of the study.

Visits to the emergency department derived from bleeding episodes are not included in this recruitment and sampling strategy. Despite emergency department visits being relatively infrequent (~0.03%) for ITP patients, this recruitment strategy will limit the generalizability of the study (22). Though, patients presenting with bleeding episodes may have varied blood platelet counts and different stages of

disease, which probably can be confusing for the emergency health care staff. Hence, this limitation in generalizability will be addressed by referring thrombocytopenic patients to the assigned hematology centre for a comprehensive consultation for potential study inclusion. Treatment adherence is another potential limitation. The use of a diary, online or physical, through text messages, and calls with periodic reminders will mitigate incomplete information collection regarding treatments.

Sample size: the primary outcome of the RCT is to measure changes in HRQoL over a two-year follow-up period using the EQ-5D-5L index scores. Therefore, we have calculated the sample size by comparing two means of those continuous outcomes. A scarcity of data is present on health-related quality of life among ITP patients, particularly when collected with the EQ-5D-5L. Nonetheless, the evidence has shown the EQ-5D index values for ITP individuals range from 0.79 to 0.82, standard deviations between 0.20 and 0.23, and minimum clinically significant differences ranging from 0.03 to 0.05 (18,19,23). Accordingly, assuming equal standard deviations in the two groups $\sigma1=\sigma2=0.15$, we used a power of 80%, a level of significance of 5%, and a difference between means of 0.04. We also considered a drop-out rate of 10%. With this information, we calculated 243 patients per arm sample size.

Sample size calculation

$$n = \frac{2\sigma^2(Z_{\alpha/2} + Z_{\beta})^2}{\delta^2}$$

Where:
n is the sample size per group
$Z\ \alpha/2$ is the critical value for a two-tailed test (1.96 for 5% significance)
$Z\beta$ is the critical value for 80% power (0.84)
σ is the standard deviation (SD) of EQ-5D-5L scores (0.15)
δ is the minimum clinically significant difference we want to detect (0.04)

$$n = \frac{(2)(0.15)^2\,(1.96+0.84)^2}{(0.04)^2}$$

$$n = \frac{0.3528}{0.0016}$$

n = 220.5 + 10% drop-out = 242.55 per group

Ethics and informed consent: selection and randomization process will not favour any particular sex, belief, or socio-economic group. Before participants sign the informed consent, a short informative form and discussions between the research coordinator in each centre and the participants will be conducted to increase and confirm patients´ comprehension of the entire study.

Additional information in plain language of the study protocol, study duration, supplementary testing required, and the opportunity to retire from the study at any time if wanted, will be explicit in the informative form. Finally, there will be an incentive for enrolled participants (labour hourly wage) compensating for the loss of working hours and reimbursement for transportation or parking expenses.

MEASUREMENT AND ANALYSIS OF OUTCOMES

We selected the HRQoL as the primary outcome over clinical or traditional endpoints. While outcomes such as platelet counts, bleeding episodes, and time to diagnosis are important to assess disease severity and natural ITP history, they may not fully capture the complexity and multidimensional burden that ITP may impose on patients' lives. For instance, platelet counts may not correlate with symptoms and how patients manage daily activities. In addition, bleeding episodes and time to diagnosis may be relevant for treatment purposes, but they do not accomplish the overall goal of improving patients´ quality of life.

HRQoL assessment offers valuable insights into the ITP care process by reflecting both the effectiveness of therapies and their impact on patients' daily activities. It also facilitates decision-making, encouraging ITP research into patient-centred care outcomes. Using HRQoL as the primary outcome, we align with current health care priorities and provide a meaningful perspective grounded in the patients' experiences. Over a two-year follow-up period, we will estimate the quality of life of selected patients, starting with baseline hematology consultation and every six-month control visit. The clinical rationale for using HRQoL measurements at various time points during ITP therapy is to provide a more reliable reflection of changes in health quality as ITP management evolves.

We will measure the primary outcome 12 months after randomization to observe a mid-term improvement in HRQoL. At this point, we will evaluate the influence of the Predict-ITP tool on health outcomes. With this approach, we will consider both first-line and part of the second-line treatment responses, including the potential need for invasive procedures such as splenectomy. By this time, patients may experience fewer bleeding events as per adjusted therapy schemes, lower hospitalization rates, and a decreased need for rescue therapies. In addition, by this time, patients may start to receive more targeted treatments, which could improve their daily activities and positively impact both physical and mental outcomes, leading to enhanced HRQoL outcomes. Previous (baseline and 6 months) and following (18 and 24 months) HRQoL measures will complete the assessment of life quality in patients suspected of ITP, comparing the impact of using the Predict-ITP tool with current clinical practice.

HRQoL can be measured through several instruments that have the ability to detect changes in health states. However, we have chosen the EuroQol's EQ-5D-5L tool because it is particularly useful as it offers a variety of country-specific value sets (14).

The patient will fill out the EQ-5D-5L tool (descriptive system and EQ visual analogue scale) through in person interview. To verify a complete understanding, the study coordinator or other health care professionals trained in the use of the

instrument will provide assistance. Paper-based and online methods are both available when necessary (14,15,24).

The following secondary outcomes will assess additional potential effects of Predict-ITP tool implementation. We will evaluate the cumulative dose—prednisolone equivalent—of corticosteroid exposure using CORTISER+, a validated web-constructed tool (25). This measure will also serve to establish a potential relationship between the cumulative dose and the occurrence of adverse events. An additional supplementary secondary endpoint will include the ITP Bleeding Scale. This scale will assess bleeding episodes at 11 anatomical sites: 9 by history and 2 by physical examination (26).

To mitigate reporting errors, clinicians will record tools' answers during consultations and follow-up visits, and research coordinators will screen for emergency room visits quarterly in an established Health Network database.

The effects of implementing the treatment protocol or requiring other therapy strategies may also produce potential harm outcomes to evaluate, such as nausea/vomiting, arthralgia/musculoskeletal pain, and headache (27). A record of adverse events and health service utilization will be available. The analysis will include the development of new symptoms.

The results will report the mean values, standard deviations (SD), minimum, median, and maximum scores of the EQ-5D index scores and EQ VAS scores for

both groups and by visit. Also, health changes over time (e.g., initial consultation, 6, 12, 18, and 24 months) will be available and presented as numbers, percentages, and averages by level of severity for the instrument dimensions. For advanced statistical analysis, a statistical software platform will be accessible.

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Appendix 9, Search strategy for review of quality-of-life studies. Available from: https://www.ncbi.nlm.nih.gov/books/NBK261553/

Chapter III – Supplementary materials

Appendix 1

Search strategy for quality of life in ITP patients *

#	Searches	Results
1	Purpura, Thrombocytopenic, Idiopathic/	7950
2	(((idiopathic* or immune* or autoimmune* or auto-immune*) adj (thrombocytopenia* or thrombocytopenic purpura*)) or (werlhof* adj disease*)).ti,ab,kf,kw.	13531
3	1 or 2	14909
4	limit 3 to yr="2009-Current"	7585
5	limit 4 to (humans and english)	5201
6	limit 5 to "all adult (19 plus years)"	2560
7	*quality of life/	117713
8	(sf6 or sf 6 or SF 6D or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.	3552
9	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab.	8056
10	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.	41
11	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab.	467
12	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.	31764
13	(euroqol or "euro qol" or "eq5d" or "eq 5d").ti,ab.	18136
14	(ITP Life Quality Index or "ILQI").ti,ab.	4
15	(hql or hqol or "h qol" or hrqol or "hr qol").ti,ab.	25666
16	health status indicator*.ti,ab.	460
17	"health related quality of living".ti,ab.	2
18	"health related quality of life".ti,ab.	61948
19	(patient* adj2 (preference* or satisfaction or acceptance)).ti,ab.	81771
20	(health adj ("state" or "status" or "states")).ti,ab.	84710
21	rating scale*.mp.	149868
22	linear scale*.mp.	545
23	visual analog*.mp.	87348
24	(categor* adj scale*).mp.	1098
25	or/7-24	538759
26	6 and 25	57

***** Modified from Loveman et al. *The clinical effectiveness and cost-effectiveness of ablative therapies in the management of liver metastases: systematic review and economic evaluation* – Appendix 9. Search strategy of quality-of-life studies (**28**).

Appendix 2

Two-components of a sample version of the EQ-5D-5L health questionnaire.

1. Descriptive system

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

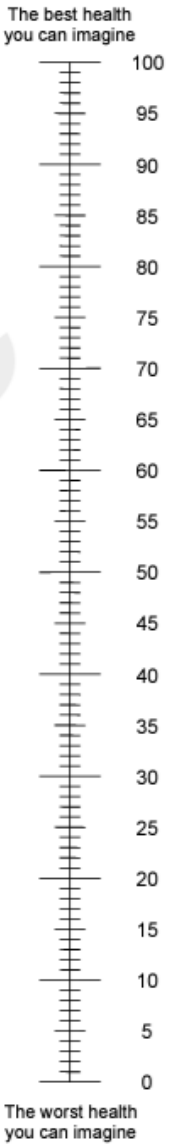
ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

2. Visual analogue scale

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



CHAPTER IV: Part C – Designing a health economic evaluation for the Predict-ITP tool trial

BACKGROUND

Due to the scarcity of resources, health systems around the globe use different methods to maximize the allocated funds for health care. To mitigate economic risk, economic evaluations help compare the health benefits and costs of different interventions. Cost-utility analysis (CUA) has gained reputation over the past decades in health care. It serves as a foundation for decision-makers to establish the more optimal option when deciding between alternatives, assessing both quantity and quality of life through quality-adjusted life years (QALYs). CUA enables the selection of an impactful health option with a reasonable economic effect and provides information to governments to facilitate resource allocation across different health care programs (1).

Dissimilar data about the diagnosis and treatment is available for ITP. Moreover, there is limited information about a holistic view of the patient's health status. This part of the study involves designing a health economic evaluation to inform stakeholders about the clinical and economic impact of implementing the Predict-ITP tool compared to current ITP care. In the present chapter, we are seeking to design a CUA from a public-payer perspective.

LITERATURE REVIEW

ITP is a condition with a broad range of clinical features and outcomes. Diagnosing this disease has resulted in a challenging task for clinicians. Lack of definitive diagnostic criteria or specific tests contributes to delayed diagnosis or misdiagnosis. These features of ITP may cause an important compromise in the lives of affected patients.

The quality of life in ITP patients may involve not only the physical health dimension but also several areas of life such as psychological, social, functional/independence, and even financial (2,3). Moreover, access to health care services and robust health care systems may play a central role in the treatment process. Health-related quality of life (HRQoL) evaluation serves as an instrument to assess clinical outcomes and is important for drug development (2). Validated HRQoL tools are relevant for valuing patient well-being and measuring the economic burden of interventions on health care systems. Nonetheless, this evidence on HRQoL is less than 10% of the ITP literature (4).

Both generic and specific tools are available to assess the quality of life of adults with ITP. These instruments evaluate different disease phases and treatments (5-10). In order to articulate these quality of life scores with economic analyses, it is crucial to measure health state utilities. For instance, using the EQ-5D and ITP-patient assessment questionnaire (ITP-PAQ), some researchers demonstrated HRQoL improvement in ITP patients using romiplostim (11).

Limited health-state-based constructed utility values for ITP patients are available to conduct health economic analyses (12). Health-utility estimation is challenging. Some concerns relate to establishing the right instrument, the frequency of assessments, the mode of administration, and data analysis. Nonetheless, several pricing, reimbursement, and health technology assessment agencies prefer using health-utility data collected directly from patients in clinical trials (13).

Existing ITP health economic literature is limited and has mainly evaluated ITP from a public-payer perspective. Some have examined ITP care cost components (14-16), while others have investigated IVIG impact (17) and second-line treatments´ economic burden, with particular interest in the most novel options and cost-effective treatment order (18-25). For instance, according to the U.S. health system perspective, Goshua et al. valued three second-line ITP therapies in 2020 US dollars (USD). They included thrombopoietin receptor agonists (TPO-RAs) (e.g., eltrombopag or romiplostim), rituximab, and splenectomy. Using the Markov model, these researchers developed a six-strategy cost-effectiveness analysis over a 20-year time horizon. The discount rate was 3% per year. They concluded that the treatment sequence starting with splenectomy followed by rituximab and then a TPO-RA agent is the most cost-effective option for patients with chronic primary ITP. However, therapies starting with TPO-RAs as the first or second sequential treatment did not represent a cost-effective strategy; they were more costly and less effective (dominated) or exceeded the willingness-to-pay threshold of $195 300 per QALY (18).

Currently, an evident absence of a comprehensive economic approach encourages the McMaster researchers to estimate the overall expenses associated with ITP care and the impact of a clinical prediction model implementation.

Cost-Utility Analysis and the Predict-ITP tool trial

We will use a cost-utility analysis (CUA) to compare the cost-effectiveness of Predict-ITP vs. the current ITP care. Quality-Adjusted Life Years (QALY) will help to assess the value of the Predict –ITP tool.

QALY combines quantity (length) and quality of life (derived from individuals' self-health-state evaluation) into a single health outcome measure. Death is equivalent to 0 QALYs, and perfect health is 1 QALY (26,27). For instance, if QALY is length of life in a determined health state (number of years of additional life) multiplied by quality of life valuated subjectively in the health state (HRQoL), a patient who lives 2 years with a quality of life of 0.8 would have gained 1.6 QALYs.

QALYs are essential in CUA to compare the cost-effectiveness of health interventions (e.g., benefits of using or not the Predict-ITP tool). They are also useful for public agencies and health care funding authorities, guiding decision-makers in assigning resources efficiently by comparing the incremental cost per QALY gained between interventions (26,27).

Incremental Cost-Utility Ratio (ICUR)

The ICUR helps to determine the cost-effectiveness of health interventions. It measures the additional cost incurred to gain one extra QALY, in this case, comparing the Predict-ITP tool group with current ITP care. The ICUR is the ratio of the difference in costs between two interventions to the difference in QALYs gained (26).

$$ICUR = \frac{(Cost_{A} - Cost_{B})}{(QALY_{A} - QALY_{B})} = \frac{(Cost_{\text{Predict-ITP}} - Cost_{\text{Current Care}})}{(QALY_{\text{Predict-ITP}} - QALY_{\text{Current Care}})}$$

Willingness-to-pay (WTP) thresholds

The WTP threshold is the maximum monetary value that an individual, society, or health care system are willing to pay for an extra unit of health gain. Interventions below the threshold are considered cost-effective (26). Thresholds vary by country. In Canada, the cost per QALY is approximately 50,000 Canadian dollars (CAD), as determined by the Canadian Drug Administration (CDA).

Cost-effectiveness acceptability curve

The cost-effectiveness acceptability curve (CEAC) compares the willingness to pay thresholds and the additional QALY gained to graphically represent the probability of a novel intervention being cost-effective (26,28).

STUDY DESIGN

The goal is to design an economic analysis measuring the health-related quality of life (HRQoL) of adults with thrombocytopenia referred to a specialized hematology centre in Canada, comparing the Predict-ITP tool to current ITP care (without the tool). Based on randomized controlled trial (RCT) data, we will validate the cost-effectiveness of the Predict-ITP tool through a cost-utility analysis. Trial-based cost-utility analyses (CUA) may represent an effective method for assessing the impact of the Predict-ITP tool. It will evaluate the quality of life and the value for money of this clinical prediction model compared to current clinical care (29).

ITP is a condition characterized by thrombocytopenia with different symptoms and treatment outcomes. Lack of standardization in the diagnostic process has led clinicians to develop several approaches to identify ITP (30,31). To find an accurate diagnostic method, McMaster researchers devised the Predict-ITP tool (32).

The lack of accuracy in diagnosis may lead to poor quality of life, as determined by unnecessary testing and inappropriate treatment. These factors may also increase costs for the health care system. The Predict-ITP tool has the potential to positively impact health outcomes and health system costs when making an ITP diagnosis at the first consultation (30,31).

The results of the Predict-ITP HRQoL trial and the costs obtained from ITP care will be the cornerstone data for the present health economic evaluation. Given the

rising health care costs and the resource scarcity in budgets worldwide, it is relevant to analyze not only health outcomes but also the cost-effectiveness of a novel health diagnostic tool for ITP care. This CUA will provide objective insights into the potential enhancement of patients' health outcomes and contribute to measuring the economic burden of ITP for a more efficient use of health care resources.

Alternative Study Designs

A cost-utility analysis (CUA) is the most appropriate type of health economic evaluation (HEE) for the proposed RCT, as it directly links the Predict-ITP tool, health-related quality of life, and costs, allowing for a comprehensive assessment of value. CUA also enables comparisons between health interventions and incorporates patients' preferences, which is crucial for patients and policymakers.

Alternative designs to the cost-utility analysis that are less appropriate for the study goal may include cost-effectiveness analysis, which focuses on a single clinical outcome rather than quality of life and does not allow for comparison across diseases. In addition, the cost-benefit analysis monetizes outcomes; therefore, it would be difficult to assign values to health quality of life improvements.

METHODS

We will enroll consecutive adult patients referred to a specialized hematology centre in Canada with a platelet blood count of less than $100x10^9$/L between January 1, 2025, and August 31, 2025. We will use a two-year within-trial time horizon. Adopting this time horizon, we will be reasonably sure that patients had a stepwise treatment with first- and second-line treatments, accounting for the possibility of exceptional access to TPO-RA agents via the provincial program. By that time, patients may have experienced the majority of investigations and therapies available for ITP.

We will adopt a cost-utility analysis approach from a public-payer perspective in Ontario, Canada. The investigations and therapies' costs will reflect the public-payer perspective. We will include costs and health outcomes relevant to the stakeholders. The costs reported in the study will be in 2024 Canadian dollars. The Bank of Canada Inflation Calculator will help to inflate prices for any services that are not available in 2024. A discount rate of 1.5% per year applies.

Cost resources will include the Ontario Physician and Laboratory Services Benefit Plan, the Ontario Drug List, the Ontario Regional Blood Coordinating Network, and direct communication with health care service providers. The Predict-ITP HRQoL trial will serve as the basis of cost estimation for patients suspected of ITP.

Answers derived from the EQ-5D-5L questionnaire will be used to calculate health utilities. We will track the concerns of patients suspected of ITP over time by measuring HRQoL scores at baseline and follow-ups at 6, 12, 18, and 24 months. Using comparative tests and regression analyses, we will evaluate the expected costs and quality-adjusted life years (QALYs). QALYs, cost per QALY, and incremental QALYs will be available.

Sensitivity analysis will incorporate uncertainty into the model parameters. Measurements of the cost-effectiveness acceptability curve (CEAC) will assess the cost-effectiveness of the Predict-ITP tool compared with not having the tool at different willingness-to-pay thresholds.

MEASUREMENT AND ANALYSIS OF OUTCOMES

Measurement of outcomes

A list of costs of ITP care services will be available. Patients will complete the EQ-5D-5L self-reported tool. The instrument's Visual Analogue Scale (VAS) will rate patients' health state on a scale of 0 to 100. The descriptive component of the EQ-5D-5L tool will evaluate five dimensions of health: mobility, self-care, undertaking usual activities, pain and discomfort, and anxiety and depression. The five-level assessment will include reporting for each dimension: no problems, slight problems, moderate problems, severe problems, and unable or extreme problems (33,34).

Responses derived from the descriptive component and the appropriate value set for Canada will provide the index values or utility scores. These scores will consist of mapping health states through the combinations of numbers gathered from responses, valuing each level for each dimension assessed. We will use the corresponding coefficients from the Canadian value set to convert health states into a health utility score. Hence, the value set will assign a utility score to each health state based on the patients' preferences. We will deploy the utility score calculations based on the EQ-5D-5L answers at multiple time points, starting with the initial hematology consultation and every six-month visit over a two-year period. This six-month periodicity aligns with the established ITP registry follow-up scheme.

Using this approach, we can observe HRQoL changes perceived by patients over time due to the natural history of the disease, as investigations and treatment progress.

We will also calculate Quality-Adjusted Life Years (QALYs) by integrating both quality and quantity of life as a single index health outcome measure, which estimates the value of medical interventions. To calculate a QALY, we multiply the Canadian value set for the EQ-5D-5L utility, ranging from −0.148 (for health state “55555”) to 0.949 (for health state “11111")—by time spent in a specific health state. This metric allows for objectively quantifying the overall burden and potential benefits of implementing the Predict-ITP tool compared with no tool in patients suspected of ITP (35).

We will use the utility scores, derived from the EQ-5D-5L questionnaire at baseline hematology consultation and at each follow-up visit (6, 12, 18, and 24 months), to model transitions between health states and determine the QALY over a two-year follow-up period. This longitudinal approach, over a two-year time horizon, estimates variations in health states over time, accounting for the chronicity and sometimes the changeable nature of the disease. Evidence suggests that evaluating HRQoL at multiple time points is crucial to observe the progression of a clinical condition, treatment responses to different classes of therapies, and long-term outcomes, particularly in chronic diseases such as ITP (36,37).

Analysis of outcomes

The data summary will display participants' characteristics, including age, sex, initial, follow-up, and minimum platelet counts. Means, medians, standard deviations, and ranges of the EQ-5D tool utility scores and QALYs will show complete descriptive statistics. Figures, graphs, and percentages will inform each dimension and level of the problem at initial consultation and follow-up visits in months 6, 12, 18, and 24, providing evidence of change during a 2-year period.

We will conduct comparative analyses between intervention groups at the above-mentioned time points during a 2-year period (e.g., difference of means of EQ-5D scores and QALYs between the intervention and control group) and variations in time of the EQ-5D scores.

A mixed-effects model will be employed. This method evaluates grouped or repeatedly non-independent observations over time. It includes fixed and random effects. Fixed effects are consistent across all participants (e.g., time points), whereas random effects account for individual variations (e.g., differences in treatment response or disease severity). By applying a mixed-effects model, we can observe longitudinal changes in health outcomes and costs, which may fluctuate with disease progression while accounting for time-dependent variability. This approach provides more accurate estimates of QALYs and ICUR over the entire study period. Evaluating individual time points separately (e.g., more pronounced HRQoL improvements during the first six months) may fail to notice

important trends, such as gradual improvements or declines, which are critical in the management of chronic conditions like ITP. The mixed-effects model improves intra-subject correlation, handling repeated observations for each patient. Furthermore, it also accommodates missing data, allowing participants to remain in the study even if some follow-up information is missing (34,38).

Variables that may influence the project outcomes (HRQoL and economic outcomes) and the factor under study (Predict-ITP tool implementation vs. current care) include age, disease severity, and baseline health status. Aged patients may experience increased healthcare service utilization and more susceptibility to complications. Disease severity (e.g., platelet counts and bleeding events) may influence not only HRQoL but also resource utilization, impacting treatment approaches (e.g., urgent care vs. stepwise management). Baseline health status, including comorbidities and their treatments, can also affect both HRQoL and resource use. We will perform linear and multivariate regression analyses to adjust these confounders. We will assess whether the Predict-ITP tool has different effects among patients' subgroups.

The cost-utility analysis will include the Incremental Cost-Utility Ratio (ICUR) calculation. We will deploy the ratio of the difference between the costs and outcomes of the proposed intervention groups. We will use the analysis of covariance, or ANCOVA, to evaluate changes in HRQoL assessment in time

(baseline, 6, 12, 18, and 24 months) and bootstrapping to estimate confidence intervals for the ICUR to address statistical uncertainty (34).

Data presentation through different modalities will include a health profile and index value. We will use the Paretian Classification of Health Change (PCHC) to compare a participant's health state over time. The approach is based on Pareto improvement principles. It consists of the comparison of participants´ health states at two time points. A patient classification involves the following states: "better" (showing improvement in at least one dimension of the EQ-5D-5L without deterioration in any other dimension), "worse" (exhibiting decline in at least one dimension with no improvement in others), "mixed" (showing both improvement and worsening in EQ-5D-5L dimensions), or "unchanged" (33).

The EQ-5D-5L index value set for Canada will report health utilities assigned to specific states of health. This index score will allow researchers to calculate the quality-adjusted life years (QALY) (24,34). We will adhere to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) recommendations for reporting quality and consistency (39). We will also ask for advice from patients, clinicians, academics, decision-makers, and policymakers. The stakeholder's engagement will enrich the study clinically and provide meaningful health and economic insights.

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Chapter IV – Supplementary materials

Appendix 1

Search strategy for health-related quality of life and health economic evaluation *****

#	Searches	Results
1	Purpura, Thrombocytopenic, Idiopathic/	7966
2	(((idiopathic* or immune* or autoimmune* or auto-immune*) adj (thrombocytopenia* or thrombocytopenic purpura*)) or (werlhof* adj disease*)).ti,ab,kf,kw.	13559
3	1 or 2	14937
4	limit 3 to yr="2009-Current"	7613
5	limit 4 to (humans and english)	5222
6	limit 5 to "all adult (19 plus years)"	2572
7	Economics/	27534
8	Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/	20069
9	cost effective*.tw,kw,kf.	190517
10	(cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	255663
11	Monte Carlo Method/	32981
12	exp "Cost"/	271228
13	(cost or costs or costing or costly).ti.	138558
14	(decision adj1 (tree* or analy* or model*)).tw,kw,kf.	29876
15	(markov or markow or monte carlo).tw,kw,kf.	88008
16	Quality-Adjusted Life Years/	16516
17	(QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf.	40084
18	((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf.	84775
19	or/7-18	695674
20	*quality of life/	118381
21	(sf6 or sf 6 or SF 6D or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.	3560
22	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab.	8076
23	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.	41
24	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab.	467
25	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.	31867
26	(euroqol or "euro qol" or "eq5d" or "eq 5d").ti,ab.	18275
27	(ITP Life Quality Index or "ILQI").ti,ab.	4
28	(hql or hqol or "h qol" or hrqol or "hr qol").ti,ab.	25805
29	health status indicator*.ti,ab.	461
30	"health related quality of living".ti,ab.	2
31	"health related quality of life".ti,ab.	62230
32	(patient* adj2 (preference* or satisfaction or acceptance)).ti,ab.	82166
33	(health adj ("state" or "status" or "states")).ti,ab.	85014
34	rating scale*.mp.	150304

35	linear scale*.mp.	547
36	visual analog*.mp.	87727
37	(categor* adj scale*).mp.	1099
38	or/20-37	540957
39	6 and 19 and 38	19

***** Modified from Brittenden J, Cotton SC, Elders A, et al. Clinical effectiveness and cost-effectiveness of foam sclerotherapy, endovenous laser ablation and surgery for varicose veins: results from the Comparison of LAser, Surgery and foam Sclerotherapy (CLASS) randomised controlled trial (40)

CHAPTER V: Discussion and conclusions in designing the Predict-ITP tool economic impact project

DISCUSSION

The McMaster ITP registry is an important source of data on thrombocytopenic patients under investigation for ITP in Canada. According to the pulled information in the ITP registry, patients diagnosed with ITP epidemiologically have similar characteristics to those reported in the literature: an increasing incidence after age 50, resulting in a growing prevalence in older adults (1). However, the female and male proportions in the selected population did not coincide with the evidence.

In general, ITP is considered a chronic condition with a non-predictable course. It has mild-to-life-threatening manifestations. Hence, diagnosing ITP is challenging. At some point during their condition, misdiagnosis may be present in up to 12% of patients suspected of having ITP (2). Methods to improve accuracy in diagnosis have arisen. One of those is the use of a clinical prediction model (CPM), the Predict-ITP tool, which combines clinical and laboratory features. The Predict-ITP tool results are promising; however, they are currently under external validation.

ITP care encompasses clinical and economic factors. Understanding the costs associated with ITP care is critical for evaluating the impact of emerging treatments and developing health care policies to allocate resources effectively (3). Cost analyses normally underestimate laboratory tests, bone marrow studies, imaging,

blood transfusions, and even several first- and second-line treatments. The available literature mainly focuses on the most recent therapies because of their enhanced effectiveness (having the intended effect) and tolerability compared to the existing medications.

The cost drivers of ITP care during 2018 for patients enrolled at the McMaster ITP registry were mainly TPO-RA agents, hospitalization, and IVIG. This aligns with the available evidence. Patients on TPO-RA agents' treatment (e.g., eltrombopag or romiplostim) showed an augmented mean cost of ITP care when compared to the average patient care cost ($76,828.48 vs. $4,181.84). In addition, individuals who underwent IVIG treatment displayed an increased overage cost of ITP care by more than five times when compared to the average cost of a patient in the cohort ($22,405.79 vs. $4,181.84). Similarly, hospitalized patients exceeded the mean cost of the cohort more than twice ($8,965.41 vs. $4,181.84).

Absolute costs varied considerably among the populations studied. This difference was particularly evident in patients on TPO-RA agents or IVIG compared with patients managed with different treatment approaches. This data also showed that one patient on romiplostim represented more than one third of total cohort expenditure during the studied period. In addition, the hospitalization services and IVIG use are significant costs of ITP management. Eltrombopag and rituximab also contributed significantly to the overall patients' treatment costs. Additional information is available in Table 1.

Percentage (%)	Cost (CAD)	Description
57,01	$ 178.820,36	Total second-line therapies
18,21	$ 57.105,00	Hospitalization
13,20	$ 41.399,01	Total first-line therapies
4,11	$ 12.900,00	Consultations
3,80	$ 11.911,70	Investigations
1,72	$ 5.383,80	ED visits
1,02	$ 3.198,96	Follow-ups visits
0,74	$ 2.311,01	Medications/blood components administration
0,19	$ 608,00	Blood components
100,00	**$ 313.637,84**	**Total Cohort Cost**

Table 1. Percentages and total ITP care costs by group for the studied population.

The Predict-ITP tool implementation in a RCT may provide a meaningful impact for the ITP diagnosis and treatment, focusing particularly on health-related quality of life. By addressing the complexity of ITP, the Predict-ITP tool can help clinicians measure the patient likelihood of having ITP, resulting in earlier and more accurate diagnosis, decreased health care service expenditure, and better health outcomes with the potential implementation of individualized treatment strategies.

Traditional endpoints in ITP studies normally concentrate on clinical parameters, such as blood platelet counts and bleeding events. However, the goal of this study is to reflect the broader and multidimensional impact of ITP by evaluating the disease beyond clinical markers while incorporating patient-centred outcomes through HRQoL. An early and accurate diagnosis of ITP allows for better treatments. Discarding ITP with the clinical prediction model, a patient may have controlled exposure to medications (e.g., corticosteroids, rescue medications, and TPO-RA agents), as well as potentially avoid splenectomy. Consequently, the Predict-ITP tool may help reduce the occurrence of adverse events and mitigate

the potential harmful effects of ITP treatment. The Predict-ITP tool, by accurately identifying ITP early, may reduce delayed diagnosis, misdiagnosis, unnecessary testing, and inappropriate treatments, alleviating not only disease burden for patients but also financial issues for health care systems. The comparison of quality-adjusted life-years and costs between the Predict-ITP tool and current ITP care through a cost-utility analysis will provide a broader picture of whether the clinical prediction model represents a good value for money. With a rising interest in cost-utility analysis in health care organizations, the findings in the present study will be useful for decision-makers, policymakers, and health technology assessment bodies in performing evidence-based judgments about ITP care management.

Limitations

The McMaster ITP Registry is a valuable resource that includes patients referred to the McMaster University Medical Centre under investigation for thrombocytopenia. However, we performed chart reviews when data entry errors or information deficiencies occurred while collecting data from the registry. We standardized the treatment doses for a 70-kg patient with ITP. In addition, for patients in ongoing treatment without stop dates, we assumed treatment duration as the earliest start date until the end of the study follow-up period (December 31, 2018), where medication indications supported this decision. Additionally, we made assumptions regarding nursing infusion time and use of standard infusion materials.

When determining the cost of ITP, we included a small sample size (n = 75) that may limit generalizability and impact the precision of health economic evaluations. Potential limitations are inherent to the population. The inclusion of patients with different management backgrounds, varied treatment timings, discrepancies in baseline blood platelet counts between diagnostic approaches, and the follow-up periods are limitations to evaluating the cost of ITP care. Nonetheless, this report offers a framework to determine the economic impact of ITP on health care systems.

To evaluate the impact of using the Predict-ITP tool, we proposed a randomized controlled trial (RCT), a study design that identifies clinically meaningful outcomes.

Even so, RCTs may exhibit limitations related to patients' perceptions and instrument restrictions when measuring health-related quality of life (HRQoL) aspects in patients with ITP. The EQ-5D-5L tool's validity is tight to generic quality of life aspects, lacking disease-specific elements of ITP, such as bleeding symptoms or fatigue. Hence, the instrument may collect partially the clinical context of patients with ITP. Moreover, HRQoL is subjective, and patients may interpret the EQ-5D questions differently, challenging the investigators to obtain consistent data to overcome the variability. Furthermore, heterogeneous variables may be present among the participants, and they include sex, age, baseline health states, disease severity, comorbidities, therapy history, and treatment exposure.

To address these limitations, we will explain to patients the project in detail, guide the participants through the entire study, apply a blinded and randomized process, calculate a convenient sample size, and stratify the analysis based on key patient characteristics (e.g., age, comorbidities, disease severity). A subgroup analysis can provide significant insights into the differential impact when implementing the tool.

The health economic evaluation is a cost-utility analysis (CUA), which will evaluate the benefits and costs of employing the Predict-ITP tool. Based on a randomized controlled trial (RCT), this analysis can provide relevant information about the value of implementing the Predict-ITP tool to assess quality of life in patients suspected of ITP. Nonetheless, there may be limits to this CUA, such as variability in health

outcomes and costs, and the lack of indirect cost estimation (e.g., productivity loss, caregiver burden). To address these constraints, first, we will adopt a mixed-effects model for QALYs and ICUR throughout the trial. To address another potential issue, we will include seven hematology centres across Canada to evaluate different healthcare settings and cost scenarios. Additionally, we will include incentives for enrolled participants (including hourly wage compensation and reimbursement for parking and transportation expenses) to assess potential productivity losses and out-of-pocket costs associated with ITP care.

Implications for clinical practice and knowledge translation

This project will describe the cost impact of the Predict-ITP tool for adults with ITP-suspected. Current clinical treatments for this disease include multiple tests, the use of different drugs (such as corticosteroids, biologics, immunosuppressants, thrombopoietin receptor agonists, etc.), and even surgical removal of the spleen. However, not all patients need treatment. It is evident that understanding ITP has continued to advance. Nonetheless, clear diagnostic criteria for ITP are not available yet.

Implementing the Predict-ITP tool in real-world settings to measure the impact on the quality of life may be crucial to conveying these findings to clinicians, scientists, policymakers, and payers. Stakeholders may use this data to make informed decisions during ITP attentions, advocate for evidence-based policies, and offer improved insights for budget allocation. Health care providers focusing on patient-centred outcomes may reduce a potential overuse of investigations and therapies.

Establishing the potential generalizability of a new ITP treatment protocol may require additional research. Nonetheless, this study will contribute to ITP clinical practice adjustments and raise awareness about the necessity of a holistic view of the patient's health status for those with a chronic condition. There may be updates to the current management guidelines for patients with ITP. A cost-utility analysis will begin alongside the RCT study. Enrolled patients will receive a copy of the final

report in non-technical language, as will clinicians and staff involved in the study. Publication of findings in professional journals and presentations at hematology society venues will disseminate new knowledge and encourage its application. Conversely, if HRQoL improvement is absent, current practice guidelines may remain unchanged, and future research may also focus on novel diagnostic and management options.

CONCLUSIONS

Implementing a more accurate and timely ITP diagnosis may reduce the health care resource utilization. Delivering ITP-targeted treatments promptly, guided by earlier diagnoses, can improve health outcomes, life quality, and economic efficiency. The present analysis may demonstrate that the longer the therapy, the more costly and potentially harmful the ITP treatment could be. Accordingly, as patient treatment strategies advance from newly diagnosed to chronic conditions, the cost of those medical technologies used increases. Furthermore, the use of medications such as TPO-RA agents and IVIG can significantly increase the cost of treating ITP. Hospitalizations and rescue therapy may also be considered major sources of ITP care costs. The implementation of the Predict-ITP tool, during its internal validation, demonstrated a substantial use reduction—by more than 50%—of ITP treatments (4). This is a particularly relevant finding because treatments may account for up to 70% of ITP care expenditure, as evidenced in this cost analysis. Therapies that reduce hospitalizations, prolonged natural disease course, and rescue treatment utilization will positively impact patients' lives and ITP's economic burden.

Overall, financial sustainability of health care systems, patients' quality of life, cost-effectiveness of treatments, and medication toxicity are some current issues across nations worldwide. The costs elicited in the present project represent the input for

the cost-utility analysis of the Predict-ITP tool. This data offers the opportunity to understand in more depth the complexity of the ITP diagnostic and therapeutic processes. The analysis of patient-centred outcomes can benefit patients, clinicians, decision-makers, and policymakers by providing better health insights and supporting the routine use of the Predict-ITP tool. This project may also demonstrate a reduction in ITP care costs by using the Predict-ITP tool, which potentially would optimize resource allocation and budget planning.

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Chapter VI: Research concepts and application to the project

I. RANDOMIZATION

It is a process that ensures each participant in a clinical trial has an identical allocation opportunity among the study groups. Randomization serves to compare clinical interventions, mitigating selection bias through an even distribution of patients' characteristics between the randomization groups (1,2). Hence, observed similarities and differences between individuals correspond exclusively to their own characteristics, needs, and clinical backgrounds.

Potential project's implications

Randomization plays a crucial role for the project, as it minimizes bias, balancing baseline characteristics, and preventing selection bias. It also contributes to ensuring the comparability of groups by distributing evenly between groups known and unknown factors (1).

For the proposed RCT, the randomization process, using a computer-generated algorithm, will assign patients to either the Predict-ITP tool arm or the current care arm. This will ensure that the differences in HRQoL, medication use, and healthcare expenditures are due to the intervention (the Predict-ITP tool) rather than sex, age, and any other prognostic baseline characteristics (2).

Multicentre RCT logistics in the HRQoL trial design

The research coordinators will oversee the logistics of randomization at each hematology centre. Nonetheless, a coordinating research team will manage the process centrally to maintain uniformity across centres. They will ensure adherence to the randomization protocol, handle technical issues, and monitor timelines (2).

The data management team using a computerized algorithm will randomize patients centrally. This approach will minimize variability across hematology centres. We will use a web-based and protected system, ensuring group allocation concealment and preventing bias during the process (2).

Hematologists in the intervention arm will implement the Predict-ITP tool. They will receive comprehensive training on the tool to ensure its consistent application and accurate interpretation of results across centres. Hematologists will also use the Predict-ITP tool results for decision-making regarding investigations, treatment initiation, or alternative management strategies. Other healthcare professionals may use this information, depending on the disease severity, if necessary.

We will use the Predict-ITP tool's results to enrich clinical workflows, refining diagnosis and treatment plans. For patients with a low probability of having ITP, the clinical prediction tool will provide information to reduce the use of unnecessary

therapies, potential medication toxicity, and healthcare costs. For patients with a high probability of having ITP, the tool will support early diagnosis and the initiation of appropriate and targeted treatments. In general, the Predict-ITP tool's outputs will document decision-making pathways for prospective evaluation of its impact on HRQoL and economic outcomes.

II. CONTAMINATION

It is a process by which the effects of the intervention also affect individuals in the control group, diluting the observed outcome (2).

Potential project's implications

Contamination could lead to underestimating the tool's impact. It may occur if hematologists treating patients in the control group have access to and apply insights from the Predict-ITP tool or if individuals share communication between arms.

To address these issues, we will train clinicians and deploy secured and strict access to the Predict-ITP tool, ensuring exhaustive adherence to protocol. We will also schedule patients on different days depending on the intervention group (e.g., Predict-ITP tool vs. no tool).

III. BLINDING

It refers to concealing the allocation of participants to intervention arms. Single blinding occurs when only patients are unaware of which intervention group they are in. Double blinding adds concealment to both patients and researchers involved in outcome measurement. Triple blinding extends not only to participants and researchers but also to those staff who manage logistics or analyze study data (2).

Potential project's implications

For the present project, clinicians will know they are using the Predict-ITP tool for making management decisions. However, participants and other staff—such as research coordinators, statisticians, and anyone who makes measurements and adjudicates outcomes involved in the study—might maintain blindness.

To mitigate potential blinding issues, all staff contributing to the project can maintain separate data collection teams to mitigate unintentional bias. Additionally, electronic surveys may limit interactions between participants and research coordinators.

IV. FUNDAMENTALS OF SAMPLE SIZE CALCULATION

The sample size aims to estimate the number of individuals needed to detect a statistically significant effect. The anticipated effect size, variability, significance level (α), and statistical power (1 – β) are key factors in calculating sample size. An adequate sample size is crucial because not enough participants (underpowered) may prevent researchers from detecting the intervention's effect, while more participants than needed (overpowered) can lead to unnecessary use of resources (2,3).

Potential project's implications

The primary outcome of the RCT is to determine differences in HRQoL over a two-year follow-up period. Therefore, the sample size should consider the expected changes in HRQoL and the identification of significant differences in QALY gains.

To address potential issues in sample size, we reviewed existing literature on HRQoL evaluated through the EQ-5D-5L tool in patients with ITP diagnosis. Another option was to conduct a pilot or feasibility study, which could provide preliminary data to test methods and verify assumptions regarding the variability of EQ-5D-5L index scores and the expected effect size.

Key components in the RCT sample size calculation

1. **Effect size (δ)**: It represents the minimum clinically significant difference in the EQ-5D-5L index scores that the study aims to detect. Based on the literature, a difference of **0.04** is considered clinically meaningful.
2. **Statistical parameters**:
    a. **Level of significance (α)**: Set at 5% (0.05) for a two-tailed test, this means that the study has a 5% probability of rejecting the null hypothesis when it is true (Type I error). The critical value for a 5% significance level in a two-tailed test is **1.96**.
    b. **Power (1 – β)**: Set at 80%. This means that there is an 80% chance of correctly detecting a difference between groups if one exits. The critical value is **0.84**.
3. **Variability (σ)**: The standard deviation (SD) of the EQ-5D-5L index scores is estimated at **0.15** based on the ranges of the ITP population. We assumed equal variability in both groups ($\sigma_1 = \sigma_2 = 0.15$).
4. **Drop-out rate**: It is estimated an additional **10%** of participants to account for potential loss of follow-up during to maintain the study adequately powered.

Sample size calculation

$$n = \frac{2\sigma^2(Z_{\alpha/2} + Z_{\beta})^2}{\delta^2}$$

Where:

n is the sample size per group
$Z\ \alpha/2$ is the critical value for a two-tailed test (**1.96** for 5% significance)
$Z\beta$ is the critical value for 80% power (**0.84**)
σ is the SD of EQ-5D-5L scores (**0.15**)
δ is the minimum clinically significant difference we want to detect (**0.04**)

$$= \frac{(2)(0.15)^2\,(1.96+0.84)^2}{(0.04)^2}$$

$$= \frac{0.3528}{0.0016}$$

= 220.5 + 10% drop-out = 242.55 per group

= 486 participants for the RCT

The standard deviation (0.15) is consistent across intervention groups and reflects the variability when measuring HRQoL in the ITP population, ensuring an accurate picture of data dispersion. A clinically significant difference of 0.04 aligns with available evidence (4-6), providing an important benchmark for identifying changes. Finally, we anticipate a 10% drop-out rate due to the close follow-up of patients enrolled at various specialized hematology centres across Canada.

V. QUALITY ADJUSTED LIFE YEARS (QALY)

In health economics, QALY is a metric that quantifies the value of health outcomes, exploring both quantity and quality of life for a given patient. A QALY represents one year in perfect health. QALY is the arithmetic product of the duration of a health state and its utility value, derived from an HRQoL instrument such as the EQ-5D-5L.

Potential project's implications

QALY is a key component in the health-economic evaluation. The Predict-ITP tool aims to reduce adverse events and healthcare expenditure. It may also improve HRQoL, contributing to higher QALY in the intervention arm. In this project, QALYs obtained from the EQ-5D-5L tool will estimate the HRQoL improvements associated with the use of the Predict-ITP tool. The importance of QALY lies in its need for the incremental cost-utility ratio (ICUR) calculation. By incorporating QALY, the ICUR captures the benefits of the Predict-ITP tool in terms of improving HRQoL and increasing life expectancy.

The ICUR is the ratio of the difference in costs between two interventions to the difference in QALYs gained (7). It measures the additional cost incurred to gain one extra QALY. The ICUR will help to determine whether the Predict-ITP tool offers good value for money by comparing its cost per QALY gained against the

established willingness-to-pay threshold, which for Canada is $50,000 per QALY. In summary, the ICUR calculation will serve to assess whether the Predict-ITP tool offers a cost-effective improvement in HRQoL for patients suspected of ITP over a two-year follow-up. If the Predict-ITP tool improves outcomes for ITP patients (e.g., reducing medication toxicity, lowering healthcare expenses, shortening time to diagnosis, and enhancing HRQoL), the resulting QALY gains will strengthen the ICUR. This may support the implementation of the Predict-ITP tool in clinical practice.

VI. CLUSTER RANDOMIZED TRIALS (CRTs)

It is an alternative randomized trial design. In a cluster randomized trial, investigators randomly assign groups or clusters of participants to the intervention and control arms rather than individuals. CRTs are particularly useful when interventions take place at the group level (2).

Potential implementation as an alternative design

In this project, a cluster-randomized design would define each hematology centre as a cluster. As randomization would occur at this level, each centre would be in either the Predict-ITP tool arm or the current care arm.

A CRT design offers several advantages. First, it reduces contamination by ensuring all clinicians within a hematology centre adhere to the same protocol (e.g., the Predict-ITP tool vs. no tool). Additionally, it closely reproduces the real-world implementation of the Predict-ITP tool in clinical practice. Finally, it facilitates operational procedures and logistics by allowing training and protocol standardization at each hematology centre. This may reduce variability in the tool's implementation.

Nonetheless, practical challenges may arise. The number of participants can vary across centres, affecting the accurate assessment of the Predict-ITP tool's true effect. To address this issue, researchers should balance the number of clusters per arm and the cluster sizes. Additionally, variations in infrastructure, patients' demographics, and clinicians' expertise across centres could influence the tool application and its measurements.

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