

# Cost Analysis of Platelet Transfusion in Italy for Patients with Chronic Liver Disease and Associated Thrombocytopenia Undergoing Elective Procedures

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**Purpose:** Platelet transfusions (PT) are commonly used as prophylaxis in patients with chronic liver disease (CLD) and severe thrombocytopenia (TCP) before invasive procedures, in order to reduce risk of bleeding. The aim of this cost analysis was to generate a comprehensive estimate of costs of platelet transfusions in Italy, focusing on patients with severe TCP due to CLD undergoing an elective procedure.

**Methods:** The research was conducted in different phases: 1) assessment of a pre-specified framework for the identification of processes related to PT; 2) estimation of resource consumption through Delphi technique and collection of unit costs through literature; 3) development of a cost analysis to estimate the overall average costs per PT, focusing on a representative patient with CLD and severe TCP. Robustness of results was tested in a sensitivity analysis.

**Results:** Despite the lack of some cost components estimation and uncertainty related to event probability, the analysis showed a total cost of 5297 € for each PT in patients with CLD and severe TCP. The total cost was largely driven by direct costs (4863 €) associated with platelet collection, transfusion, and management of refractoriness, which accounted for 92% of total.

**Conclusion:** In an environment of limited resources, it is crucial for the healthcare service to have accurate and inclusive information on transfusion costs, incorporating not only the cost of blood products but also those related to collection and management. The analysis showed that platelet collection and administration costs add substantially to the cost of platelet products themselves. As expected, the highest cost was the transfusion process itself (44% of total), followed by refractoriness (43% of total). Since limited literature exists concerning these cost estimates, this analysis represents a step forward in understanding the economic burden of patients with CLD and severe TCP scheduled to undergo an invasive procedure.

**Keywords:** cost analysis, chronic liver diseases, transfusions, platelet concentrates, TPO-RA, pharmacoeconomics

## Introduction

Chronic liver disease (CLD) is a long-term disease that can lead to progressive and irreversible liver damage with consequent gradual substitution of healthy tissue with fibrotic tissue. Overall CLD prevalence in Italy is estimated to be around 4.5% of the population, with more than 2,3 million people affected.<sup>1,2</sup> Severe thrombocytopenia (TCP), defined as a platelet count (PLT CT)  $< 50 \times 10^9/L$ , is one of the most frequent complications encountered in patients with advanced CLD, occurring in 14% of people suffering from cirrhosis in Italy.<sup>3</sup> Severe TCP represents a clinical challenge for patients who need to undergo invasive surgical procedures,<sup>3</sup> as the low platelet count increases the risk of hemorrhage or severe bleeding with a consequent delay or even cancellation of the elective procedure, which poses a significant burden on patients' health and quality of life.<sup>4</sup> Moreover, patients with TCP require significantly greater medical care than CLD

patients without TCP, due to increased laboratory tests, outpatient and emergency room visits, as well as more frequent hospitalizations.<sup>5,6</sup>

Currently, for patients who need to undergo invasive surgical procedures, in the absence of specific therapies for CLD and severe TCP, the circulating platelet pool is restored through the infusion of platelet concentrates (PCs). PCs are blood-derived preparations containing a high number of platelets obtained from the processing of donated blood, which are commonly used as prophylaxis before an invasive surgical procedure in patients with CLD and severe TCP to reduce the risk of bleeding. The current consensus is that patients should receive a platelet transfusion (PT) in the perioperative phase when the number of platelets falls below  $50 \times 10^9/L$  of blood.<sup>7</sup>

In Italy, transfusion activities are part of the Italian National Health Service (*Servizio Sanitario Nazionale*, SSN). Transfusions are guaranteed as part of the “Health Benefit Basket” (*Livelli Essenziali di Assistenza*, LEA). Blood can be donated at Blood Transfusion Services (BTS) located at hospital transfusion centers or at blood transfusion units run by various associations of volunteers (eg, AVIS - *Associazione Volontari Italiani Sangue*, FIDAS - *Federazione Italiana Associazioni Donatori Di Sangue*), which supply hospitals daily or weekly with blood components.<sup>8</sup>

There are many issues related to the transfusion of platelets such as limited efficacy, transfusion reactions (from 5 to 31%), along with difficulties in terms of collection, processing, testing and storage requirements, possibly leading to platelet wastage.<sup>9–11</sup> Due to these aspects, which are not well quantified in the Italian literature, the resource consumption and healthcare expenditure associated with transfusions can be substantial, especially for patients with CLD and severe TCP who might undergo several invasive surgical procedures and that, in the absence of alternatives or specific pharmacological treatments, require platelet transfusions.<sup>12</sup>

To date, the full cost of PT in Italy is not well documented in the literature. The objective of this study is to estimate both direct and indirect costs of PT in the Italian context, with a focus on patients with CLD and severe TCP, undergoing an elective procedure.

## Materials and Methods

The study was developed in four steps: conceptual framework evaluation, resource consumption estimate, unit cost collection and the development of a cost analysis model. The economic burden associated to platelet transfusions in Italy for patients with CLD and severe TCP undergoing elective procedures was estimated considering both direct costs (ie, blood components, laboratory tests and visits, transport of blood components, time of hospital staff, delayed procedure, and hospital-acquired infections - HAI - for refractoriness onset) and indirect costs (ie, loss of productivity for donors and patients).

### Conceptual Framework Evaluation

In order to identify all relevant direct and indirect costs associated with platelet collection, transfusion, refractoriness occurrence and related resource consumption, the conceptual framework originally developed by Barnett et al 2018 for the United States context and described elsewhere<sup>5</sup> was considered and adapted to the Italian landscape. Specific information related to the management of platelet transfusions in Italian clinical practice were mainly retrieved from the Istituto Superiore di Sanità report (ISTISAN) by Catalano et al 2020 in which national level data regarding the Italian blood system are systematically and annually collected from “*Sistema Informativo dei Servizi TRAsfusionali*, SISTRA”.<sup>13</sup>

### Resource Consumption

Based on the premise that a group opinion is more valid and reliable than individual opinion,<sup>14</sup> a Delphi process was used to collect information and insights regarding the resources spent on platelet transfusion, transportation and monitoring in the Italian context.

In the Delphi method the participants share their opinions anonymously over several rounds of survey. The method encourages participants to review their responses and to take into consideration those aggregated of the other participants, while avoiding forced consensus which can drive experts to have conformist opinions due to peer influence.<sup>15</sup> This method has four mandatory characteristics: (i) iteration of the process, which allows participants to revise their answers without being influenced by others in the group; (ii) controlled feedback, provided by impartial facilitators that inform the group members of the opinion of their peers; (iii) statistical aggregation, which can be presented numerically and/or graphically; (iv) anonymity of the individual responses,

which avoids social burden.<sup>15–20</sup> The Delphi process was carried out with a panel of 6 stakeholders (two transfusion nurses and three transfusion nurse coordinators in hematology and transfusion wards, one gastroenterologist expert of CLD) coming from three different regions of Italy (Lombardy, Lazio, Puglia) and working in different hospital facilities, aiming to represent North, Center and South Italy. To minimize the drop-out rate and speed up the process,<sup>21</sup> a web-platform (“Welphi”) was used to implement this panel.<sup>22</sup> Welphi is a user-friendly and responsive platform that allows participants to confront ideas in an asynchronous, online, participatory and interactive manner.<sup>22</sup> In our study, this process was developed in 3 rounds with a duration of 7 days each, where participants were able to log in and out at their convenience. By opting for 3 rounds as the stopping criteria, stability across rounds could be assessed. In the first round, the questionnaire included 3 main sections: section I was devoted to collect information to characterize the management of blood components in hospitals in Italy; section II focused on patients with CLD who are transfused before elective surgery, while section III was dedicated to transfusion-refractory patients. Each section included a set of qualitative and quantitative questions. However, not all questions were answered by all participants, since the flow of the questionnaire could differ based on participants answers to selected questions (eg, internal or external BTS). In the first round, the questionnaire was submitted to participants, while in the second round they were able to see the aggregate anonymous answers provided by other panelists during the previous round, with statistic measures and charts, as well as their own answers. The third round was run to assess the stability of results and to reach a final consensus among the experts. Based upon this information, participants were invited to either change or keep their answers.

The Delphi lasted one month (May 2021 – June 2021) and a zero-dropout rate was achieved in all rounds.

In the absence of specific published studies or reviews regarding the requirement of platelet units, the Clinical Study Reports of ADAPT-1 and ADAPT-2 Phase 3 studies investigating the thrombopoietin receptor agonist (TPO-RA) avatrombopag in the same cohort of patients (ie, patients with CLD and severe TCP before an elective procedure) were considered. In both studies, the patients assigned randomly to the placebo arm (N=82 ADAPT-1, N=76 ADAPT-2) received an average of 5.5 units of platelets per transfusion.<sup>23</sup> The pooled results of ADAPT-1 and ADAPT-2 studies<sup>24</sup> also informed about the number of patients incurring in different elective procedures, such as endoscopy, chemoembolization and colonoscopy, relevant for the calculation of the opportunity cost of a procedure delay.

## Unit Costs Collection

Unit costs for each relevant resource identified were obtained or estimated from national tariffs,<sup>25–27</sup> national statistics,<sup>28,29</sup> and relevant literature.<sup>30–32</sup> Direct costs associated to the time of healthcare professionals (HCP) and indirect costs for patients and donors were evaluated through the human capital approach (HCA).<sup>33</sup> Following this method, costs were estimated valuing the time lost for platelet transfusion process at the relevant expected gross income (patient and donor). The HCA was adopted for the estimation of indirect costs associated to the platelet collection phase (donors’ time), the transfusion process (time to reach the hospital, time for transfusion, time for monitoring) and the possibility for the patient of developing refractoriness after the first transfusion (time for the additional transfusion, time for monitoring, time for tests, procedure delay). Expected gross income was estimated considering salary and employment rate of donors and patients obtained from the job pricing salary outlook (report 2020)<sup>30</sup> and the official employment rate published by the Italian National Institute of Statistics (ISTAT).<sup>28,29</sup>

For direct costs associated to the time of health professionals, time was valued considering the salary of health professionals based on ISTAT and Italian Ministry of Economy and Finance’s (MEF) estimates.<sup>29,32</sup>

To estimate the cost associated to laboratory tests and visits, as well as the cost of Diagnosis Related Group (DRG) for the extra-time spent in hospital by patients in the case of refractoriness, official national tariffs were utilized.<sup>25,27</sup> In the case of refractoriness (ie, repeated failure to achieve satisfactory level of blood platelets in a patient following a platelet transfusion),<sup>34</sup> in line with Barnett et al 2018,<sup>5</sup> the possibility of a procedure delay was considered; besides this cost, since the procedure delay is linked to a prolonged length of stay, a HAI cost was also considered.<sup>31</sup>

## Cost Analysis

In order to estimate the overall costs per platelet transfusion per patient with CLD and severe TCP, a cost analysis was developed in *Microsoft Excel*. All costs were estimated per single transfusion and were specified with respect to patients

with CLD and severe TCP, who require prophylaxis platelets prior a surgical procedure. Costs are expressed in 2021 Euro.

A sensitivity analysis was conducted to test the robustness of base case results and to evaluate the uncertain parameters of the cost analysis.

## Results

The present analysis provides a comprehensive estimate of the costs (direct and indirect) of transfusing platelets for the Italian NHS.

## Conceptual Framework

The conceptual framework identified direct, indirect and intangible costs associated with all the processes involved in the transfusion process in the United States.<sup>5</sup>

Most of the items were positively evaluated for the subsequent cost valorization; contrarily, some items, like patient copays, were not included because not relevant in the Italian context. Indeed, in the US these procedures are publicly financed while in Italy donors are volunteers and donations are anonymous and unpaid. The phases included in the original conceptual framework are described in [Table 1](#).

**Table 1** Conceptual Framework for Estimating the Cost of a Platelet Transfusion Before an Elective Procedure in a Patient with Chronic Liver Disease and Thrombocytopenia Developed by Barnett et al 2018<sup>5</sup> and Items Included in the Italian Cost Analysis

Conceptual Framework Phase	Item	Inclusion in the Italian Cost Analysis	Cost Type
PLATELET COLLECTION	DONOR RECRUITMENT	Yes	DIRECT
	DONOR SCREENING	Yes	
	PLATELET COLLECTIONS	Yes	
	MANAGEMENT OF AEs	Yes	
	ROUTINE PROCESSING (TYPING, SPLITTING, LABELING UNITS)	Yes	
	SPECIAL PROCESSING (IRRADIATION, PATHOGEN REDUCTION)	No <sup>a</sup>	
	PRIMARY BACTERIAL TESTING	Yes	
	QUALITY CONTROL	Yes	
	STORAGE	No	
	TRANSPORTATION TO TRANSFUSION SERVICE	Yes	
	LOST PRODUCTIVITY FOR DONORS	Yes	INDIRECT
PLATELET COLLECTION: TRANSFUSION SERVICE	STORAGE	Yes	DIRECT
	QUALITY CONTROL	Yes	
	INVENTORY MANAGEMENT	Yes	
	SECONDARY BACTERIAL TESTING	Yes	
	SPECIAL PROCESSING (IRRADIATION, PATHOGEN REDUCTION, WASHING)	Yes <sup>a</sup>	
	TRANSPORTATION TO TRANSFUSION LOCATION	Yes	

(Continued)

**Table 1** (Continued).

Conceptual Framework Phase	Item	Inclusion in the Italian Cost Analysis	Cost Type
PLATELET TRANSFUSION	PLATELETS	Yes	DIRECT
	PLATELET TRANSFUSION SUPPLIES/MATERIALS	Yes	
	HEALTHCARE PROVIDER LABOR	Yes	
	PATIENT COPAYS	No	
	LAB ASSESSMENT OF PLT CT BEFORE AND AFTER TRANSFUSION	Yes	
	LOST PRODUCTIVITY FOR PATIENT/CAREGIVER	Yes <sup>b</sup>	INDIRECT
AEs RELATED TO PLATELET TRANSFUSION	TREATMENT OF AEs	No	DIRECT
	IF A MAJOR AE, DELAY IN PROCEDURE	No	
	IF DELAY, ADDITIONAL TRANSFUSION(S)	No	
	POTENTIAL NEED TO SWITCH TO WASHED OR VOLUME REDUCED UNITS	No	
	EVALUATION OF AEs BY THE TRANSFUSION SERVICE	No	
	LOST PRODUCTIVITY FOR PATIENT/CAREGIVER	No	INDIRECT
REFRACTORINESS TO PLATELET TRANSFUSION	DELAY IN PROCEDURE	Yes	DIRECT
	TESTING OF THE PATIENT FOR THE ADDITIONAL PLATELET TRANSFUSION(S) (eg, HLA MATCHING)	Yes	
	HIGHER ACQUISITION COSTS OF HLA-MATCHED OR CROSS-MATCHED PLATELET UNIT	Yes	
	ADDITIONAL PLATELET TRANSFUSION(S)	Yes	
	PHYSICIAN AND BLOOD BANK DIRECTOR TIME TO PLAN ADDITIONAL PLATELET TRANSFUSIONS	Yes	INDIRECT
	LOST OF PRODUCTIVITY FOR PATIENT/CAREGIVER	Yes <sup>b</sup>	

**Notes:** Intangible costs were not considered in the Italian adaptation. <sup>a</sup>In the analysis, considered just in hospital. <sup>b</sup>In the analysis, considered just for the patient.

## Platelet Collection

To estimate costs associated to the platelet collection phase, an average number of screening tests, visits, and blood collection procedures per donor - including blood component separation activities and bags – were considered. It was taken into account that newly registered donors who have never donated blood are screened with some tests that are performed once only. Alternatively, regular donors, who routinely donate blood, perform only routine tests.<sup>13,27</sup> Moreover, since hospitals refund associations of volunteers (eg, AVIS, FIDAS) a quota that reflects the costs incurred by the association for its activities, the refund was weighted for the number of donors coming from those associations. Such costs include donor recruitment activities (eg, telephone calls, texts, updates of periodic donors) and promotional initiatives.<sup>35</sup>

Indirect costs of donors were estimated considering the age distribution of donors<sup>13</sup> and one lost working day (donation allows for one day off).

The parameters, the unit costs and sources associated with platelet collection phase are detailed in [Table 2](#).

**Table 2** Platelet Collection Parameters: Estimated Cost

Item	Type	Value	Description
Annual cost per donor <sup>a</sup>	Direct	237 € <sup>27,56</sup>	All tests and procedures were weighted by the average blood collection per donor/year (1.5) with the exception of tests performed with annual frequency (1.0) and tests performed only at the first donation (0.2)
Total annual cost of platelet collection procedures	Direct	398,848,058 € <sup>13</sup>	Calculated by multiplying the annual cost per platelet collection procedure by the units of blood collected/year
Voluntary associations activities refund	Direct	24 € <sup>35</sup>	Calculated by multiplying the cost of refund to voluntary associations by the number of donors coming from those associations (38.5%, from Delphi Panel)
Cost per blood component	Direct	92 € <sup>13,27,35</sup>	Calculated by dividing the total annual cost of platelet collection procedures for the total blood components produced and by adding the voluntary associations activities refund
Lost productivity for donor	Indirect	28 € <sup>13,30</sup>	Assuming 1 day lost from work due to the donation, divided for blood component and computing distribution of donors age and gender

**Notes:** <sup>a</sup>Including screening tests, visit and blood collection procedures performed on donors (from outpatient national tariffs: code 89.7, 90.62.2, 91.18.3, 91.19.5, 91.22.4, 91.10.3, 90.47.2, 90.65.3, 90.64.4, 90.49.3, 90.49.2, 90.27.1, 90.16.3, 90.04.5, 90.14.3, 90.14.1, 90.43.2, 90.38.5, 90.22.3),<sup>27</sup> and empty bags for blood separation<sup>56</sup>.

## Platelet Transfusion

The direct costs of a platelet transfusion described in the conceptual framework (Table 1) are borne by both the NHS and the patient.

The average cost for the transfused units of platelets was estimated considering the different types of PCs (buffy coat PCs from single donor, buffy coat PCs from pool and apheresis PCs leukodepleted) and the different procedures that platelets may undergo (freezing, washing and irradiation).

PCs can be obtained from whole blood donation (platelet-rich plasma or buffy coat) or apheresis. Buffy coats coming from a single donor or from multiple donors undergo centrifugation and subsequent filtration, to remove undesired cells (eg, white blood cells) and obtain leukodepleted concentrates. In case of apheresis, platelets are collected through a system that is able to reduce the content of leukocytes and therefore this PC is already leukodepleted.<sup>36</sup>

The platelet content within each PC differs according to the collection method: in accordance with current legislation, a single unit of PC should contain at least  $2-3 \times 10^{11}$  platelets independently of whether they are produced from whole blood donations (eg, single or pool buffy coats) or by apheresis.

According to Italian literature, an “adult platelet dose” is equal to  $2-5 \times 10^{11}$  platelets and it is conventionally composed of five to eight PCs from whole blood or from a buffy coat pool.<sup>37-39</sup>

The proportion of PCs requiring to be frozen (43%), washed (16%) or irradiated (26%) was estimated based on the consensus reached during the Delphi Panel, while the distribution among different PCs (2% receive buffy coat PCs from single donor, 75% receive buffy coat PCs from pool and 23% receive apheresis PCs leukodepleted) was estimated based on the most recent ISTISAN report.<sup>13</sup>

The literature review yielded no published estimates on the proportion of platelets frozen, washed or irradiated in the transfusion itself. The percentage of frozen PCs obtained from Delphi Panel may be related to the difficulties related to the preservation of fresh platelets. Indeed, cryopreservation can be adopted in some cases, to prolong platelet shelf life thus providing long-term accessibility in situations where fresh products are limited or unavailable.<sup>40</sup>

In clinical settings, platelets are washed before administration to patients to prevent transfusion side effects.<sup>41</sup> In a large Italian survey promoted by Italian Society of Hemapheresis and Cellular Manipulation (SIdEM), platelet washing was performed in 31.3% of the centers and was more frequently used in centers with a larger volume of activity, while platelet irradiation was performed by 65.6% of responders.<sup>42</sup>



By multiplying the average cost of the different PCs and procedures for the transfused units of platelets (5.5), the platelet product alone results in an overall cost of 1963 €/per transfusion. In line with Barnett et al results, the acquisition cost of platelets emerged as the highest cost in the transfusion phase.<sup>5</sup>

Transport of blood for hospitals with an external BTS (33%), platelets count, monitoring and laboratory tests were also calculated in this phase, considering time spent by physicians, nurses and other medical staff on transfusion itself and subsequent monitoring activities. Time spent was based on the Delphi panel consensus.

Indirect costs of productivity loss per patient for the time spent for transportation, transfusion and monitoring were also calculated.

The parameters, the unit costs and sources associated with platelets transfusion phase are detailed in Table 3.

**Table 3** Platelet Transfusion Parameters: Estimated Cost

Item	Type	Value	Description
Platelets units per transfusion	–	5.5 <sup>23,24</sup>	Average number of units required by placebo arm of ADAPT-1 and ADAPT-2 studies
Transport to hospital (patient)	Direct	10 € <sup>57</sup>	Considering a round-trip in an average distance of 12.7 km (coming from Delphi Panel), assuming an average speed of 70 km/h and a cost/km of 0.38 € <sup>a</sup>
Buffy coat platelet concentrates (single donor) + leukodepletion	Direct	446 € <sup>26</sup>	Considering irradiation in 26% of cases, platelets washing in 16% of cases and fresh platelets usage in 57% of cases (% coming from Delphi Panel)
Buffy coat platelet concentrates (pool) + leukodepletion	Direct	300 € <sup>26</sup>	
Apheresis platelet concentrates (leukodepleted)	Direct	538 € <sup>26</sup>	
Laboratory assessment of platelet count and other tests on patient and monitoring <sup>b</sup>	Direct	127 € <sup>27–29,32</sup>	Considering that transfusion and monitoring after transfusion last in total 3.7 hours and is supervised by physicians (23%), nurses (46%) and other medical staff (31%) dedicated to minimum 4 patients simultaneously (coming from Delphi Panel) and their gross salary/h <sup>c</sup>
Transportation from an external BTS to hospital (relevant for hospitals without an internal BTS) <sup>d</sup>	Direct	6 € <sup>28,29,32,57</sup>	Considering 2.5 people belonging to “other medical staff” and their gross salary/h <sup>c</sup> transporting an average of 19 blood bags each time on an average distance of 12.7 km (coming from Delphi Panel) and a cost/km of 0.62 € <sup>e</sup>
Lost productivity for patient (transport, transfusion and monitoring) <sup>f</sup>	Indirect	247 € <sup>24,28–30</sup>	Considering an average gross salary for a representative patient/h, whereas patients need to be in hospital 21 hours before the transfusion and 67% of patients (coming from Delphi Panel) need to go to hospital before the transfusion to do cross-matching tests for 60 minutes (assumption) plus the time needed for transfusions and monitoring (3.7 hours)

**Notes:** <sup>a</sup>Considering the best-selling car in Italy, Fiat panda. <sup>b</sup>Including visits and tests performed on patient (from outpatient national tariffs: code 89.7; 90.62.2, 91.49.2, 90.65.4, 90.73.2).<sup>27</sup> including platelet counts performed twice and time of health professionals to perform those procedures and ultimately multiplied per units of platelets transfused (5.5). <sup>c</sup>The only type of contract available to estimate the gross salary of health professionals was the SSN one, therefore the estimates reported relate only to the public sector. <sup>d</sup>Estimated in 33% of hospitals based on Delphi Panel answers. <sup>e</sup>Considering the most popular car utilized for this type of activities in Italy, Automedica Subaru Forester. <sup>f</sup>Considering normal distribution of age, with a mean age of 57.3 years and 62.9% male patients (placebo arm from ADAPT-1 and ADAPT-2 studies)<sup>24</sup>.

## Refractoriness to Platelet Transfusion

Patients with CLD and severe thrombocytopenia may require multiple platelet transfusions, which can easily lead to platelet refractoriness.<sup>5</sup>

Platelet refractoriness, which refers to the situation when a patient's platelet count does not increase as expected after a platelet transfusion, can have immune or nonimmune causes.<sup>5</sup> Immune causes include alloimmunization to HLA

(Human Leukocyte Antigen) and/or platelet-specific antigens due to prior exposure during pregnancy, or from transfusions and/or transplantation.<sup>43</sup>

Incidence of refractoriness was retrieved from Barnett et al,<sup>5</sup> by considering an average frequency from the range of 20–47% reported in its article.

From our research, there were no information about how many patients show refractoriness in Italy; a survey conducted in 64 Italian centers highlighted that the diagnosis of platelet refractoriness is still managed with a high degree of heterogeneity and often overlooked,<sup>42</sup> therefore it is possible that this percentage could vary across considered hospitals. Also, as for the incidence of refractoriness, one additional transfusion was considered in the case of refractoriness from Barnett et al.<sup>5</sup>

As reported in the conceptual framework, the cost of platelets themselves, the additional tests performed as well as the valorization of the time of medical professionals supervising the additional transfusion and monitoring/platelet count costs have been estimated. Moreover, since the patient cannot undergo the elective procedure in the case of refractoriness, a cost opportunity and a cost linked to the patient's productivity loss (ie, 2 days of hospitalization waiting for the elective procedure) for the delayed surgery were calculated.

The parameters, the unit costs and sources associated with refractoriness to platelet transfusion are detailed in Table 4.

**Table 4** Refractoriness to Platelet Transfusion Parameters: Estimated Cost

Item	Type	Value	Description
Refractoriness incidence	–	33.5% <sup>5</sup>	Average between 20% and 47%
Number of additional transfusions	–	1.0 <sup>5</sup>	–
Cost of repeated and additional laboratory assessment of platelet count and other tests on patient and monitoring	Direct	89 € <sup>27</sup>	Considering 45% patients who will repeat laboratory tests <sup>a</sup> and 54% patients who will make HLA typing tests <sup>b</sup> (% coming from Delphi Panel). Considering also that transfusion and monitoring after transfusion last in total 3.7 hours and is supervised by physicians (23%), nurses (46%) and other medical staff (31%) dedicated to minimum 4 patients simultaneously (coming from Delphi Panel) and their gross salary/h <sup>c</sup>
Buffy coat platelet concentrates (single donor) + leukodepletion	Direct	433 € <sup>26</sup>	Considering irradiation in 26% of cases, platelets washing in 16% of cases, fresh platelets usage in 62% of cases and usage of HLA matched platelets <sup>d</sup> in 54% of cases (% coming from Delphi Panel)
Buffy coat platelet concentrates (pool) + leukodepletion	Direct	287 € <sup>26</sup>	
Apheresis platelet concentrates (leukodepleted)	Direct	526 € <sup>26</sup>	
Cost opportunity for delayed elective surgery	Direct	4109 € <sup>23–25,29,32,34</sup>	Considering that 48% of patients will delay the elective procedure <sup>e</sup> and 34 minutes will be needed to postpone the surgery by a physician (coming from Delphi Panel)
Cost of HAI	Direct	390 € <sup>31,58</sup>	Based on HAI frequency (3.9%) and HAI cost (inflated to 2021) for two extra days of hospitalization (coming from Delphi Panel)
Lost productivity for patient	Indirect	94 € <sup>28–30</sup>	Considering 2 days to be waited for the rescheduled elective procedure (coming from Delphi Panel)

**Notes:** <sup>a</sup>Including visits and tests performed on patient (from outpatient national tariffs: code 89.7; 90.62.2, 91.49.2, 90.65.4, 90.73.2).<sup>27</sup> <sup>b</sup>From outpatient national tariffs: code 90.50.1.<sup>27</sup> <sup>c</sup>The only type of contract available to estimate the gross salary of health professionals was that of the SSN one, therefore the estimates reported relate only to the public sector. <sup>d</sup>From outpatient national tariffs: code 99.74.<sup>27</sup> <sup>e</sup>Elective procedures were retrieved from the placebo arm of the pooled study of ADAPT-1 and ADAPT-2, weighted for the % of patients and matched with DRGs tariffs to estimate a cost where the hospital is unable to occupy the operating room with another procedure (DRG considered: 191, 192, 493, 494, 361, 412, 362, 315, 124, 125, 535, 536, 547, 548, 104, 185).<sup>24,25</sup>



## Total Cost

Total cost of platelet transfusion is presented in Table 5. As a base case, all direct costs related to the transfusion of platelets in patients with CLD and severe TCP were calculated. Assuming a societal perspective, indirect costs for patients were also factored in.

Overall, the total mean costs in a representative patient with CLD and severe TCP per prophylactic platelet transfusion were estimated at 5297 € and the highest cost category was the platelet transfusion phase, accounting for 44% of total PT process costs, followed by refractoriness costs (43%) and collection costs (13%).

Overall direct costs were estimated at 4863 €, accounting for 92% of the total cost and based on all the activities required for laboratory tests and visits, including hemovigilance, PCs and related procedures (ie, irradiation, washing, frozen use, leukodepletion), the time of health professionals, transport, all the additional (eg, supplementary PC, cost-opportunity for procedure delay, HAI) and repeated (eg, laboratory tests and visits) activities in case of refractoriness.

The remaining 8% of overall costs (435 €) were associated with the indirect costs that included productivity loss for donors and patients among all phases whether relevant.

**Table 5** Total Cost (Direct and Indirect) of a Platelet Transfusion

Phase	Type of Cost	Item	Cost per Transfusion
Platelet collection	Direct	Donors screening, platelets' collection, hemovigilance, routine processing	509 € <sup>a</sup>
	Indirect	Donor loss of productivity	155 € <sup>a</sup>
	<b>Total (direct + indirect)</b>		<b>663 € (13%)</b>
Platelet transfusion	Direct	Patient transport	16 € <sup>b</sup>
	Direct	Blood transport	2 € <sup>c</sup>
	Direct	Platelets blood component	1963 € <sup>a,d</sup>
	Direct	Laboratory tests and Monitoring	127 € <sup>e</sup>
	Indirect	Patient loss of productivity	249 €
	<b>Total (direct + indirect)</b>		<b>2357 € (44%)</b>
Refractoriness to platelet transfusion	Direct	Additional transfusion	709 € <sup>a,d,f,g</sup>
	Direct	Monitoring	30 € <sup>f</sup>
	Direct	Procedure Delay	1376 € <sup>f</sup>
	Direct	HAI	131 € <sup>f</sup>
	Indirect	Patient loss of productivity	31 € <sup>f</sup>
	<b>Total (direct + indirect)</b>		<b>2277 € (43%)</b>
<b>Total Direct Costs (% of the total)</b>			<b>4863 € (92%)</b>
<b>Total Indirect Costs (% of the total)</b>			<b>435 € (8%)</b>
<b>Total</b>			<b>5297 € (100%)</b>

**Notes:** In bold are reported totals. <sup>a</sup>Cost multiplied by transfused units (5.5). <sup>b</sup>Cost of transport for transfusion process and cross-matching tests, performed days before the transfusion (relevant only for 67% of patients). <sup>c</sup>Weighted average between 67% of hospitals with an internal BTS (no cost) and 33% of hospitals with an external BTS (6 €), % retrieved from Delphi Panel. <sup>d</sup>Weighted cost of platelets concentrates by % patients receiving different concentrates.<sup>13</sup> <sup>e</sup>Cost multiplied by transfused units (5.5) with the exception of general visit (89.7) and blood sampling (91.49.2), performed just one time only on patient. <sup>f</sup>Weighted cost on 33.5% patients refractory to transfusion. <sup>g</sup>Considering HLA-matched platelets concentrates.

## Sensitivity Analyses

Different sensitivity analyses were performed. The first two scenarios assessed the minimum and the maximum value for some parameters; in particular, a minimum and a maximum amount of time was considered for the tests performed for regular and first-time donors (the minimum was calculated excluding the cost of some visits performed only during the first donation), for the refractoriness incidence (ranging from 20% to 47%)<sup>5</sup> as well as the possibility for the hospital to efficiently use the operating room for another procedure (accounting just for the time of medical staff spent to replace the procedure) (Table 6). Additionally, the Delphi panel highlighted a possible platelet wastage of 10% of the total, then a third sensitivity analysis was considered. From the base case, the results vary from a +19% (6289 €) to a -33% (3540 €), whereas considering 10% platelet wastage would increase the cost of a +6% (5629 €).

**Table 6** Sensitivity Analyses

Phase	Type of Cost	Item	Cost per Transfusion (Min)	Cost per Transfusion (Max)	Cost per Transfusion (with 10% Wastage)
Platelet collection	Direct	Donors screening, platelets' collection, hemovigilance, routine processing	490 € <sup>a,b</sup>	578 € <sup>a,c</sup>	559 € <sup>a</sup>
	Indirect	Donor loss of productivity	155 € <sup>a</sup>	155 € <sup>a</sup>	170 € <sup>a</sup>
	<b>Total (direct + indirect)</b>		<b>644 €</b>	<b>732 €</b>	<b>730 €</b>
Platelet transfusion	Direct	Patient transport	16 € <sup>d</sup>	16 € <sup>d</sup>	16 € <sup>d</sup>
	Direct	Blood transport	0 € <sup>e</sup>	6 € <sup>f</sup>	2 €
	Direct	Platelets blood component	1963 € <sup>a,g</sup>	1963 € <sup>a,g</sup>	2160 € <sup>a,g</sup>
	Direct	Laboratory tests and Monitoring	127 € <sup>a</sup>	127 € <sup>a</sup>	130 € <sup>a</sup>
	Indirect	Patient loss of productivity	249 €	249 €	249 €
	<b>Total (direct + indirect)</b>		<b>2355 €</b>	<b>2361 €</b>	<b>2557 €</b>
Refractoriness to platelet transfusion	Direct	Additional transfusion	423 € <sup>h</sup>	995 € <sup>i</sup>	773 € <sup>i</sup>
	Direct	Monitoring	18 € <sup>h</sup>	42 € <sup>i</sup>	31 € <sup>i</sup>
	Direct	Procedure delay	3 € <sup>h,k</sup>	1931 € <sup>i</sup>	1376 € <sup>i</sup>
	Direct	HAI	78 € <sup>h</sup>	184 € <sup>i</sup>	131 € <sup>i</sup>
	Indirect	Patient loss of productivity	19 € <sup>h</sup>	44 € <sup>i</sup>	31 € <sup>i</sup>
	<b>Total (direct + indirect)</b>		<b>540 €</b>	<b>3195 €</b>	<b>2343 €</b>
<b>Total Direct Costs (% of the total)</b>			<b>3118 € (88%)</b>	<b>5841 € (93%)</b>	<b>5179 € (92%)</b>
<b>Total Indirect Costs (% of the total)</b>			<b>422 € (12%)</b>	<b>447 € (7%)</b>	<b>450 € (8%)</b>
<b>Total</b>			<b>3540 € (100%)</b>	<b>6289 € (100%)</b>	<b>5629 € (100%)</b>
Δ from base case			-33%	+19%	+6%

**Notes:** In bold are reported totals. <sup>a</sup>Cost multiplied by transfused units (5.5). <sup>b</sup>Considering just regular donors. <sup>c</sup>Considering just first-time donors. <sup>d</sup>Cost of transport for transfusion process and cross-matching tests, done days before the transfusion (relevant only for 67% of patients). <sup>e</sup>Considering hospitals with an internal BTS (no cost). <sup>f</sup>Considering hospitals with an external BTS (6 €). <sup>g</sup>Weighted cost of platelets concentrates by % patients receiving different concentrates. <sup>h</sup>Weighted cost on 20% patients refractory to transfusion. <sup>i</sup>Weighted cost on 47% patients refractory to transfusion. <sup>k</sup>Weighted cost on 33.5% patients refractory to transfusion. <sup>l</sup>Considering that hospital is able to efficiently use the operating room.

## Discussion

The economic burden associated with platelet transfusions is not well documented in Italy and no studies have been identified in the literature that estimate the full Italian cost associated with platelet transfusions in patients with CLD and severe TCP in Italy.

The real economic burden that platelet transfusions pose on healthcare services can be perceived as low or underestimated, as the cost frequently considered does not account for multiple procedures and resources that are required for platelet collection and transfusion, management of transfusion-related risk and refractoriness.

To date, this is the first study conducted in Italy proposing a novel evidence-based approach to estimate the full cost associated with prophylactic platelet transfusions in the Italian context, with a focus on patients with CLD and severe TCP needing a surgical procedure. The analysis aimed to raise awareness on the costs of transfusion which are borne not only by the NHS but also by society, including donors and patients. The inclusion of direct costs, independently of whom is the payer, is of particular interest considering both the rising concerns regarding the NHS sustainability<sup>44</sup> and the social implications of catastrophic healthcare expenditure.<sup>45</sup>

At international level, several publications have found that the healthcare costs of patients with CLD and thrombocytopenia are substantial. Most specifically, the cost of platelet transfusions appears to be a relatively large contributor to this burden.<sup>34</sup>

Among published studies, Poordad et al 2012<sup>6</sup> conducted a retrospective analysis in the US assessing the impact of PT on health resource utilization and expenditure, including hospitalizations, accident and emergency (A&E) visits and outpatient visits among CLD patients with TCP. The study highlighted that CLD patients with thrombocytopenia who received a platelet transfusion had a higher probability of having an additional outpatient visit and hospitalization than those who did not receive a platelet transfusion. Platelet transfusions were associated with significantly increased hospitalization costs (USD 25802), outpatient office costs (USD 3367) and total costs (USD 29717) compared to the costs of patients without transfusion.<sup>34,46</sup>

The study conducted by Barnett et al<sup>5</sup> aimed to assess the cost of platelet transfusion in patients with CLD and TCP undergoing elective procedures in the US. Through the development of a conceptual framework, the authors covered a full range of resource items including direct, indirect and intangible costs.<sup>5</sup> Taking into consideration all phases of platelet transfusion in CLD patients with TCP undergoing an elective procedure, the total direct cost per platelet transfusion was estimated to be in the range of USD 5258–13117. The majority of costs were attributable to the transfusion itself (USD 3723–4436), followed by the cost of refractoriness (USD 874–7578). Indirect and intangible costs were not factored in.

The main differences between our analysis and Barnett et al's analysis are related to i) the approach adopted for the estimation of resource consumption, ii) the inclusion in the analysis of the costs associated with transfusion-related Adverse Events (AEs), iii) the estimation of indirect costs.

Differently from Barnett et al, where the authors drew the cost elements from different sources with different study designs, resource consumption in our study was assessed through a Delphi-panel-approach, in order to combine evidence-based knowledge and Real-World experience of clinicians.

As for AEs costs, the US framework included in the final estimate both the costs related to the management of AEs and opportunity costs of delayed procedures in the event of platelet refractoriness and Treatment-Related Adverse Events (TRAЕ), while our analysis incorporated only opportunity costs related to refractoriness due to the small incidence of AEs in the Italian context.<sup>13</sup>

Lastly, all the indirect costs identified in the US framework were included in the final estimation, with the sole exception of the loss of productivity of caregivers.

Overall, when compared to the cost estimates presented by Barnett et al for US, we found that Italian estimates are lower, accounting for USD 5590 (considering the comparison only for direct costs and the parity purchase power – PPP).<sup>47</sup>

Our estimates present some limitations, mostly related to the Delphi panel design and to the exclusion or variability of some cost elements.

The first limitation concerns the design of the Delphi panel. Although there is no general agreement on the size of the panel in the Delphi studies,<sup>48</sup> the limited number of experts involved (n=6) and geographic distribution (considering 3 regions across North, Center and South of Italy) may fail to reflect the heterogeneous reality in Italy.

A second study limitation is related to the collection and estimation of unit costs; despite unit cost estimates were based on official Italian tariffs, official Italian statistics databases and relevant literature, there may be some variability at a local level related to differences in ambulatory outpatient care, as each Italian Region can choose their tariff schemes autonomously. Moreover, we were not able to match all the elective procedures performed by patients with CLD and severe TCP with Italian DRGs, hereafter some assumptions were made.

Thirdly, some cost items were excluded for lack of information, leading to a potential underestimation of the full economic burden of platelet transfusion in patients with CLD and severe TCP. Furthermore, indirect costs associated with a caregiver's loss of productivity were not considered. This cost element may be substantial especially for patients with advanced CLD who may undergo multiple elective procedures and/or may experience refractoriness, causing additional transfusions.

Regarding AEs, as described in the Italian ISTISAN report, the incidence of AEs related to platelets is small (accounting for 0.1% of all transfusions and 0.2% of platelet transfusions), thus we choose to adopt a conservative approach and to not include in the analysis the cost associated with the management and treatment of AEs or the cost opportunity associated with delays in the elective procedure due to AEs onset.<sup>13</sup> Moreover, these costs might also vary depending on the severity of the events and on their potential long-term sequelae, which may be difficult to quantify based on patient condition and disease.

In addition, some relevant parameters such as refractoriness to platelet transfusions and PCs processing were uncertain. In order to assess their impact on results, sensitivity analysis was performed.

Despite some limitations, an effort has been made to estimate costs associated with all relevant phases related to transfusions in patients with CLD and severe TCP undergoing elective procedures. In a context where the attention to overall expenditure and use of resources is increasing, this analysis was conducted to inform the discussion and provide a piece of comprehensive evidence from Real-World clinical practice.

The results of the present analysis can in fact integrate and facilitate a health technology assessment (HTA), where costs and benefits of introducing new technology reducing the need for PT in Italy for patients with CLD and associated thrombocytopenia undergoing elective procedures may be assessed. HTA is of paramount relevance to enhance rational decision-making in health financing strategies.<sup>49–51</sup>

Recent advances in the understanding of thrombopoiesis and the role of its key regulator (thrombopoietin, TPO) have led to the development and regulatory approval of TPO-RAs. TPO-RAs reliably stimulate platelets and have the potential to reduce the clinical and economic burden currently associated with PT, in patients with CLD and severe TCP<sup>52</sup> as they have a specific mechanism of action that stimulates the endogenous production of functional platelets, providing a gradual and sustained increase (above  $50 \times 10^9$ ) in the PLT CT over time.<sup>52</sup> It is expected that in the near future the introduction of new technologies, such as TPO-RAs, may reduce the need of PT as demonstrated in randomized clinical trials and hence, potentially, the associated management costs. Also, a cost effectiveness-analysis conducted in the US recently showed that a TPO-RA (avatrombopag) compared with PT resulted in a cost saving of 4250 \$ per person when compared to platelet transfusions.<sup>53</sup> Moreover, measures to reduce PT-related costs may include implementing management algorithms, updating guidelines or protocols to include appropriately licensed treatment alternatives. The availability of pharmacologic medications, with the ability to restore the circulating platelet pool and minimize the risk of bleeding in patients with CLD scheduled for a surgical procedure, could be important not only to reduce the usage of platelets, an often scarce and costly blood resource, but at the same time to improve patient's condition and quality of life while limiting healthcare costs.<sup>5,12</sup>

## Conclusion

The presented study has shown a substantial economic burden associated with PTs in patients with CLD and thrombocytopenia, whilst also providing useful evidence for future economic evaluations of upcoming medicines. To date, in absence of reliable estimates of the costs of administering a transfusion, the ancillary costs of transfusions are frequently excluded from economic evaluations of policy strategies or healthcare interventions.

The analysis revealed that platelet administration costs add substantially to the cost of the platelet products themselves. We believe that this study provides meaningful evidence to understand the burden of platelet transfusion in Italy, carried by both NHS and patients.

The Real-World Evidence (RWE) may play an important role in the future to further confirm and validate our findings, completing them with estimates of full cost of platelet transfusions in Real-World clinical practice.

## Abbreviations

AEs, Adverse Events; AVIS, Associazione Volontari Italiani Sangue; A&E, Accident and Emergency; BTS, Blood Transfusion Service; CLD, Chronic Liver Disease; DRG, Diagnosis Related Group; FIDAS, Federazione Italiana Associazioni Donatori Di Sangue; HAI, Hospital-Acquired Infections; HCA, Human Capital Approach; HCP, Healthcare Professionals; HLA, Human Leukocyte Antigen; ISTAT, Italian National Institute of Statistics; ISTISAN, Istituto Superiore di Sanità report; LEA, Livelli Essenziali di Assistenza; MEF, Italian Ministry of Economy and Finance; NHS, National Health System; PCs, Platelet Concentrates; PLT CT, Platelet Count; PPP, Parity Purchase Power; PT, Platelet Transfusion; RWE, Real-World Evidence; SidEM, Italian Society of Hemapheresis and Cellular Manipulation; SISTRA, Sistema Informativo dei Servizi TRASfusionali; SSN, Servizio Sanitario Nazionale; TCP, Thrombocytopenia; TPO, Thrombopoietin; TPO-RA, Thrombopoietin Receptor Agonist; TRAE, Treatment-Related Adverse Events.

## Ethics Statement

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines. According to Italian law regulating the role of the Ethics Committee in Italy, (Legislative Decree No. 211 of 24 June 2003, Transposition of Directive 2001/20/EC – Section 6)<sup>54</sup> the Ethics Committee shall give its opinion, before a clinical trial commences, on any issue requested. Since this article is not based on an interventional or retrospective study and does not contain any sensitive and specific information on humans based on confidential or public databases, we did not require any response, approval, or informed consent. The analysis was based on previously conducted/published studies and expert opinions collected through a Delphi Panel, therefore did not involve any patient-level data. With regard to the Delphi Panel, all the panelists (ie, medical professionals) agreed to participate in the online panel on a voluntary basis and their answers were analyzed using aggregated methods, in accordance with the EU Regulation No. 679 of 04 May 2016.<sup>55</sup> The study was also performed following the ISPOR CHEERS (Consolidated Health Economic Evaluation Reporting Standards) practices.<sup>33</sup>

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

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