

## Management of chronic liver disease-associated severe thrombocytopenia in Spain: a view from the experts

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### ABSTRACT

**Background:** chronic liver disease (CLD) patients often present thrombocytopenia (TCP) and when severe, it may prevent them from undergoing necessary invasive procedures due to an increased bleeding risk. The lack of scientific evidence makes it impossible to determine key aspects of the current management and associated healthcare burden of these patients in Spain.

**Purpose:** to gain insight into the current situation of patients with CLD-associated severe TCP undergoing invasive procedures in Spain, based on the experience of clinical experts.

**Methods:** national Delphi study involving 32 medical experts.

**Results:** the estimated prevalence of CLD-associated severe TCP is approximately 5,967, with an annual incidence of 1,148 new patients. Patients undergo a median of 1 (0-3) invasive procedures/year. Platelet transfusions (PTs) are the standard option to raise platelet counts and are associated with significant burden. The achievement of target platelet levels ( $\geq 50 \times 10^9/l$ ) after a transfusion is not routinely measured. The lack of effectiveness and short life span of transfused platelets can lead to procedure cancellations and bleeding events, which potentially affect patient outcomes. Adverse events occur in 1-25 % of patients, including mild (febrile and allergic reactions) and severe events (e.g., trans-

fusion-related acute lung injury). Between 5-15 % of patients are unfit to receive PTs and approximately 3 % are treated off-label with thrombopoietin receptor agonists.

**Conclusions:** this study provides a snapshot of the current situation in Spain, highlighting that the current management is poorly standardized and suboptimal in some cases. The results suggest the benefit of developing a consensus document to address some of these shortcomings and to advance in the search for alternatives to PTs.

**Keywords:** Thrombocytopenia. Chronic liver disease. Platelet transfusion. Delphi. Epidemiology. Treatment. Thrombopoietin receptor agonists.

### INTRODUCTION

Thrombocytopenia (TCP) is a common hematological condition characterized by a low platelet count and classified as severe when the platelet count is  $\leq 50 \times 10^9/l$  (1). TCP is present in up to 84 % (2,3) of patients with chronic liver disease (CLD), which encompasses a range of disorders characterized by fibrosis and inflammation, most notably chronic hepatitis and cirrhosis. CLD starts in an asymptomatic

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phase, termed compensated (Child-Pugh A) and is gradually followed by the development of clinically evident complications in the decompensated phase (Child-Pugh B and C), where patients usually require an increasing number of invasive, potentially hemorrhagic interventions (4). The main causes of TCP are a decrease in platelet production, an increase in platelet destruction and a sequestration of platelets in the spleen (1). A decrease in platelet production results from reduced levels of thrombopoietin, a hormone produced by the hepatocytes that regulates platelet release into the circulation, which is present in low levels in severe liver damage (5). CLD patients often undergo invasive procedures for diagnosis and treatment. In fact, severe TCP may preclude or delay them, further complicating patient care (6,7). Severe TCP requiring platelet transfusion occurs in only 1-2.4 % of CLD patients (1,2,8).

Two thrombopoietin receptor agonists have been recently approved in Europe for the treatment of CLD-associated severe thrombocytopenia (9-11). None are yet commercialized in Spain. In the absence of an available pharmacological treatment approved for this indication, platelet transfusions represent the current option to increase platelet count in these patients. However, their effectiveness in the clinical practice is variable and patients may develop refractoriness (absence of response) after multiple transfusions (12). Platelet transfusions are associated with a series of risks, including infections, non-hemolytic reactions, transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI) (12,13). In addition, logistic issues further complicate transfusions. Between three and five blood donations are needed to obtain one bag of pooled platelets, platelets must be stored at 22 °C under continuous shaking and they have a short shelf-life (average of five days), resulting in up to 16 % of collected platelets being discarded (14).

Currently, there are no specific clinical guidelines or consensus for the management of patients with CLD-associated TCP in Spain, other than general blood components transfusion guidelines (15). Given the scarcity of the published literature, this study aimed to obtain a picture of the current situation and determine key unmet needs in Spain based on the opinion and experience of medical experts.

## METHODS

A rapid literature review was performed focused on CLD-associated thrombocytopenia articles to identify publications relevant for the design of the Delphi questionnaire. The focus of the search were articles published before November 2018 by Spanish clinicians and/or in the context of the Spanish healthcare system. The criteria used for the literature review followed the PICOTS (population, intervention, comparator, outcome, time, setting) framework (16). Exclusion criteria were duplicated articles, articles written in a language other than Spanish or English and articles related to animal studies. There was no time span limit. Inclusion criteria were defined according to the following research questions of the Delphi questionnaire: epidemiology, patient flow (diagnosis, follow-up and invasive procedures), clinical management (current available alternatives, associated logistics and burden, treatment guidelines and protocols) and the use of resources and key unmet

needs. Search sources consisted of international databases (PubMed, Google Scholar and Cochrane) and the Spanish national biomedical database (MEDES). Grey literature searches were performed with Google, websites of Spanish scientific societies and websites of patient associations.

## Delphi Study

The study was performed using a modified Delphi methodology; a semi-structured, two round consultation, face-to-face meeting (17). The Delphi study incorporated both a respondent group (32 experts: 19 hepatologists, eight hematologists and five heads of transfusion centers from 11/17 regions in Spain) and a consultation group (a subgroup within the respondent group, formed by 8/32 experts: six hepatologists and two hematologists from 6/17 regions) (Fig. 1). The study was performed between February and June 2019.

The Delphi method is recommended for use in the health-care setting as a reliable means of determining a situation for which there is little or no definitive evidence and where expert opinion is important (18). Studies have demonstrated that the modified Delphi method can be superior to the original Delphi method and perceived as highly effective (17).

A first round Delphi questionnaire was developed and consisted of 38 questions divided into the same sections as the literature review described above. The second-round questionnaire was designed based on an analysis of the returned data from the first round. The questionnaire served to validate responses from the first Delphi round. Results obtained after the two rounds of consultations were aggregated, analyzed and discussed by the consultation group at an in-person workshop.

Epidemiological data were estimated by extrapolating individual information provided by study participants for each hospital. First, they were extrapolated to the population in their respective region and later to the full Spanish population using data from the Spanish National Institute for Statistics (Instituto Nacional de Estadística) (19).



**Fig. 1.** Location of experts who completed the Delphi questionnaires. A total of 32 experts from eleven regions in Spain participated in the Delphi study.

## RESULTS

### Literature review

The literature review in scientific databases and grey literature resulted in three articles (1,20,21) being retained. These articles provided little information for the development of the Delphi questionnaire. Fortea JI et al. (2019) (20) provided some information on the current management of hemostatic alterations and associated disorders in cirrhosis in Spain, introduced the use of platelet transfusions before invasive procedures to raise the platelet count in cirrhotic patients with thrombocytopenia and provided examples of interventions that these patients underwent due to their liver disease. Rios P et al. (2005) (21) provided further examples of interventions that these patients underwent due to CLD. Finally, Afdhal N et al. (2008) (1) provided information on the percentage of patients with CLD that presented severe thrombocytopenia.

No publications were found on epidemiology, patient flow, the use of resources and unmet needs of CLD-associated thrombocytopenia in Spain. Furthermore, little information was found on the management of these patients; there was no information regarding the associated logistics and burden of currently available treatments, treatment guidelines or protocols.

### Delphi Study

The estimated prevalence of CLD-associated TCP in Spain is 5,967 patients, which represents 15.5 patients per 100,000 adult inhabitants (0.0155 % of the Spanish adult population). Of these, 33 % are compensated and 66 % are decompensated patients. The estimated annual incidence is 1,148 new patients each year, which equates to three new patients per 100,000 adult inhabitants per year (0.00298 % of the Spanish adult population).

Compensated patients (in the asymptomatic phase of the disease) visit the hospital a median of 2 (range: 1-3) times per year, while this figure increases to a median of 4 (range: 2-8) times per year for decompensated patients (in the symptomatic phase of the disease). The medical specialties in charge of managing these patients vary across hospitals and regions. Patients are followed up by a hepatologist in 64 % of the cases and by a hepatologist in coordination with a hematologist in 36 % of cases. However, interventions in these patients are performed with the involvement of a number of other medical specialties (e.g., general and specialized surgeons, anesthetists, radiologists, odontologists). Each patient undergoes a median of 1 (range: 0-3) invasive procedure per year. The most common procedures performed in these patients in Spain are therapeutic endoscopy (29 % of all procedures), endoscopic variceal ligation (25 %) and dental procedures (13 %). A full list of procedures performed in these patients, classified according to their performance frequency and potential associated bleeding risk (classified as major or minor) is shown in table 1. Figure 2 summarizes the clinical management pathway these patients undergo within the Spanish National Healthcare System (NHS), from routine clinical follow-up to performed invasive procedures.

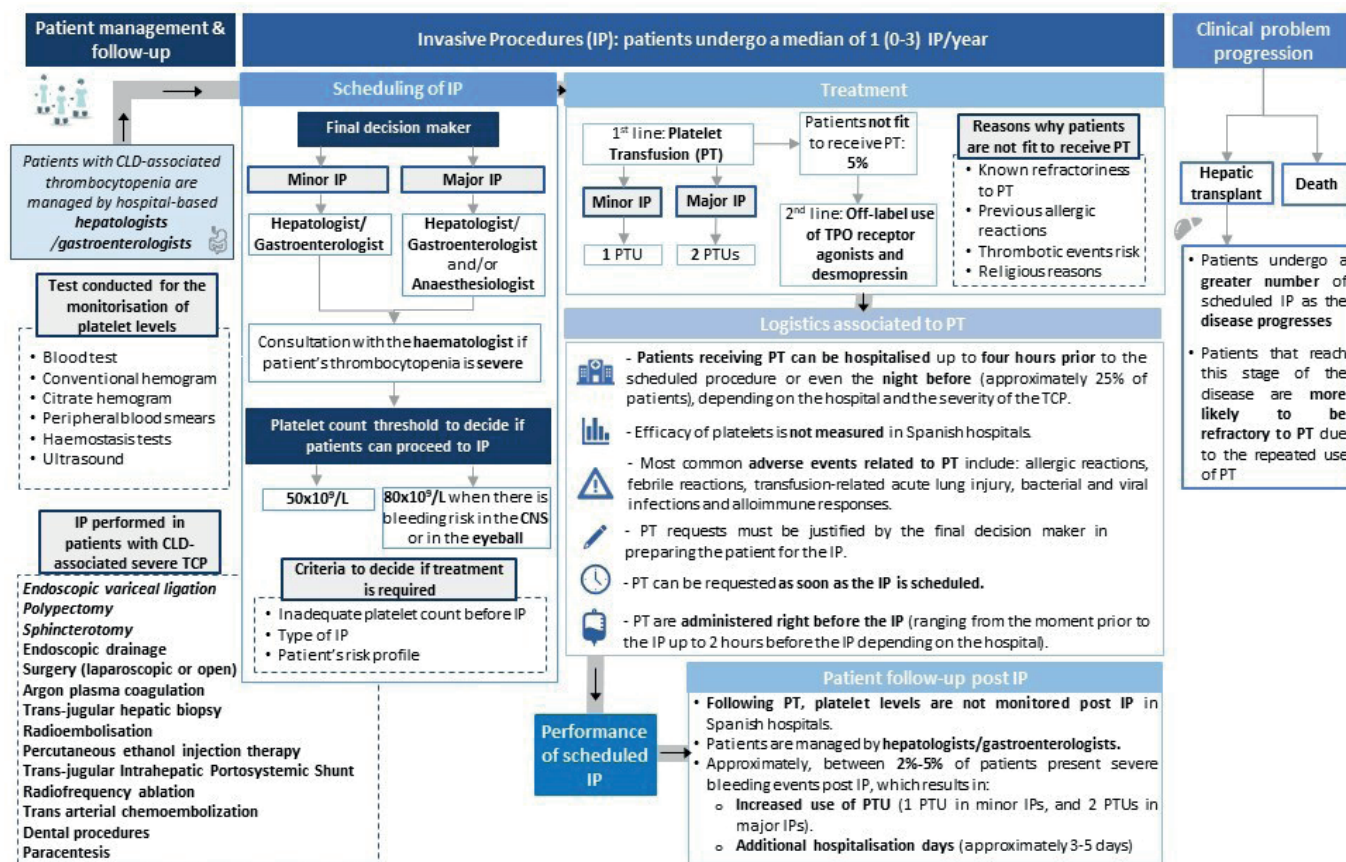
Platelet transfusions represent the current standard option to raise platelet levels in these patients. Ideally, platelet transfusions should be performed immediately before the procedure, but there is high variability among hospitals and medical specialties on the timing of the transfusion. The majority (77 %) of patients receive the transfusion less than an hour before the procedure, 8 % between two and four hours before and 15 % of more than four hours before the procedure. Study participants have indicated that approximately 25 % of patients are hospitalized the night before the invasive procedure because of the platelet transfusion process itself.

The median platelet count cut-off value for deciding on a platelet transfusion in Spain is  $50 \times 10^9/l$  (Fig. 2), ranging

**Table 1.** Types of invasive procedures in patients with CLD-associated severe TCP

Invasive procedure	Type	Frequency of invasive procedures/year in patients with CLD-associated severe TCP (out of total invasive procedures performed in these patients)
Therapeutic endoscopy (polypectomy and sphincterotomy)	Major	33.5 %
Endoscopic variceal ligation	Minor	19.2 %
Argon plasma coagulation	Minor	5.1 %
Trans-jugular hepatic biopsy	Major	6.9 %
Radioembolization	Major	1.9 %
Percutaneous ethanol injection therapy	Major	0.4 %
Trans-jugular intrahepatic portosystemic shunt	Major	7.3 %
Radiofrequency ablation	Major	5.2 %
Transarterial chemoembolization	Major	8.2 %
Dental procedures	Major/Minor	12.4 %

CLD: chronic liver disease; TCP: thrombocytopenia. Major invasive procedure: an invasive procedure with a high associated bleeding risk. Minor invasive procedure: an invasive procedure with a low associated bleeding risk.



**Fig. 2.** Patient pathway of adult patients with chronic liver disease-associated severe thrombocytopenia who undergo invasive procedures in Spain (CLD: chronic liver disease; CNS: central nervous system; IPs: invasive procedures; PTs: platelet transfusions; PTU: platelet therapeutic unit; TCP: thrombocytopenia; TPO: thrombopoietin. Major IP: an IP with a high associated bleeding risk. Minor IP: an IP with a low associated bleeding risk).

from 20 x 10<sup>9</sup>/l for minor procedures to 100 x 10<sup>9</sup>/l for ocular or central nervous system surgery. The desirable minimum increase is 20 x 10<sup>9</sup>/l from baseline. However, only 15 % of the study participants monitor the effectiveness of platelet transfusions in practice. The number of platelet therapeutic units (PTUs) is defined as one bag of platelets) transfused per invasive procedure varies according to the type of the procedure performed. A median of 1 (range: 1-3) PTUs for minor, increasing to a median of 2 (range: 1-4) PTUs in the case of major invasive procedures (Fig. 2).

The key safety concern with platelets relates to their biological nature, which may present potential risks of unknown viral or bacterial contamination. In fact, as many as 25 % of patients receiving platelet transfusions present adverse events, the most common being non-hemolytic febrile reactions (42.5 %) and allergic reactions (52 %). Despite the administration of platelet transfusions, major hemorrhagic events occur in 5 % and 2 % of these patients after undergoing major and minor invasive procedures, respectively. Major hemorrhagic events are associated with an extension of in-patient hospital stay of 3-5 additional days.

A median of 5 % (range: 0-40 %) of patients are unfit to receive platelet transfusions (Fig. 2), mainly due to refractoriness (35 %), previous allergic reactions (35 %), religious reasons (25 %) and thrombotic risk (5 %). Of all unfit

patients, 54 % (equivalent to 3 % of the total number of patients with CLD-associated severe TCP in Spain) undergo off-label pharmacological treatment with eltrombopag (43 %) (22), romiplostim (30 %) (23) and/or desmopressin (27 %) (24). Approximately 2 % of patients with CLD-associated thrombocytopenia in Spain do not receive any treatment before an invasive procedure. A median of 5 % (range: 0-15 %) of scheduled invasive procedures are cancelled each year due to a high risk of bleeding derived from a baseline low platelet count (76 %), the increased risk of bleeding because the patient has not achieved the increased platelet count required after a PT (21 %) and a supply shortage of platelet concentrates (3 %).

According to the experts, the median cost of a PTU in Spain is 356.62 €, ranging from 250 € (if the PTU comes from a pool of platelets) to 500 € (if the PTU comes from plateletpheresis). Participants estimated that the average cost of treating these patients in Spain can range approximately between 627.46 € and 3,561.57 €, depending on the occurrence of severe bleeding events during the procedure, the use of rescue therapy and hospitalization.

There are no clinical practice guidelines or consensus documents in Spain on the management of patients with CLD-associated severe TCP. Thus, the decision to transfuse is made on a one-to-one basis according to the clinician's

judgment and considering several criteria such as insufficient levels of platelets before the procedure, the type of procedure that will be performed and the patient's individual risk profile based on clinical history (Fig. 2).

Study participants have identified the main unmet needs in the management of adult patients with CLD-associated severe TCP who undergo invasive procedures in Spain. Firstly, the development of clinical guidelines and/or protocols that could contribute to standardization of the management of these patients across Spain was identified as the major unmet need (reported by 75 % of hematologists and 61 % of hepatologists). Secondly, the availability of alternatives that reduce the use of platelet transfusions (100 % of hematologists and heads of transfusion centers and 83 % of hepatologists) are safer than the current option (PTs) (75 % of hematologists, 50 % of heads of transfusion centers, and 56 % of hepatologists) and are more effective than PTs (63 % of hematologists, 75 % of heads of transfusion centers, and 61 % of hepatologists) in these patients.

## DISCUSSION

The literature review performed as part of this study revealed the current lack of scientific evidence and publications and the absence of clinical guidelines for CLD-associated severe thrombocytopenia patients in Spain. This study provides a current overview of key aspects of how patients with CLD-associated severe thrombocytopenia are managed in Spain and what it entails for the healthcare system, contributing in part to fill some of the gaps in the current evidence.

CLD-associated severe thrombocytopenia is a serious, although infrequent clinical problem. The epidemiological data estimated by study participants for Spain is in line with that reported in Europe (25). Despite representing the current standard of care, platelet transfusions are not considered as an optimal method for raising the platelet count in patients due to their relatively low effectiveness, the fact that any increase in platelet count lasts only a matter of hours and the complications associated with the transfusion procedure. Study participants are particularly concerned with the potential safety risk associated with the biological nature of platelets and also with the increased risk of refractoriness in these patients, as they are exposed to multiple platelet transfusions over time as their disease progresses.

The increased risk of hemorrhagic events during invasive procedures in patients with CLD-associated severe TCP is also a widely recognized clinical problem in the literature (26-29). The increased hospital stay due to severe bleeding events during invasive procedures, the delays and/or cancellations of procedures and the unsatisfactory effectiveness of platelet transfusions can represent a meaningful economic burden for the Spanish NHS. Cancellation of scheduled invasive procedures can be associated with a high opportunity-cost for the Spanish NHS. It could also negatively affect patients' prognosis, as these patients only undergo invasive procedures when necessary and unavoidable due to the severity of their underlying condition.

Study results show that there are no clinical practice guidelines in Spain on the management of patients with CLD-as-

sociated severe TCP. This could explain the heterogeneity of approaches followed by clinicians nationwide and provide an explanation for the wide range of values reported for key parameters in the study. For example, the great disparity in the number of platelet therapeutic units used per intervention or the variability in clinical management of patients by different medical specialties across Spanish hospitals. Importantly, final decisions on the use and timing of platelet transfusions before an invasive procedure are not only based on platelet count but also on the type of procedure and the patient's bleeding risk according to their clinical history and the clinician's experience. Study participants also report that thrombopoietin receptor agonists are sometimes used off-label to treat patients with CLD-associated severe TCP prior to an invasive procedure.

The limitations of this study are those derived from the methodology used to obtain the information, since there is a clear lack of published data and a complete absence of patient registries. The Delphi approach allows information to be obtained based on the opinion of the experts who treat these patients. Therefore, the data obtained from these studies must be considered as estimates and should be validated in specifically designed epidemiological studies and would also benefit from the creation of patient registries.

This study presents, for the first time, a snapshot of the current situation of patients with CLD-associated severe TCP undergoing invasive procedures in Spain based on the experience of clinical experts. At the time of writing, there are no published data on the objectives of this study in Spain, making the findings reported more relevant.

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