A systematic literature review on the use of platelet transfusions in patients with thrombocytopenia

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Background

Thrombocytopenia (TCP) is a common hematologic condition, usually characterized by a platelet count (PC) of $<150 \times 10^9/L$, but definitions can range from $\leq 100 \times 10^9/L$ to $\leq 180 \times 10^9/L$ [1]. The causes of TCP are varied and include decreased platelet production, increased platelet destruction, increased splenic sequestration, and/or dilution [2]. Similarly, treatment is dependent on underlying cause but may involve platelet transfusion (PT), thrombopoietin receptor (TPO-R) agonists, bone marrow transplant (BMT) or other treatments [2]. PTs are frequently administered to hospital patients with platelet consumptive/destructive disorders such as thrombotic thrombocytopenic purpura (TTP), heparin-induced thrombocytopenia (HIT) and immune (previously idiopathic) thrombocytopenia (ITP). Clinically, TCP may independently predict major bleeding [3], which can complicate the management of patients with cancer, chronic liver disease (CLD), and ITP, resulting in delayed or canceled procedures [4–6]. In addition, TCP can limit the frequency and dose of chemotherapy [7], leading to protracted hospital stays, treatment modification, and increased economic burden [7,8].

PT has been used for over 50 years for active bleeding and prophylaxis in high-risk populations (eg, cancer patients or TCP patients undergoing invasive procedures) [9–12]. Most guidelines recommend a PC threshold of $50 \times 10^9/L$ to prevent hemorrhage prior to invasive procedures but vary depending on the type of procedure [10,11,13,14]. Although widely used, PTs are associated with a variety of risks including infection (that may result in sepsis) [15–17], transfusion reactions and alloimmunization (up to 40%) [18–20]. PTs are associated with higher odds ratios of arterial

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thrombosis and mortality among TTP and HIT patients [21], and with higher rates of transfusion-associated circulatory overload (TACO) [22] and transfusion-related acute lung injury [23]. Any transfusion-related intervention can increase the risk of TACO which has been shown to be under-reported [24]. Thrombocytopenic patients who receive PTs also have a variety of underlying conditions and diseases, making the decision to transfuse difficult in light of potential risks [11,12,25–27].

There are practical, logistical and quality control issues associated with platelet preparation and storage and donor platelet quality varies [28,29]. There is currently no routine testing of platelet quality (such as the percentage of active platelets) [29] and quality is negatively affected by prolonged storage times [30]. PTs must be delivered under strict local/national guidelines that may be difficult to meet [31–34]. Although 94% of PTs in the USA are collected through apheresis, leukocyte reduction in whole blood collection is often avoided in an effort to reduce costs, despite evidence suggesting that it reduces -related adverse reactions [35]. In addition, the demand for platelet components is rising substantially worldwide, placing pressure on an already scarce resource [36].

There is currently a lack of concrete evidence on the efficacy and effectiveness of PT in patients with TCP (ie, at risk for bleeding), making clinical decisions difficult. To date, minimal research has been conducted to evaluate and understand the current burden and benefit-risk trade-off of PT use in TCP patients. Therefore, this multi-topic, global systematic literature review (SLR) was conducted to investigate current treatment patterns, benefit-risk assessments, as well as the economic, societal and humanistic burden of therapeutic and prophylactic PT in the TCP patient population.

Methods

Data sources and searches

A SLR was conducted to identify key literature evaluating the use of PT in the TCP population specific to each of the following domains: (1) Randomized controlled trials (RCTs): namely, efficacy and safety, and (2) Real-world evidence (RWE): namely, epidemiology and treatment patterns, effectiveness and safety, as well as humanistic and societal burden, and (3) Economic burden. Separate and unique searches were performed for each domain. Efficacy and effectiveness were reviewed separately. Efficacy is defined as the evaluation of whether an intervention produces the expected result under ideal circumstances, such as RCTs, whereas effectiveness is a measure of the degree of beneficial effect in ‘real-world’ clinical settings [37].

Publications indexed from 1998 to June 27, 2018 (May 23, 2018 for the economic burden domain) were identified from the following sources: MEDLINE® (1946 to present); Embase (1974 to present); Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials; Database of Abstracts of Reviews of Effects; Health Technology Assessment database, UK NHS Economic Evaluation database; and reference lists from relevant systematic reviews. Full search terms and search strategies are provided in the appendix (Appendix Table A1). Additional manual searches were conducted.

This study is reported in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [38] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols statement [39].

Study selection

Two independent reviewers screened titles and abstracts to identify relevant publications based on pre-defined inclusion and exclusion criteria (see Appendix Table A2), and then full text publications were assessed, with any discrepancies resolved by a third independent reviewer.

The patient population was restricted to adults with TCP receiving PT (e.g. such as, but not limited to, patients with chemotherapy-induced TCP, patients with bone marrow suppression, and patients with or without CLD undergoing elective invasive procedures).

Specific to epidemiology, treatment patterns and economic burden, only studies that pertained to the USA, Japan or European Union Five (France, Germany, Italy, Spain and UK) were included. For the remaining searches, studies were not restricted to a geographic location.

Data extraction and quality assessment

Data from studies meeting pre-specified criteria were extracted using Excel tables by 1 reviewer and validated for accuracy and quality by a second reviewer. Outcomes of interest varied according to the domain evaluated, and are summarized in Appendix Table A2. For RCTs, quality was assessed using the Cochrane Risk of Bias Tool for RCTs [40], and RWE studies were assessed using the Newcastle-Ottawa Scale [41]. A risk of bias assessment in RCTs is provided in Appendix Table A3 and a quality assessment of RWE studies in Appendix Table A4.

Data synthesis and analysis

Detailed evidence tables were created and studies summarized by project reviewers. Due to the heterogeneity of interventions examined, and the range of
methods between studies, tables were designed to capture relevant study findings. Study results are presented as a descriptive narrative synthesis.

**Results**

A total of 3425 abstracts were identified through database searches as well as additional sources (Figure 1). Following omission of duplicates \((n = 625)\) 2800 abstracts were screened and 2456 excluded. A total of 344 full-text publications were assessed and from these 150 were excluded leaving 194 publications, with 190 studies included (see Appendix Table A5).

**RWE: epidemiology and treatment patterns**

The treatment patterns of PT were identified in 79 publications. The patient populations were TCP overall in 55 publications, TCP and elective invasive procedure in 20 publications and CLD TCP and elective invasive procedure in 4 publications. The epidemiology and treatment patterns reported in 77 of these 79 publications are summarized in Appendix Table A6. The remaining 2 studies looked at either compliance among 113 patients who received PT [42] or the role of the CD40 ligand in adverse reactions to PT [43].

**Patient types in which platelet transfusions were used**

The use of PT was reported in several studies including large cohorts (>1000 patients with TCP). A review of admissions to a single institution over 5 years, found that of 40,693 patients, 9158 (22.5%) patients had TCP (PC \(< 100 \times 10^9/L\)) [44]. Approximately a quarter (24.5%) of those patients with TCP were transfused platelets. Use of PT in a total of 3743 patients with chronic ITP was analyzed and 1.7% received platelets [45]. In a population of 18204 patients undergoing interventional radiology procedures, 2060 (11.3%) had a PC \(\leq 100 \times 10^9/L\) prior to their procedure [46]. Approximately a tenth (9.9%) of these patients received pre-procedural platelets, and their median baseline PC was 39 \(\times 10^9/L\) compared to 77 \(\times 10^9/L\) for those who did not require pre-procedural PT. In a study of 47,159 patients undergoing chemotherapy for solid tumors, over 4800 patients had a PC \(\leq 150 \times 10^9/L\) [47]. PTs were reported in 2.5% of the 47159 patients treated.

**Platelet transfusions by age**

Use of PT by age was reported in one study treating patients with non-Hodgkin lymphoma [48]. A total of 23 of the 108 patients received platelets during treatment. A quarter (26%) of patients aged 65 years or older required a PT, whilst a smaller proportion (18%) of patients aged less than 65 years required a PT.

**Therapeutic versus prophylactic platelet transfusions**

The use of PT for therapeutic or prophylactic purposes was reported in 3 studies. Over 7400 PTs administered to 503 patients over 6 months were analyzed [49]. Patients receiving prophylactic PT were compared to those receiving therapeutic PT. Nearly three quarters

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Figure 1. Global PRISMA diagram. PRISMA = Preferred reporting items for systematic reviews and meta-analysis; RCT = randomized controlled trial; RWE = real-world evidence. *8 of 194 publications were captured and/or extracted in more than one domain.
Platelet transfusions in patients with chronic liver disease

The use of PTs in patients with CLD undergoing elective invasive procedures was reported in 4 publications. In Benson et al. 64% of 525 liver transplant patients required at least 1 unit of intra-operative PT [52]. In a study by Pillarsetti et al. of cardiac catheterization in 43 patients with end-stage liver disease, of 12 patients with PC <60 × 10^9/L, 5 patients received PT compared to none of the 31 patients with PC >60 × 10^9/L [53]. Mean baseline PC in those receiving PT was 34.8 × 10^9/L compared to 93.0 × 10^9/L in those who did not receive PT. Giannini et al. studied 121 patients with liver cirrhosis, and the prevalence of TCP (PC <150 × 10^9/L) and severe TCP (PC <75 × 10^9/L) was 84% and 51%, respectively [54]. A pre-procedural PT was administered to 7 (14%) of 50 patients with TCP who had an invasive procedure. There was no significant difference in mean PC between those who received PT (45.3 × 10^9/L) and those who did not (51.9 × 10^9/L). Of the patients with severe TCP, 32 patients had an invasive procedure. The proportion of bleeding and non-bleeding patients with severe TCP who had an invasive procedure and received prophylactic PT was 40% and 14%, respectively. A total of 363 patients with cirrhosis were included in a study by Napolitano et al. examining PC and bleeding following invasive procedures [55]. Bleeding events were recorded in 8 patients with a pre-procedural PC <150 × 10^9/L, 5 of whom had received prophylactic PT. Of an additional 10 patients with a pre-procedural PC <150 × 10^9/L who did not experience post-procedural bleeding, 6 patients had received prophylactic PT. The authors reported that post-infusion PC was barely affected.

In summary, the use of PT in patients with TCP varied widely across studies, from 0% to 100% of patients; in studies with large cohorts (>1000 patients with TCP), PT administration ranged from 1.7% [45] to 24.5% [44] of patients. When indications for use were reported, transfusions were generally prophylactic rather than therapeutic.

RCTs: efficacy and safety

The efficacy and safety of PTs were discussed in 47 publications covering 43 primary RCTs, with 1 publication including 2 RCTs [56] and 5 publications [57–61] including additional analyses of 4 of the RCTs [62–65]. Prophylactic PT was the intervention in 34 of the 43 primary RCTs, being compared with no treatment in 5 studies, with other treatments in 2 studies, and included in both intervention and comparator arms in the remaining 27 studies. The efficacy and safety results for the 7 RCTs comparing prophylactic PT with best supportive care alone or with other treatments are summarized in Table 1. The remaining 9 of the 43 primary RCTs looked at other drugs to treat TCP, with therapeutic PT included as best supportive care in both arms. There was significant heterogeneity in primary outcome measures, with some reporting the effects on PC and requirement for therapeutic PT, while others focused on adverse events (AEs) including risk of bleeding and transfusion reactions.

Underlying etiology of TCP was CLD in 8, chemotherapy-induced in 2, hematological malignancies in 2, and mixed in 25 (broadly ‘hematological’ in 16) RCTs. All were performed in a non-emergency setting, when patients were thrombocytopenic but not actively bleeding, and PT was used prophylactically to raise PC. Most studies allowed for therapeutic use of PT in any of the treatment arms if patients began actively bleeding, and strategies of prophylactic versus therapeutic use were formally compared in 1 study [68].

Platelet transfusions: bleeding events and platelet count response

Only 5 RCTs (of the 7 in Table 1) compared prophylactic PT with no intervention/best supportive care. In 2 studies in patients with Dengue fever prophylactic PT did not significantly reduce bleeding rates, with 1 study [66] showing the primary outcome of clinical bleeding occurred in 21% of the PT group vs 26% of the controls (p = 0.16), and the other that prophylactic PT did not prevent severe bleeding or shorten time to bleeding cessation [26]. Lye et al. reported that prophylactic PT was associated with more AEs (13 vs 2 in control group, p = 0.0064), although most were non-severe and all fully resolved [66]. The effect of prophylactic PT on PC was transient, with no difference in mean daily PC between the 2 groups except on Day 2. Khan-Assir et al. [26] reported that approximately half the patients showed no response to PT when measured by post-transfusion platelet increment (PPI), although overall PPI was higher at 24 and 72 h post-transfusion in the group who had received
| Article          | TCP Etiology                                                       | PC Criteria for Inclusion | Intervention | Sample Size | Effect on PC | Need for TPT | Bleeding-related Events                                                                 | Other AEs                                                                 |
|------------------|-------------------------------------------------------------------|---------------------------|--------------|-------------|--------------|--------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Lye 2017 [66]    | Dengue and TCP                                                    | PC ≤ 20 × 10⁹/L          | PPT 4U/day if PC ≤ 20 × 10⁹/L in transfusion group; best supportive care alone in control group | 372 (188 PPT, 184 control); ITT analysis: 369 (187 PPT, 182 control). | NR           | NR           | Clinical bleeding (by Day 7 or hospital discharge) occurred in 21% of PPT group vs 26% of control group (p = 0.16). Possibly/probably/definitely related to transfusion: urticaria (3), maculopapular rash (1), pruritus (1), chest pain (1), and 3 SAEs with 1 case each (anaphylaxis, TRALI, fluid overload). | PPT group: 3 severe transfusion reactions, 2 deaths. |
| Khan-Assir 2013 [26] | Dengue and TCP                                                    | PC <30 × 10⁹/L          | PPT          | 87 (43 PPT, 44 control) | 53.6% (22/43) in PPT were non-responders Mean PPI higher in PPT vs no PPT at 24 and 72 h. Patients with lower baseline PC more like to be non-responders. | NR           | NR           | PPT did not prevent development of severe bleeding or shorten time to cessation of bleeding. |
| Veelo 2012 [67]  | Mixed (ICU with uncorrected mild coagulation disorders). Undergoing planned percutaneous dilatational tracheotomy. | PC = 40–100 × 10⁹/L (31.9%); prothrombin time 14.7–20.0 s (56.9%); and/or active treatment with aspirin (31.9%). 20.8% had ≥ 1 factor. Had or were expected to have TCP (PC <30 × 10⁹/L for ≥ 5 days) | FFP and/or PPT (17 patients received PPT alone, 12 received FFP alone, and 6 received both FFP/PPT). PPT if PC <10 × 10⁹/L vs no-PPT | 72 (Randomized: 35 FFP/PPT, 37 control; Analyzed 31 FFP/PPT, 33 control). | NR           | NR           | Median blood loss: FFP/PPT = 3.0 g vs control = 3.0 g (p = 0.96).                  |                                                                                         |
| Stanworth 2013 [65] | Mixed (hematologic malignancies: chemotherapy or SCT)            | PC = 40–100 × 10⁹/L (31.9%); prothrombin time 14.7–20.0 s (56.9%); and/or active treatment with aspirin (31.9%). 20.8% had ≥ 1 factor. Had or were expected to have TCP (PC <30 × 10⁹/L for ≥ 5 days) | FFP and/or PPT (17 patients received PPT alone, 12 received FFP alone, and 6 received both FFP/PPT). PPT if PC <10 × 10⁹/L vs no-PPT | 600 (299 PPT, 301 no-PPT) | NR           | NR           | 43% (128/298) in PPT group vs 50% (151/300) in no-PPT group experienced bleeding of WHO grade 2, 3 or 4 up to 30 days after randomization (p = 0.06 for non-inferiority). The number of days with bleeding episodes (WHO grade 2, 3 or 4) during follow-up was higher (p = 0.004) and time to first bleeding episode shorter (p = 0.02) for the no-PPT group compared to the PPT group. | Proportion of patients with SAE was not significantly different between the groups (7% PPT vs 6% no-PPT). There was 1 transfusion-related SAE in the PPT group (urticaria and angioedema). |
| Stanworth 2014 [60] | Subgroup analysis of Stanworth 2013 for autoHSCT vs chemo/alloHSCT | As above                 | As above     | 600 (AutoHSCT 421; chemo/alloHSCT 179) | NR           | NR           | The reduction in proportion of patients experiencing WHO grade 2, 3 or 4 bleeding seen in the PPT group was greater for chemo/alloHSCT vs autoHSCT (interaction p = 0.04). With no-PPT, the chemo/alloHSCT group showed shorter time to first bleeding episode vs autoHSCT group (HR 1.84 vs 1). | Number of patients with SAE for autoHSCT was 10 with PPT vs 15 with no-PPT, and for chemo/alloHSCT was 10 with PPT vs 3 with no-PPT. Difference between subgroups reached significance (interaction p = 0.02). |

(Continued)
### Table 1. Continued.

| Article | TCP Etiology | PC Criteria for Inclusion | Intervention | Sample Size | Effect on PC | Need for TPT* | Bleeding-related Events | Other AEs |
|---------|--------------|---------------------------|--------------|-------------|--------------|---------------|------------------------|-----------|
| **Wandt 2012 [68]** | Mixed (Hypoproliferative TCP, undergoing intensive chemotherapy for AML or autoHSCT for hematological cancers) | NR | TPT when bleeding occurred vs PPT when morning PC ≤ 10 x 10^9/L | 396 randomized (197 PPT, 199 TPT); 391 analyzed | NR | Mean number of PT was reduced by 33.5% with TPT strategy (1.63) vs PPT (2.44) (p < 0.0001). Reduction was 31.6% with AML and 34.2% with autoHSCT. | 1.12, p = 0.08). Increased number of days with bleeding with no-PPT was similar for both subgroups. | 12 deaths: 2 from fatal cerebral hemorrhage in TPT group, 5 in each group unrelated to major bleeding. |
| **Basu 2012a [64]** | CLD (undergoing planned percutaneous liver biopsy) | NR | A: PPT B: ROM C: ELT (A = 18, B = 23, C = 24) | Pre-op PC (x 10^9/L): PPT 183.8 vs ROM 232.0 (p < 0.05) and vs ELT 189.9 x 10^9/L (NS). 4 w post-op PC (x 10^9/L): PPT 85.9 vs ROM 366.2 and vs ELT 173.6 (both p < 0.001) | NR | No post-biopsy bleeding or hematoma observed in any group. | AEs were only quoted for all 3 groups combined, with the most common being erythema post-injection site 39%, myalgia 24% and local skin rash 20%. |
| **Basu 2012b [59]** | | | | | | | | |
| **Stanca 2010 [69]** | CLD (undergoing dental extraction) | PC = 30–50 x 10^9/L and INR 2–3 | FFP (10 mL/kg) and or PPT (1 unit) vs DDAVP (300 µg intranasal) | 43 randomized (22 FFP/PPT, 21 DDAVP); 36 completed study (19 FFP/PPT, 17 DDAVP) | NR | Only 1 patient in the FFP/PPT group required rescue transfusion (additional FFP but no PT). | One patient in FFP/PPT group had post-procedural bleeding and required additional FFP (but no PT). | One patient in FFP/PPT group had an allergic reaction at end of transfusion, effectively treated with diphenhydramine. |

AE = adverse event; AML = acute myeloid leukemia; autoHSCT = autologous HSCT; chemo/alloHSCT = chemotherapy/allogeneic HSCT; CLD = chronic liver disease; CNS = central nervous system; DDAVP = desmopressin; ELT = eltrombopag; FFP = fresh frozen plasma; HR = hazard ratio; HSCT = hematopoietic stem cell transplant; ICU = intensive care unit; INR = international normalized ratio; IQR = interquartile range; NR = not recorded; PC = platelet count; PPI = post-transfusion platelet increment; PPT = prophylactic PT; PT = platelet transfusion; ROM = romiplostim; SAE = serious adverse event; SCT = stem cell transplant; TCP = thrombocytopenia; TPT = therapeutic PT; TRALI = transfusion-related acute lung injury; WHO = World Health Organization.

*Patients could receive TPT in any study arm across all studies if clinically indicated, including for active bleeding.
prophylactic PT. There were 3 severe transfusion reactions and 2 deaths in the treatment group.

The effect of prophylactic PT on bleeding risk was more mixed in patients with hematological malignancies. Stanworth et al. reported a lower rate of World Health Organization (WHO) grade ≥2 bleeding with prophylactic PT (43% vs 50% control, \( p = 0.06 \) for non-inferiority), although background rate was still high [65]. The prophylactic group also had significantly fewer days with bleeding (\( p = 0.004 \)) and a longer time to first bleeding episode (\( p = 0.02 \)). The proportion of patients with serious AEs was comparable (7% for prophylactic vs 6% control group). Only Wandt et al. formally compared prophylactic PT (PC \( \leq 10 \times 10^9/L \)) with therapeutic PT [68]. Therapeutic use resulted in a 33% reduction in the mean number of PTs given (1.63 therapeutic PTs vs 2.44 prophylactic PTs, \( p < 0.0001 \)). Risk of WHO grade ≥2 (42% vs 19%, \( p < 0.0001 \)) and grade 4 (5% vs 1%, \( p = 0.0159 \)) bleeding was greater in the therapeutic group.

A study by Veelo et al. compared prophylactic PT with no intervention in Intensive Care Unit (ICU) patients undergoing elective percutaneous dilatational tracheotomy, who had mild coagulation disorders [67]. Of note only 32% of patients had TCP and not all (66%) of the intervention group received prophylactic PT. Those who had prothrombin time 14.7–20.0 s, PC 40–100 \( \times 10^9/L \), and/or active treatment with acetylsalicylic acid were randomized to either fresh frozen plasma (FFP) and/or prophylactic PT or no transfusion. Median blood loss and incidence of intratracheal bleeding were similar between the 2 groups.

Two RCTs (included in Table 1), both in patients with CLD and TCP, compared prophylactic PT to other treatments. Basu et al. randomized patients to either prophylactic PT or a TPO-R agonist (romiplostim or eltrombopag) prior to elective percutaneous liver biopsy [59,64]. Following treatment the pre-procedural PC achieved was significantly lower with prophylactic PT (183.8 \( \times 10^9/L \)) than romiplostim (232.0 \( \times 10^9/L \), \( p < 0.05 \)) but similar to eltrombopag (189.9 \( \times 10^9/L \), \( p = \) not significant [NS]). No post-biopsy bleeding or hema
toma was observed in either group. Stanca et al. [69] reported that intranasal desmopressin was as effective as FFP and/or prophylactic PT in achieving hemostasis in patients with CLD and TCP undergoing dental extraction.

Platelet doses
Six RCTs reported on patient response to different platelet doses, with most using bleeding risk as the primary endpoint and threshold for prophylactic PT of PC \( <10 \times 10^9/L \). The studies differed in their definitions of low (1.1–3.1 \( \times 10^11 \)), standard/medium (0.5–6 \( \times 10^{11} \)) and high (1–5 \( \times 10^{11} \)) dose PT, with significant overlap between groups. Although median number of PT was usually higher with lower doses of platelets, the median number of overall platelets transfused was lower [63,70–72]. Overall, WHO bleeding ≥ grade 2 did not vary significantly between different platelet doses [63,70,71,73], but 1 study [73] was stopped early due to higher rate of grade 4 bleeding in the low dose group (5.2% vs 0% with standard dose). One study showed that relative risk of requiring subsequent therapeutic PT was higher with low platelet doses and transfusion-free interval was shorter [74].

Platelet storage, administration and preparation
The remaining 21 platelet intervention RCTs focused on different methods of platelet storage, administration and preparation, including pathogen inactivation and white blood cell depletion, and the primary endpoints are presented in Appendix Table A7. Five were Phase III trials and in the 21 studies the number of patients randomized ranged from 16 [75,76] to 842 [77]. Efficacy measures included platelet corrected count increment (CCI, defined by formula [78]), bleeding time and time to initiate clotting, while safety included the incidence of transfusion reactions and bleeding. Ten of the RCTs had a primary endpoint related to CCI, and 4 of these demonstrated a significant reduction in CCI at 1 h with various methods of pathogen reduction technol
gy (PRT) including photochemical treatment (PCT) [78–81], whereas 5 did not [82–86], with the remaining study showing a significant reduction in CCI when platelets were stored for 6–7 days as compared to 1–5 days [87]. Three of the RCTs had a primary endpoint related to incidence of transfusion reactions, with 2 studies showing a significant reduction in reactions with use of either a platelet additive solution (PAS) [78] or plasma depletion [88], whilst one study showed no significant difference in reactions between plasma removal and 2 methods of pre-
storage white blood cell reduction [89]. Three of the RCTs had a primary endpoint of bleeding. One study demonstrated the rate of WHO grade 2 bleeding was equivalent between PCT and conventional platelets [62] whilst another study showed the criteria for non-
inferiority for WHO grade 2–4 bleeding with PRT com
pared to controls was met for the intention-to-treat analysis but not the per-protocol analysis [90]. The third study also looked at WHO grade 2–4 bleeding, with non-inferiority achieved for pathogen-reduced platelets in PAS compared to untreated platelets in PAS, but not achieved when compared to untreated platelets in plasma [77].

Non-platelet transfusion therapies including TPO-
R agonists
Nine RCTs investigated non-PT therapies. The majority
were in CLD patients with TCP requiring an invasive
procedure, demonstrating that TPO-R agonists (lusu-
trombopag [91–93], eltrombopag [94] or avatrombo-
pag [56]) increased PC and thereby significantly more
patients met the primary outcome of reduced need for pre-procedural prophylactic PT and any bleeding rescue therapy, including therapeutic PT, compared to placebo (65%–93% out of a total of 624 patients combined across studies for TPO-R agonists vs 13%–38% out of a total of 475 patients combined across studies for placebo, all \( p < 0.01 \)). Two further studies in patients with hematological malignancies suggested that TPO-R agonists (eltrombopag and romiplostim) may be an efficacious alternative to prophylactic PT [95,96]. The final study, in chemotherapy-induced TCP patients, showed that the thrombopoietic agent pegylated recombinant human megakaryocyte growth and development factor can improve PC and reduce need for therapeutic PT [97].

In summary, data from RCTs that compared prophylactic PT with either no intervention or best supportive care were mixed regarding the effect of prophylactic PT on increasing PC and reducing bleeding risk.

RWE: effectiveness and safety

The effectiveness and safety of PTs was discussed in 75 publications, of which 49 included populations of TCP overall, 20 of TCP and invasive elective procedure and 5 of CLD TCP and elective invasive procedure. Data for the effect of PTs on PCs, bleeding and other safety-related events are summarized in Appendix Tables A8–A10. One paper only reported on PT use around the time of delivery in pregnant women with TCP [98].

Platelet transfusions and platelet count response

The effect of PTs on PC was reported in 36 publications with readings 10 min to 72 h post-transfusion, when reported. PTs were generally effective, to some degree, with an increase in PC seen in most patients (\(-4 \times 10^9/L\) to \(262.9 \times 10^9/L\)). One study, that focused on 27 patients receiving PT in the ICU setting, reported that a single PT resulted in a median PC increase of \(14 \times 10^9/L\) measured at 5.2 h post-PT (based on 57 non-overlapping PTs), however, no PC increase was reported for 13 patients (48.1%) after 17 PTs [99]. In another study, also specific to the ICU setting, based on 5700 PTs, the median PC increase after a single PT was \(23 \times 10^9/L\) measured at a median of 7 h post-PT, however 21.8% of transfusions had an ineffectual PC increase of \(<5 \times 10^9/L\) [100]. The independent predictor of an ineffectual response with the greatest odds ratio (1.84 [95% confidence interval: 1.24–2.73], \( p = 0.0024 \)) was liver disease followed by a number of other factors. Refractoriness, defined as a PC increase \(<5 \times 10^9/L\) following PT or 3 consecutive days of PT, was reported in several studies. In a publication examining the safety of endoscopy interventions, 23% of patients were refractory [101]. In a second publication of all hospitalized patients receiving PT over a 6-month period, 22% of patients were refractory [102]. Charbonnier et al. found that only 10 patients out of a total of 1408 with acute myeloid leukemia (AML) were refractory to PT, whilst Wandt et al. stated that platelet refractoriness of clinical significance related to alloimmunization was not reported in their study in AML patients [103,104].

Platelet transfusions and bleeding events

Bleeding events (including minor, major and fatal) were reported in 31 publications (Appendix Table A9). Therapeutic PT and prophylactic PT were compared in the study by Charbonnier et al. of patients with AML [103]. Death from hemorrhage was reported in 2.4% and 0.4% of patients receiving therapeutic PT or prophylactic PT, respectively. The clinical impact of PT in patients with TTP was also investigated [105]. Of 54 patients analyzed, platelets were administered to 33 patients. Death due to hemorrhage was reported in 1 of the 33 patients who received PT and in 1 of 21 patients who received no PT. In a study of over 10,000 hospitalizations for TTP, PT was associated with higher odds ratios of thrombosis and death [21]. Death due to bleeding was also reported in 4 other publications [106–109] (Appendix Table A9). In 50 patients with CLD who underwent invasive procedures, peri-procedural bleeding was reported in 10 patients, of which 40% received prophylactic PT [54].

In 874 patients with cirrhosis, 21 patients (2.4%) had major bleeding after invasive procedures [110]. Platelets were administered pre-procedure to 4 patients and 1 of these developed major bleeding. Post-procedure, PTs were given to 5 patients, of which 2 were in the major bleeding group (in 1 of these PT was given with FFP). The effect of PT in 79 invasive procedures in 42 patients with cirrhosis was analyzed [111]. In 61 procedures, patients received platelets pre-procedure with 3 patients experiencing post-procedural bleeding. Of 18 invasive procedures where patients did not receive platelets pre-procedure, no patient experienced post-procedural bleeding.

Platelet transfusions and safety-related events

A total of 44 publications reported safety-related events. Eighteen studies included mortality data for patients with PT compared to those without PT (Table 2). Statistically significant odds or hazard ratios were reported for increased risk of death after PT in 8 studies [44,46,112,116–118,123,125]. However, in 1 study, death was more frequently reported in patients who had not received PT compared to those that had (2.6% and 0%, respectively, \( p = 0.05 \)) [113]. Despite a higher frequency of deaths for patients administered platelets, the risk of death with PT was actually lower following regression analysis adjusted for covariates, including nadir PC, red blood cell transfusion and need for hemodialysis [112]. Another study reported...
death in the same proportion of patients with or without PT (24% for both, \(p = 0.97\)) [105]. The transfusion of platelets can result in infection and, in severe cases, sepsis. Patient death due to sepsis was reported in 3 publications [105,127,128]. Several studies also reported infection or sepsis associated with PT. Wandt et al. investigated at two different PC triggers (PC count of \(<10 \times 10^9/L\) or \(<20 \times 10^9/L\)) for prophylactic PT in patients with AML [104]. Four of the 7 patients with major (WHO grade 3 or 4) bleeding complications (all in group with PC trigger of \(<20 \times 10^9/L\)) had associated serious infections and sepsis. The safety post-implantation of totally implantable venous access ports was assessed in 181 patients with TCP (55, 58 and 68 patients with mild (PC: 100–150 \(\times 10^9/L\)), moderate (PC: 50–100 \(\times 10^9/L\)) and severe (PC: \(<50 \times 10^9/L\)) TCP, respectively) [129]. Platelets were only administered to patients with severe TCP. Infection was reported in 4% and 9% of patients with mild or moderate TCP, respectively. In the patients with severe TCP, 10% of patients had an infection. Complication rates following dental extraction in 68 patients with TCP were examined, with 32 patients requiring PT [130]. There were 2 cases of infection (2.9% of study population), and 1 of these had received PT. In a multi-center study of patients admitted to ICUs between 2008 and 2013, the association between PT and hospital-acquired infection was investigated [17]. PT was associated with infection. 7.7% of patients with PT had infections compared with 1.4% without PT (\(p = 0.01\)). Infection was also reported in 2 studies in patients with CLD. In 1 study, no significant odds ratio associated with PT for infection was reported [52], whilst a different study reported a statistically significant odds ratio (2.53 [2.0, 3.2], \(p = 0.001\)) [131].

In summary, real-world observational studies demonstrated that PT was generally effective to some degree in increasing PC but did not always translate into a clinically significant increase in PC nor a reduction in bleeding risk. While these studies

### Table 2. Mortality in patients with platelet transfusion compared with patients without platelet transfusion.

| Article | PICOS classification | Treatment/subgroups | N | Deaths (% of patients) | Mortality OR (95% CI) |
|---------|----------------------|---------------------|---|-----------------------|----------------------|
| Arnold 2016 [112] | TCP overall | PT | 5621 | 10.7 | 0.66 (0.46, 0.96) |
| | | No PT | 37,413 | 6.5 | \(p = 0.029\) |
| Beneke 2017 [113] | TCP overall | PT | 44 | 0 | 2.6 |
| | | No PT | 206 | 0 | \(p = ns\) |
| Chandran 2015 [44] | TCP overall | PPT | 1792 | 22.5 within 1 month | 1.8 (1.5, 2.1) |
| | | No PPT | 1792 | 14.3 within 1 month | \(p < 0.001\) |
| Chen 2011 [114] | TCP and elective invasive procedure | PT, PC \(<10 \times 10^9/L\) | 10 | 0 | NR |
| | | No PT, PC \(<10 \times 10^9/L\) | 20 | 0 | NR |
| | | No PT, PC 10–30 \(\times 10^9/L\) | 24 | 0 | NR |
| | | No PT, PC \(\geq 30 \times 10^9/L\) | 27 | 0 | NR |
| Duffy 2013 [115] | TCP and elective invasive procedure | Pre-procedure PT | 14 | 43 | NR |
| | | No PT | 41 | 5 | NR |
| Goel 2014 [116] | TCP overall | TTP hospitalizations, PT | NR | NR | 2.02 (1.26, 3.22) |
| | | TTP hospitalizations, no PT | NR | NR | \(p < 0.001\) |
| | | HIT hospitalizations, PT | NR | NR | 4.72 (1.53, 14.53) |
| | | HIT hospitalizations, no PT | NR | NR | \(p < 0.01\) |
| | | ITP hospitalizations, PT | NR | NR | 1.06 (0.79, 1.42) |
| | | ITP hospitalizations, no PT | NR | NR | \(p = 0.07\) |
| Guerrero 2017 [117] | TCP overall | PT | 302 | NR | 1.39 (1, 1.94) |
| | | No PT | 2270 | NR | \(p = 0.005\) |
| Kuter 2017 [118] | TCP overall | PT | 442 | NR | 2.81 (1.54, 5.12) after PT, \(p < 0.001\) |
| Lee 2016 [119] | TCP overall | PT | 486 | 0.2 | \(p = 0.43\) |
| | | No PT | 302 | 0.0 | \(p = 1.00\) |
| Lye 2009 [120] | TCP overall | PPT | 188 | 1 | \(p = 0.001\) |
| | | Non-PPT | 68 | 0 | NR |
| Makroo 2014 [121] | TCP overall | PT | 30 | 60 | NR |
| | | No PT | 21 | 10 | \(p = 0.30\) |
| Otrock 2015 [122] | TCP overall | PT | 23 | 13 | \(p = 0.001\) |
| | | No PT | 32 | 3 | \(p = 0.001\) |
| Sethi 2017 [123] | TCP overall | PT | 209 | 1.9 | \(p = 0.024\) |
| | | No PT | 430 | 0.2 | \(p = 0.001\) |
| Swisher 2009 [124] | TCP overall | PT | 33 | 24 | \(p = 0.97\) |
| Tran 2010 [125] | TCP overall | PT/major bleed | NR | 12 | \(p = 0.12\) |
| | | No PT/major bleed | NR | 9 | \(p = 0.07\) |
| Warner 2017 [46] | TCP and elective invasive procedure | No PT | 203 | 21.7 | 2.55 (1.76, 3.68) |
| | | No PPT | 1857 | 9.8 | \(p = 0.001\) |
| Warner 2016 [125] | TCP and elective invasive procedure | Pre-procedure PT | 71 | 27 | 3.20 (1.80, 5.67) |
| | | No PT | 789 | 10.1 | \(p = 0.001\) |
| Yoshii 2014 [126] | TCP overall | PT | 48 | 23 | \(p = ns\) |
| | | No PT | 215 | 17.7 | \(p = ns\) |

Ci = confidence interval; IT = heparin-induced thrombocytopenia; HR = hazard ratio; ITP = immune thrombocytopenia; NR = not reported; ns = not significant; OR = odds ratio; PICOS = population, interventions, comparators, outcomes, study design; PPT = prophylactic platelet transfusion; PT = platelet transfusion; TCP = thrombocytopenia; TTP = thrombotic thrombocytopenia purpura.

*Hazard ratio presented in this publication.
demonstrated an association between PT and safety events, results with regards to increased mortality rate following PT were varied, with either no difference or an increased mortality rate associated with PT.

**RWE: humanistic and societal burden**

Two publications discussed the humanistic and societal burden of PT. The first reported completed surveys from 294 patients classified as a population of TCP overall and 73 surgeons and anaesthesiologists. Fewer patients rated transfusion as ‘very often’ or ‘always risky’ compared to their physicians (20% and 39%, respectively, \( p = 0.001 \)) [132]. The second study recruited a population of TCP and elective invasive procedure of 25 patients who were receiving their first transfusion. One third of patients were ‘concerned or worried’ about receiving the transfusion [133].

**Economic burden**

The economic burden of PT was discussed in 26 publications. Most (19 of 26) included a population of TCP overall, and 4 included a population of CLD TCP and elective invasive procedure. Patients in the 3 remaining publications were not classified but involved PT patients in 2 publications. The third was a survey of the National Blood Collection in the USA and included information from hospitals, blood centers and cord blood banks. Costs, including those associated with transfusion-related events, were reported in 23 of the 26 publications. These data are summarized in Table 3. The 3 remaining publications reported on the number of units transfused or transfusion episodes [49,104,154].

The overall costs of PTs were assessed at a tertiary care hospital in the USA [102] where a median hospitalization cost of $27,750 was reported. This varied depending on the service used with internal medicine/other costs lowest at $13,856 and the highest cost associated with BMT ($58,729). Notably, there was a statistically significant difference in mean cost between refractory and non-refractory patients ($103,956 and $37,818, respectively; \( p < 0.001 \)).

A cost analysis based on data from the Trial of Prophylactic Platelets trial [65,140] suggested that prophylaxis resulted in lower rates of bleeding compared to no prophylaxis. The authors examined the cost of prophylaxis and no prophylaxis policies. The total health care costs per 30 days, per patient were statistically significantly higher in the prophylaxis group compared to the no prophylaxis arm ($16,753 and $14,992, respectively). There was a statistically significant difference in favor of no prophylaxis in the cost of the units transferred and of the investigations and medications between the prophylaxis and no prophylaxis arm. In a separate publication, the health care costs of patients undergoing chemotherapy cycles complicated by TCP was compared to cycles in those same patients not complicated by TCP [142]. The mean cost of providing prophylaxis for a cycle was $792. Furthermore, the mean cost of treatment of bleeding was higher in TCP cycles compared to control cycles ($237 and $14, respectively). The mean cost of treating other complications was also higher in TCP cycles compared to control cycles, resulting in mean total costs of $6866 for TCP cycles and $4875 for control cycles (\( p < 0.001 \)).

The wholesale acquisition cost of PT was compared to that of the TPO-R agonists romiplostim and eltrombopag in a randomized, double blind clinical pilot trial [64]. Both romiplostim and eltrombopag increased pre-operative PC to a similar or greater extent as PT with a cost of less than 50% of PT ($2284 and $2991, based on off-label dosing, respectively compared to $7500 for PT). In another study, the usual standard of PTs was compared to the use of recombinant human interleukin-11 (rhIL-11, oprelvekin) for prophylaxis of severe chemotherapy-induced TCP [141]. The overall cost of the usual standard of PT over the 3-week chemotherapy cycle was $3495 compared to $5328 for rhIL-11 group over the same period. Although, the rhIL-11 group had fewer PTs and therefore avoided potential adverse reactions to transfusion, the cost of the drug was substantial, resulting in a higher overall cost.

An additional cost associated with PT is the treatment of transfusion-related events. The annual cost of such events was reported in 2001 for the USA [135]. Hospitalization due to transfusion-related sepsis cost $6408, whilst treating hepatitis B or C virus transfusion-related events cost between $1228 and $17,412 a year. In a further publication the estimated average treatment cost for acute-transfusion reactions (ATRs) in Germany was reported [136]. Grade 1 ATRs such as chills, fever and urticaria cost on average €104. For Grade 2 ATRs such as urticaria with itching, hypotension or fever >40°C, the average cost was €238. Finally, Grade 3 allergic and bacterial ATRs cost €1200 and €21,984, respectively.

Across publications reporting PT costs in CLD patients, the reported estimated cost for 1–2 PTs ranged from $500 [138] to $1639 [69], while the total estimated costs of PT were reported as $5258–13,117 in 1 publication and $4800–11,000 in another [134,138].

In summary, the available data show that PT represents a substantial cost burden. The economic costs associated with PTs extends beyond the collection and delivery of transfusion units, and there are significant costs associated with transfusion-related events.

**Conclusions**

PT has been considered the ‘gold-standard’ treatment for increasing PC in thrombocytopenic patients [155], and is recommended in current guidelines [10,11,13]. However, researching the efficacy and effectiveness
Table 3. Summary of the economic burden of platelet transfusions and comparators.

| Article | PICOS Classificationa | Outcome | Subgroup | Sample Size | Cost | Year | P |
|---------|-----------------------|---------|----------|-------------|------|-------|---|
| Barnett 2018 [134] | CLD TCP and elective invasive procedure | Total estimated cost of a PT | All | NR | 5258–13,117 USD | 2017 | NR |
| Basu 2012b [59] | CLD TCP and elective invasive procedure | Cost (wholesale acquisition cost) | PT, Romiplostim, Eltrombopag | 18, 23, 24 | 500–1000 USD | 2012 | NR |
| Bell 2003 [135] | TCP overall | Random-donor pooled platelet concentrate | Single-donor apheresis platelets, Pathogen inactivation cost per unit, Annual cost of treating transfusion-related sequelae | All | 469 USD, 100 USD, 45,776 USD | 2001 | NR |
| Berger 2013 [136] | TCP overall | Estimated average costs of ATRs Grade 1 | All | NR | 104 EURO | 2013 | NR |
| Birchall 2017 [137] | TCP overall | Cost of dose | All | 1,781 PTs | 193 GBP | 2016/17 | NR |
| Brown 2007 [138] | CLD TCP and elective invasive procedure | Average cost of care during cycles | Patients with TCP, Patients without TCP | All | 6866 USD, 4875 USD | <0.001 |
| Campbell 2014 [140] | TCP overall | Costs of PLT units transfused per 30 day per patient | No prophylaxis, Prophylaxis | 301, 299 | 966 USD, 11,976 USD | <0.001 |
| Cantor 2003 [141] | TCP overall | Expected costs per 3-week cycle | Usual care, rhl-11 | 27 | 5328 USD | 2003 | NR |
| Elting 2003 [142] | TCP overall | Reported cost per PT | All | NR | 590 USD | 1999 | NR |
| FDA 2006 [143] | NR (PT patients) | Costs of bacterial testing of single unit WBD PLTs and speciation of bacterially contaminated PLTs (transfusion services) | Low annual cost, Medium annual cost, High annual cost | 164,000, 164,000, 164,000 | 446,095 USD, 892,333 USD, 1,338,370 USD | 2013 | NR |
| Forsythe 2017 [144] | TCP overall | Rescue medication/transfusion costs | Eltrombopag + PT, Romiplostim + PT | 650, 380 | 1220 USD, 1906 USD | 2017 | NR |

(Continued)
of PT is challenging, with limited numbers of RCTs, with a variety of outcome measures and clinical outcomes. This SLR has demonstrated that TCP patients are a heterogeneous group. In studies including large cohorts (>1000 patients with TCP), PT use varied widely between 1.7% and 24.5% of patients [44,45]. Some variability may be explained by the differences in patient baseline characteristics both between and within studies, including type of procedure, underlying medical condition(s), and patient age. Evidence for the impact of these differences is largely lacking, although one study in patients with non-Hodgkin lymphoma showed that older patients had a higher incidence of PT [48].

In one real-world observational study comparing therapeutic PT versus prophylactic PT in patients with AML [103], death from hemorrhage was reported in more patients receiving therapeutic PT than prophylactic PT. Also, in one RCT comparing therapeutic PT versus prophylactic PT [68], the grade 4 bleeding risk was greater in the therapeutic group; however therapeutic use resulted in a 33% reduction in the mean number of PTs given. Data from trials directly comparing prophylactic PT with no intervention/best supportive care were mixed regarding the effect of prophylactic PT on increasing PC and reducing bleeding risk [26,65–68]. One study demonstrated increases in PC with PT but rates of non-response were high [26], and in another study PC increases were only transient [66]. Studies reporting on the response to different platelet doses suggested that lower doses led to an overall reduction in number of platelets transfused [63,70–72], although one study was stopped early due to a higher rate of grade 4 bleeding in the low dose group [73]. PC threshold for intervention varied widely, due to heterogeneity in patient type and procedure, and ranged from <10 to ≤100 x 10^9/L [46,139]. This is reflected in a recent guideline update from the American Society of Clinical Oncology that recommends PC thresholds ranging from 10 to 50 x 10^9/L depending on patient characteristics or whether the patient will undergo invasive procedures [10]. These data support further investigation of PT strategies and doses to ensure that the benefits of PTs are maximized whilst minimizing the risks.

Real-world observational studies demonstrated that although PT might be effective to some degree in increasing PC, it did not always translate into a clinically

| Article                  | PICOS Classification | Outcome                                                                 | Subgroup                 | Sample Size | Cost       | Year | P     |
|-------------------------|----------------------|-------------------------------------------------------------------------|--------------------------|-------------|------------|------|-------|
| Jimenez-Marco 2014 [145]| TCP overall          | Cost of outdated PLT units                                             | Pre PRT PLT              | NR          | 310,861 USD | 2014 | NR    |
|                         |                      |                                                                         | Post PRT PLT             | NR          | 2368 USD   |      |       |
| Juskewitch 2017 [146]   | TCP overall          | Cost of apheresis PLT (institution-run blood bank)                     | All                      | NR          | 460 USD    | 2017 | NR    |
| Lin 2017 [147]           | TCP overall          | Mean reimbursement costs of 14,115 bleeding-related episodes           | All                      | 6651        | 5606 USD   | 2013 | NR    |
| Meehan 2000 [102]       | TCP overall          | Total hospitalization costs (median) per admission                     | All                      | 245         | 27,750 USD | 2000 | NR    |
|                         |                      | Total hospitalization costs (mean)                                     | Refractory               | 63          | 103,956 USD| <0.001|
| Paessens 2012 [148]     | TCP overall          | Mean cost of PT of 189 CT lines                                        | All                      | 229         | 37,818 USD | 2016 | NR    |
| Riley 2012 [149]        | TCP overall          | Simulated total cost/patient                                           | Low-dose strategy        | 259         | 4504 USD   | 2012 | NR    |
| Staginnus 2004 [150]    | TCP overall          | Estimated net cost                                                     | Medium-dose strategy     | 259         | 5658 USD   |      |       |
| Stang 2010 [69]         | CLD TCP and elective | PT- fixed costs                                                         | Without IBS NR           | 19          | 16,908 YEN | 2004 | NR    |
|                        | invasive procedure   | PT- single donor platelets costs with blood transfusion treatment       | With IBS NR              | 19          | 20,806 YEN |      |       |
|                        |                      | Approximate costs per patient associated with blood transfusion treatment | All                      | 19          | 537 USD    | 2008 | NR    |
|                        |                      | Approximate costs per patient associated with desmopressin treatment    | All                      | 19          | 932 USD    |      |       |
|                        |                      |                                                                        | All                      | 17          | 700 USD    |      |       |
| Stokes 2018 [151]       | TCP overall          | Mean costs of administering blood (PLT) per unit transfused            | All                      | NR          | 84 USD     | 2014 | S     |
| Whittaker 2011 [152]    | NR (PT patients)     | Mean hospital amount paid per apheresis PLT (leukocyte reduced)        | All                      | NR          | 535 USD    | 2011 | NR    |
| Whittaker 2016 [153]    | NR (PT patients)     | Mean hospital amount paid per apheresis PLT (leukocyte reduced)        | All                      | NR          | 517 USD    | 2013 | NR    |

**Abbreviations:** AIDS = acquired immune deficiency syndrome; ATL = adult T-cell lymphoma; ATR = acute transfusion reaction; BMT = bone marrow transplantation; CIT = chemotherapy-induced thrombocytopenia; CLD = chronic liver disease; CT = chemotherapy; GBP = Pound sterling; HAM = HTLV-I-associated myelopathy; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HTLV-I = human T-cell lymphotropic virus type I; IBS = intercept blood; PRT = pathogen reduction technology; PICOS = population, interventions, comparators, outcomes, study design; PT = platelet transfusion; rhIL-11 = recombinant human interleukin-11; TCP = thrombocytopenia; USD = United States dollar; WBD = whole blood derived.

**PICOS classification based on population, interventions, comparators, outcomes and study design.**

**A stringent prophylactic-platelet transfusion policy <10 x 10^9/L for stable patients and <20 x 10^9/L in the presence of major bleeding or additional risk factors. A trigger of <50 x 10^9/L was introduced for patients undergoing invasive procedures.**

**Units of currency not provided in the publication.**
significant reduction in bleeding risk [54,111], and refractoriness was a significant problem [101,102]. PT was also associated with safety concerns, including an increased infection risk in some studies [17,131]. Studies varied as to whether mortality rate was higher following PT, with 8 showing a significantly increased odds ratio/hazard ratio [44,46,112,116–118,123,125], although in one the rate was lower after regression analysis adjusted for covariates [112], and others showed no difference [105]. It is noteworthy that in individual RWE studies comparing PT versus no PT, patients receiving PT might have been at higher risk than patients who did not receive PT which can create potential bias when comparing results.

Publications that discussed the humanistic burden of PT demonstrated that 20% of patients rated transfusion as ‘very often’ or ‘always risky’ [132] while one third of patients were ‘concerned or worried’ about receiving PT [133]. Limited research on the humanistic and societal burden of PT means that the impact of this procedure on patient experience and quality of life is also largely unknown.

Evidence is lacking for the cost-effectiveness of PT, and most studies examining the economic burden of PT in this SLR did not distinguish between prophylactic and therapeutic use. Available data show that PT represents a substantial cost burden [102], and this includes the higher costs associated with the management of transfusion-related AEs [135,136] and particularly those associated with PT-refractory status [102]. Measures to decrease PT-related costs could include implementing uniform management algorithms, as well as updating guidelines and protocols to include appropriately licensed treatment alternatives such as pharmacotherapy options.

Due to this growing evidence of the limitations of PT, alternative treatment approaches to increase PC are being investigated. Studies with TPO-R agonists demonstrated promising results in reducing patients’ need for pre-procedural prophylactic PT and any bleeding rescue therapy, including therapeutic PT, from 65% to 93% vs 13% to 38% for placebo [56,91–94]. Although PTs are used to varying degrees for increasing PC in TCP, it is important to understand the limitations of PTs, and to explore the use of alternative treatment options where available.

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Availability of data and material

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

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### Table A1. Search terms and search strategy.

#### Search strategy: randomised controlled trials

| Database          | Search terms                                                                 | Limits*                                                                 |
|-------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Medline and Embase on 27-Jun-2018 | exp thrombocytopenia/ OR thrombopenia?.mp. OR thrombocytopenia?.mp. OR thrombocytopenic.mp. AND exp platelet transfusion/ OR thrombocyte transfusion?.mp. OR platelet transfusion?.mp. | Publication dates: Year 1998 to current. Study type: (Randomized controlled trial (topic)/ OR randomized controlled trial/ OR random allocation/ OR double blind method/ OR single blind method/ OR clinical trial/ OR exp clinical trials (topic)/ OR (clinical trial/ OR clinical trial, phase i/ OR clinical trial, phase ii/ OR clinical trial, phase iii/ OR clinical trial, phase iv/ OR multicenter study/)) OR (Randomized controlled trial.pt. OR controlled clinical trial.pt. OR random allocation.sh. OR double blind method.sh. OR single blind method.sh. OR clin$.adj25 trial$.tw OR ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$ or dummy$)).tw. OR placebo/ OR placebo$tw. OR placebo$.sh. OR random$.tw.) NOT (case report.tw. OR letter/ OR historical article/) Species: Humans |
| Cochrane on 27-Jun-2018 | Thrombocytopenia (MESH descriptor; explode all trees) OR thrombopenia:ti,ab,kw (and word variations of) OR thrombocytopenia:ti,ab,kw (and word variations of) AND Platelet transfusion (MESH descriptor; explode all trees) OR thrombocyte transfusion*:ti,ab,kw (and word variations of) OR platelet transfusion*:ti,ab,kw (and word variations of) | Publication dates: From year 1998 Study type: Trials |

#### Search strategy: economic burden

| Database          | Search terms                                                                 | Limits*                                                                 |
|-------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Medline and Embase on 22-May-2018 | exp thrombocytopenia/ OR thrombopenia?.mp. OR thrombocytopenia?.mp. OR thrombocytopenic.mp. AND exp platelet transfusion/ OR thrombocyte transfusion?.mp. OR platelet transfusion?.mp. AND exp costs/ OR exp cost analysis/ OR exp health care costs/ OR exp economics/ OR exp value of life/ OR (burden adj5 (disease or illness)).tw. OR (cost$ or economic$ or expenditure$ or price$ or pharmacoeconomic$).tw. OR (resource adj5 (allocation$ or utilit$)).tw. OR (value adj5 money).tw. | Publication dates: Year 1998 to current. Countries: Japan OR Japanese OR US OR USA OR American OR Europe OR European OR France OR French OR Germany OR German OR Spain OR Spanish OR Italy OR Italian OR UK OR United Kingdom OR EU-5 OR EU5 OR (England OR Scotland OR Ireland OR Wales OR English OR Scottish OR Welsh OR Irish OR British OR Great Britain).mp. Species: Humans |
| Cochrane on 23-May-2018 | Platelet transfusion (MESH descriptor; explode all trees) OR thrombocyte transfusion*:ti,ab,kw (and word variations of) OR platelet transfusion*:ti,ab,kw (and word variations of) | Publication dates: From year 1998 Study type: Economic evaluations |

#### Search strategy: real-world evidence: effectiveness and safety, epidemiology and humanistic burden

| Database          | Search terms                                                                 | Limits*                                                                 |
|-------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Medline and Embase on 27-Jun-2018 | exp thrombocytopenia/ OR thrombopenia?.mp. OR thrombocytopenia?.mp. OR thrombocytopenic.mp. AND exp platelet transfusion/ OR thrombocyte transfusion?.mp. OR platelet transfusion?.mp. | Publication dates: Year 1998 to current. Study type: Epidemiologic studies/ OR clinical study/ OR case control study/ OR family study/ OR longitudinal study/ OR retrospective study/ OR (prospective study/ NOT randomized controlled trials/) OR cohort analysis/ OR (cohort adj (study OR studies)).mp. OR (case control adj (study OR studies)).tw. OR (follow up adj (study OR studies)).tw. OR (observational adj (study OR studies)).tw. OR (epidemiologic adj (study OR studies)).tw. OR (cross sectional adj (study or studies)).tw. OR cohort studies/ OR case control.tw. OR cohort analy$.stw. OR longitudinal.tw. OR retrospective.tw. OR cross sectional.tw. OR cross-sectional studies/ NOT Letter/ OR historical article/ Species: Humans |
Table A1. Continued.

Search strategy: additional handsearches

| Database | Websites |
|----------|----------|
|          | French National Authority for Health (HAS) (France) |
|          | French National Blood Service (EFS) (France) |
|          | Institute for Quality and Efficiency in Healthcare (IQWIG) (Germany) |
|          | Spanish Agency for Health Technology Assessment (AETS) (Spain) |
|          | Committee on Pharmaceuticals/Italian Medicines Agency (AIFA) (Italy) |
|          | National Institute for Health and Care Excellence (NICE) (UK) |
|          | Joint UK Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) (UK) |
|          | Food and Drug Administration (FDA) (USA) |
|          | Agency for Healthcare Research and Quality (AHRQ) (USA) |
|          | Pharmaceuticals and Medical Devices Agency (PMDA) (Japan) |
|          | European Medicine Agency (EMA) (Europe) |

Conference searches (all were indexed in Embase):
|          | International Society of Blood Transfusion (ISBT) |
|          | British Blood Transfusion Society (BBTS) |
|          | AABB Center for Cellular Therapies (AABB) |
|          | European Hematology Association (EHA) |
|          | American Society of Hematology (ASH) |
|          | International Society of Hematology (ISH) |
|          | American Association for the Study of Liver Diseases (AASLD) |
|          | European Association for the Study of the Liver (EASL) |
|          | European Society for Medical Oncology (ESMO) |
|          | American Society of Clinical Oncology (ASCO) |

*Duplicates removed.

Table A2. Detailed inclusion and exclusion criteria.

| Domain | Inclusion criteria | Exclusion criteria |
|--------|--------------------|--------------------|
| RCT: efficacy and safety | Adults (≥18 years) with TCP having elective invasive procedures or surgeries | Children (<18 years) |
|         | Adults (≥18 years) with CLD TCP having elective invasive procedures or surgeries | Adults receiving PT on emergent-basis |
|         | Adults (≥18 years) with TCP (such as but not limited to CIT, bone marrow suppression) | Mixed population with outcomes not separable by the POI |
| Interventions | PT or PT as BSC | NA |
| Comparators | Difference between treatment arms in PT used as BSC of more than 30% | NA |
| Outcomes of interest | Efficacy: Increase in PC, CCI and platelet response | NA |
|         | Total bleeding events and fatal, life-threatening and other individual bleedings | NA |
|         | Safety: Total AEs, SAEs and severe AEs | NA |
|         | Complications, infections, allergic reactions, TRALI and TACO | NA |
|         | All-cause mortality | NA |
| Study design | RCT | Animal/in vitro studies; letters, comments; individual case reports; editorials |
| Publication year | Publications indexed in the databases since 1998; abstracts or other materials from conferences from the last 10 years/meetings | NA |
| Language | No restrictions on language | NA |
| Other | NA | NA |

RWE: effectiveness, safety, epidemiology and humanistic burden

| Domains | Inclusion criteria | Exclusion criteria |
|---------|--------------------|--------------------|
| Adults (≥18 years) with TCP having elective invasive procedures or surgeries | Children (<18 years) |
| Adults (≥18 years) with CLD TCP having elective invasive procedures or surgeries | Adults receiving PT on emergent-basis |
| Adults (≥18 years) with TCP (such as but not limited to CIT, bone marrow suppression) | Mixed population with outcomes not separable by the POI |
| Interventions | PT or PT as BSC | NA |
| Comparators | NA | NA |
| Outcomes of interest | Efficacy: Increase in PC, CCI and platelet response | NA |
|         | Total bleeding events and fatal, life-threatening and other individual bleedings | NA |
|         | Safety: Total AEs, SAEs and severe AEs | NA |
|         | Complications, infections, allergic reactions, TRALI and TACO | NA |
|         | All-cause mortality | NA |
| Study design | Prospective or retrospective observational studies | Animal/in vitro studies; letters, comments; individual case reports; editorials |
| Publication year | Publications indexed in the databases since 1998; abstracts or other materials from conferences from the last 10 years/meetings | NA |
| Language | No restrictions on language | NA |
| Other | Focus on US, EU-5, Japan; sample size ≥30 patients | NA |

(Continued)
### Table A2. Continued.

| Domain                  | Inclusion criteria                                                                 | Exclusion criteria                                                                 |
|-------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| **Economic burden**     | **Populations** Adults (≥18 years) with TCP having elective invasive procedures or surgeries | Adults (≥18 years) with TCP having elective invasive procedures or surgeries (<18 years) |
|                         | Adults (≥18 years) with CLD TCP having elective invasive procedures or surgeries   | Adults (<18 years) with TCP having elective invasive procedures or surgeries (<18 years) |
|                         | Adults (≥18 years) with TCP (such as but not limited to CIT, bone marrow suppression) | Adults receiving PT on emergent-basis mixed population with outcomes not separable by the POI |
| **Interventions**       | PT or PT as BSC                                                                    | NA                                                                                |
| **Comparators**         | Non-PT interventions; no comparator                                               | NA                                                                                |
| **Outcomes of interest**| Costs associated with PT AE / complications following PT                           | Resource use (number of PT doses, number of admissions, etc.)                      |
| **Study design**        | Any                                                                               | Animal/in vitro studies; letters, comments; individual case reports; editorials   |
| **Publication year**    | Publications indexed in the databases since 1998; abstracts or other materials from conferences from the last 10 years/meetings | NA                                                                                |
| **Language**            | No restrictions on language                                                        | NA                                                                                |
| **Other**               | Focus on US, EU-5, Japan                                                           | NA                                                                                |

AE = adverse event; BSC = best supportive care; CCI = corrected count increment; CIT = chemotherapy-induced thrombocytopenia; CLD = chronic liver disease; EU = European Union; NA = not applicable; PC = platelet count; POI = population of interest; PT = platelet transfusion; RCT = randomized controlled trial; RWE = real world evidence; SAE = serious adverse event; TACO = transfusion-associated circulatory overload; TCP = thrombocytopenia; TRALI = transfusion-related acute lung injury; US = United States.

### Table A3. Risk of bias assessments of randomized controlled trials.

| Article                          | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Attrition bias | Reporting bias |
|----------------------------------|---------------------------|------------------------|----------------------------------------|-------------------------------|------------------------|---------------------|----------------|----------------|---------------|
| Afdhal 2012 [94]                 | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Afdhal 2017 [91]                 | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Khan-Assir 2013 [26]             | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Basu 2012 [64]                   | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| de Wildt-Eggen 2000 [78]         | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Diedrich 2009 [87]               | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Garban 2018 [77]                 | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Goodrich 2010 [79]               | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Habibi 2011 [156]                | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Heddie 1999 [88]                 | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Heddie 2002 [89]                 | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Heddie 2009 [73]                 | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Izumi 2015 [92]                  | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Janetzko 2005 [82]               | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Johansson 2012 [75]              | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Johansson 2013 [76]              | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Kantarijan 2010 [96]             | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Kerckoffs 2010 [80]              | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Khalaftahlah 2013 [157]          | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Klumpp 1999 [74]                 | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Lozano 2011 [81]                 | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Lu 2013 [70]                     | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Lye 2017 [66]                    | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| MacLennan 2015 [158]             | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| McCulloough 2004 [62]            | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Moskowitz 2007 [97]              | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Platzbecker 2015 [95]            | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Sensebe 2004 [72]                | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Siemonsen 2006 [83]              | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |
| Slichter 2006 [159]              | Low risk                  | Low risk               | Low risk                               | Low risk                      | Low risk               | High risk           | Low risk       | Low risk       | Low risk       |

(Continued)
### Table A3. Continued.

| Article                  | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Reporting bias | Other bias |
|--------------------------|----------------------------|------------------------|----------------------------------------|-------------------------------|-------------------------|---------------------|---------------|------------|
| Slichter 2010 [63]       | Low risk                   | Unclear                | Unclear                                | Unclear                       | Low risk                | Low risk            | Low risk       |            |
| Stanca 2010 [69]         | Low risk                   | Low risk               | High risk                              | High risk                     | Low risk                | Low risk            | Low risk       |            |
| Stanworth 2013 [65]      | Low risk                   | Low risk               | High risk                              | High risk                     | Low risk                | Low risk            | Low risk       |            |
| Tateishi 2018 [93]       | Low risk                   | Low risk               | Low risk                               | Unclear                       | Low risk                | Low risk            | Low risk       |            |
| Terrault 2017a [56]      | Low risk                   | Unclear                | Low risk                               | Low risk                       | Low risk                | High risk           | Low risk       |            |
| Terrault 2017b [56]      | Low risk                   | Unclear                | Low risk                               | Low risk                       | Low risk                | Low risk            | Low risk       |            |
| Timmouthe 2004 [71]      | Low risk                   | Unclear                | Low risk                               | Unclear                       | Low risk                | Unclear            | Low risk       |            |
| Vadhan-Raj 2002 [85]     | Low risk                   | Low risk               | Unclear                                | Unclear                       | Low risk                | Low risk            | High risk      |            |
| Van Der Meer 2017 [90]   | Unclear                    | Unclear                | Low risk                               | Unclear                       | Low risk                | Low risk            | High risk      |            |
| van Rhenen 2003 [84]     | Unclear                    | Unclear                | Low risk                               | Unclear                       | Low risk                | Low risk            | Unclear        |            |
| Veelo 2014 [86]          | Unclear                    | Unclear                | Low risk                               | Unclear                       | Low risk                | Low risk            | Low risk       |            |

*Assessment of Study NCT01972529.

Table A4. Newcastle-Ottawa quality assessment of real-world evidence studies.

| Article                  | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Assessment of the design or analysis controlled for confounders | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts | AHRQ standard |
|--------------------------|-----------------------------------------|-------------------------------------|---------------------------|------------------------------------------------------------------------|----------------------------------------------------------------|------------------------------------------|----------------------------------|----------------|
| Akpunonu 2014 [160]      | NA                                      | NA                                  | NA                        | NA                                                                     | NA                                                              | NA                                       | NA                               | NA              |
| Al Zaabi 2014 [161]      | NA                                      | NA                                  | NA                        | NA                                                                     | NA                                                              | NA                                       | NA                               | NA              |
| Alkilai 2017 [162]       | NA                                      | NA                                  | NA                        | NA                                                                     | NA                                                              | NA                                       | NA                               | NA              |
| Al-Samkari 2018 [163]    | NA                                      | NA                                  | NA                        | NA                                                                     | NA                                                              | NA                                       | NA                               | NA              |
| Andrade-Campos 2015 [48] | NA                                      | NA                                  | NA                        | NA                                                                     | NA                                                              | NA                                       | NA                               | NA              |
| Ang 2008 [42]            | NA                                      | NA                                  | NA                        | NA                                                                     | NA                                                              | NA                                       | NA                               | NA              |
| Antun 2013 [164]         | NA                                      | NA                                  | NA                        | NA                                                                     | NA                                                              | NA                                       | NA                               | NA              |
| Arnold 2016 [112]        | A                                       | A                                   | A                         | A                                                                      | B                                                               | A                                        | UTD                              | Poor            |
| Arnold 2006 [99]         | NA                                      | NA                                  | NA                        | NA                                                                     | NA                                                              | NA                                       | NA                               | NA              |
| Aubron 2017 [17]         | A                                       | A                                   | A                         | A                                                                      | A                                                               | A                                        | A                                | Good            |
| Beneke 2017 [113]        | A                                       | C                                   | A                         | A                                                                      | C                                                               | B                                        | A                                | A              |
| Benson 2011 [52]         | NA                                      | NA                                  | NA                        | NA                                                                     | NA                                                              | NA                                       | NA                               | NA              |
| Bh at 2016 [165]         | NA                                      | NA                                  | NA                        | NA                                                                     | NA                                                              | NA                                       | NA                               | NA              |
| Birchall 2017 [137]      | NA                                      | NA                                  | NA                        | NA                                                                     | NA                                                              | NA                                       | NA                               | NA              |
| Blumberg 2006 [43]       | NA                                      | NA                                  | NA                        | NA                                                                     | NA                                                              | NA                                       | NA                               | NA              |
| Callow 2002 [139]        | NA                                      | NA                                  | NA                        | NA                                                                     | NA                                                              | NA                                       | NA                               | NA              |
| Chan 2002 [160]          | NA                                      | NA                                  | NA                        | NA                                                                     | NA                                                              | NA                                       | NA                               | NA              |
| Chandran 2015 [44]       | A                                       | A                                   | D                         | A                                                                      | AB                                                              | D                                        | A                                | Poor            |
| Chaouli 2004 [167]       | NA                                      | NA                                  | NA                        | NA                                                                     | NA                                                              | NA                                       | NA                               | NA              |

(Continued)
Table A4. Continued.

| Article | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis controlled for confounders | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts | AHRQ standard |
|---------|----------------------------------------|------------------------------------|--------------------------|-------------------------------------------------|-------------------------------------------------|---------------------|---------------------------------|---------------------------------|-----------------|
| Charbonnier 2014 [103] | A | A | D | A | C | D | A | D | Poor |
| Chen 2011 [114] | A | A | A | B | C | A | A | D | Poor |
| Chern 2011 [168] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Cheung 2014 [133] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Chien 2014 [169] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Cirasino 2010 [170] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Davaasambuu 2013 [171] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Delaitre 2000 [172] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Duffy 2013 [115] | A | A | A | A | C | A | UTD | A | Poor |
| Dizerba 2016 [173] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Eder 2013 [174] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Elting 2001 [154] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Engele 2016 [131] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Feliciano 2016 [175] | A | A | A | A | C | A | A | B | Poor |
| Fillmore 2013 [130] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Frigaa 2015 [176] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Fujimura 2002 [177] | A | A | D | A | C | E | UTD | B | Poor |
| Gerber 2007 [178] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Giannini 2010 [54] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Goel 2014 [116] | A | A | A | B | A | B | UTD | D | Poor |
| Goel 2015 [21] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Greeno 2007 [49] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Guerrero 2017 [117] | A | A | A | A | AB | A | A | A | Good |
| Guerrero 2014 [179] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Habr 2015 [50] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Hashiguchi 2015 [180] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Hitron 2011 [181] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Hussein 1998 [182] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Jones 2016 [183] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Jubelirer 2011 [184] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Kander 2014 [185] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Keulers 2018 [129] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Kluge 2004 [186] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Krishna 2014 [101] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Kuter 2017 [118] | A | A | A | A | C | A | A | A | Poor |

(Continued)
| Article            | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis controlled for confounders | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts | AHRQ standard |
|-------------------|-----------------------------------------|------------------------------------|---------------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------|----------------------|------------------------------------------------|----------------------------------|----------------|
| Kwon 2017         | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                          | NA                   | NA                                             | NA                               | NA             |
| Lawrence 2001     | A                                       | A                                  | A                         | A                                                                   | C                                                                                           | A                    | A                                             | A                  | Poor           |
| Lee 2016[119]     | A                                       | A                                  | A                         | A                                                                   | C                                                                                           | A                    | UTD                                           | D                  | Poor           |
| Levin 2003[189]   | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Li 2018[110]      | B                                       | A                                  | A                         | A                                                                   | C                                                                                           | A                    | UTD                                           | D                  | Poor           |
| Limkemann 2015[190] | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Lye 2009[120]     | B                                       | A                                  | A                         | A                                                                   | C                                                                                           | A                    | UTD                                           | D                  | Poor           |
| Mahavas 2015[191] | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Makroo 2014[121]  | A                                       | A                                  | A                         | A                                                                   | C                                                                                           | A                    | UTD                                           | D                  | Poor           |
| Mathias 2007[192] | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| McDonald 2012[193] | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Meehan 2000[102]  | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Mohd Hayat 2016[194] | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Moulis 2015[195]  | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Nandagopal 2016[196] | A                                      | A                                  | A                         | A                                                                   | C                                                                                           | A                    | UTD                                           | D                  | Poor           |
| Napolitano 2016[53] | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Neukirchen 2009[197] | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Nevo 2007[198]    | A                                       | A                                  | A                         | A                                                                   | AB                                                            | A                    | A                                             | B                  | Good           |
| Nevo 2007[199]    | A                                       | A                                  | A                         | A                                                                   | C                                                                                           | A                    | A                                             | A                  | Poor           |
| Nevo 2001[200]    | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Ning 2016[100]    | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Niwa 2009[201]    | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Noris 2014[98]    | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Norol 1998[202]   | B                                       | A                                  | A                         | A                                                                   | C                                                                                           | A                    | UTD                                           | D                  | Poor           |
| Otrock 2015[122]  | A                                       | A                                  | A                         | A                                                                   | C                                                                                           | A                    | A                                             | A                  | Poor           |
| Palo 2010[203]    | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Park 2015[111]    | D                                       | C                                  | D                         | A                                                                   | C                                                                                           | D                    | UTD                                           | D                  | Poor           |
| Pillarisetti 2011[53] | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Poordad 2011[204] | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Pugmire 2006[205] | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Qureshi 2007[206] | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Rabon 2018[207]   | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Ramos 2018[208]   | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Ramos 2016[209]   | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Ranucci 2017[210] | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Rao 2002[211]     | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
| Raval 2015[22]    | NA                                      | NA                                 | NA                        | NA                                                                  | NA                                                                                           | NA                   | NA                                            | NA                 | NA             |
### Table A4. Continued.

| Article                      | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis controlled for confounders | Assessment of outcome of interest | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts | AHRQ standard |
|------------------------------|-----------------------------------------|------------------------------------|---------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------|---------------------------------------------|---------------------------------|------------------|
| Rodeghiero 2010 [212]        | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Roubinian 2016 [213]         | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Saleh 2009 [45]              | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Samuelson 2016 [214]         | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Samuelson 2017 [106]         | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Sanz 2010 [215]              | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Schmidt 2018 [126]           | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Schuh 2013 [216]             | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Sekeres 2010 [217]           | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Sethi 2017 [123]             | B                                       | A                                  | A                         | A                                                                     | A                                                                               | A                                        | A                             | A                               | Good             |
| Shreenivas 2018 [218]        | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Singh 2012 [219]             | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Spahr 2008 [107]             | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Swisher 2009 [105]           | A                                       | A                                  | A                         | A                                                                     | C                                                                               | A                                        | UTD                           | D                               | Poor             |
| Tada 2018 [220]              | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Takahashi 2011 [221]         | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Tessier 2015 [222]           | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Toor 2000 [108]              | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Tran 2010 [124]              | A                                       | A                                  | A                         | A                                                                     | C                                                                               | B                                        | UTD                           | D                               | Poor             |
| Tsukune 2016 [223]           | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Vecchio 2005 [224]           | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Vetter 2014 [132]            | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Vigil-De Gracia 2006 [225]   | A                                       | A                                  | A                         | A                                                                     | C                                                                               | A                                        | UTD                           | D                               | Poor             |
| Vijenthira 2017 [226]        | A                                       | A                                  | A                         | A                                                                     | C                                                                               | B                                        | A                             | D                               | Poor             |
| Virgili 2015 [227]           | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Wallace 2003 [127]           | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Wandt 1998 [104]             | A                                       | A                                  | A                         | A                                                                     | C                                                                               | A                                        | A                             | A                               | Poor             |
| Wandt 2006 [51]              | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Wang 2002 [228]              | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Warner 2017 [46]             | A                                       | A                                  | A                         | A                                                                     | B                                                                               | A                                        | UTD                           | D                               | Poor             |
| Warner 2016 [125]            | B                                       | A                                  | A                         | A                                                                     | B                                                                               | A                                        | UTD                           | D                               | Poor             |
| Wu 2012 [229]                | A                                       | A                                  | D                         | A                                                                     | C                                                                               | D                                        | UTD                           | D                               | Poor             |
| Wu 2009 [47]                 | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |
| Yoshio 2014 [126]            | A                                       | A                                  | A                         | A                                                                     | B                                                                               | A                                        | UTD                           | D                               | Poor             |
| Ypma 2012 [109]              | NA                                      | NA                                 | NA                        | NA                                                                     | NA                                                                              | NA                                       | NA                            | NA                              | NA               |

(Continued)
Table A4. Continued.

| Article                      | Selection | Comparability | Outcome |
|------------------------------|-----------|---------------|---------|
|                              | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | AHRQ standard of cohorts on the basis of the design or analysis controlled for confounders | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts |
|------------------------------|-----------|---------------|---------|
| Rehman 2002 [230]            | NA        | NA            | NA      | NA | NA | NA | NA | NA |
| Zeidler 2011 [231]           | NA        | NA            | NA      | NA | NA | NA | NA | NA |
| Zhou 2017 [232]              | NA        | NA            | NA      | NA | NA | NA | NA | NA |

AHRQ = Agency for Healthcare Research and Quality; NA = not applicable; UTD = unable to determine.
*Letters A to E correspond to answers to questions of the Newcastle-Ottawa quality assessment scale (41).

Table A5. Overview of all studies by patient population classification.

| Article domain* | Number of studies | Population classification | Total number of patients (where reported) |
|-----------------|-------------------|---------------------------|------------------------------------------|
|                 | TCP overall | TCP + elective IP | CLD TCP and elective IP | No classification |
| All             | 190      | 139                 | 31                        | 17 | 3 | 458,480 |
| RCT             | 43       | 34                  | 1                         | 8 | 0 | 8276 |
| RWE             | 129      | 92                  | 30                        | 7 | 0 | 431,355 |
| Effectiveness and safety | 75     | 51                  | 19                        | 5 | 0 | 339,140 |
| Epidemiology/treatment patterns | 79     | 55                  | 21                        | 3 | 0 | 359,613 |
| Humanistic burden | 2      | 1                   | 1                         | 0 | 0 | 319 |
| Economic        | 26       | 19                  | 0                         | 4 | 3 | 20,517 |

CLD = chronic liver disease; IP = invasive procedure; RCT = randomized controlled trial; RWE = real-world evidence; TCP = thrombocytopenia.
*Some studies were captured and/or extracted in more than one domain.
**Table A6.** Summary of the epidemiology and treatment patterns by population.

| Article | PICOS classification | TCP etiology grouped | Overall study population | Mean baseline PC × 10⁹/L (SD) | Age (Years), mean (SD) | Male, n (%) | TCP population / subgroup | PT type (PPT or TPT) | Number with TCP | Number with PT | % of those with TCP receiving PT |
|---------|----------------------|----------------------|--------------------------|--------------------------------|-----------------------|-------------|----------------------------|---------------------|----------------|--------------|----------------------------------|
| Cirasino 2010 [170] | TCP overall | ITP | 120b | NR | 58.3 (18.8)b | 46 (38.3)b | All (ITP hospitalizations) | PPT and TPT | 120b | 25b | 21b |
| Fujimura 2002 [177] | TCP overall | ITP | 284 | NR | 24.8c | 0 (0) | All (ITP patients) | TPT | 284 | 59 | 20.8 |
| Kwon 2017 [187] | TCP overall | ITP | 570d | NR | 45 (15.7) | 17 (23) | All (ITP patients) | NR | 73 | 37 | 22 |
| Mahevas 2015 [191] | TCP overall | ITP | 37 | NR | 12 (32.4) | NR | All (ITP patients; multi-refractory) | NR | 37 | 22 | 60 |
| Mathias 2007 [192] | TCP overall | ITP | 113 | 17c | 65c | NR (NR) | All (patients with PC <150 × 10⁹/L) | NR | 113 | 8 | 7 |
| Rodeghiero 2010 [212] | TCP overall | ITP | 610 | 77c | 54.6 (18.2) | 194 (32) | All (ITP patients) | NR | 610 | 2 | 2 |
| Saleh 2009 [45] | TCP overall | ITP | 3743 | NR | 1774 (47.4) | 22 (37) | All (ITP patients) | NR | 3743 | 2 | 1.7 |
| Takahashi 2011 [221] | TCP overall | ITP | 331 | 20.2 (13.9)f | 221 (66.8%) | Patients who developed TCP after receiving linezolid | NR | 128 | 21 | 16 |
| Tran 2010 [124] | TCP overall | ITP | 50,275 | NR | 45.9 (1.3) | NR | All (ITP patients) | TPT | 50,275 | 2 | 1.7 |
| Tsukune 2016 [223] | TCP overall | ITP | 213 | NR | 65 (30.5) | NR | All (ITP patients) | NR | 213 | 52 | 24.4 |
| Andrade-Campos 2015 [48] | TCP overall | CIT | 108 | NR | 60.1 (NR) | 48 (44.4) | All (patients with PC ≥100 × 10⁹/L) | NR | 108 | 23 | 21 |
| Chaoui 2005 [167] | TCP overall | CIT | 98m | NR | 52 | 62 (63) | NR | All (patients with CIT) | PPT | 98 | 12 | 26 |
| Elting 2001 [154] | TCP overall | CIT | 47 | NR | 54 (9) | 31 (66) | All (patients with CIT) | PPT | 47 | 42 | 89 |
| Hashiguchi 2015 [180] | TCP overall | CIT | 609 (1262 chemotherapy cycles) | NR | 52 | NR (48) | Chemotherapy cycles | PPT | 1262 | 532 | 42.2 |
| Hitron 2011 [181] | TCP overall | CIT | 291 | NR | 60 | 0 (0) | Patients with PC <50 × 10⁹/L | PPT and TPT | 43 | 8 | 19 |

(Continued)
| Article | PICOS classification | TCP etiology grouped | Overall study population | Mean baseline PC × 10^9/L (SD)a | Age (Years), mean (SD)a | Male, n (%)a | TCP population / subgroup | PT type (PPT or TPT) | Number with TCP | Number with PT | % of those with TCP receiving PT |
|---------|---------------------|----------------------|--------------------------|-------------------------------|------------------------|-------------|--------------------------|------------------|----------------|----------------|----------------------------------|
| Pugmire 2006 | TCP overall | CIT | 54 | 111.7^{i} 48.3^{i} | 74.6 (15.0) | 0 (0) | Patients administered rhIL-11 on C1C1 who developed TCP | PPT and TPT | 5 | 1 | 20 |
| Shreenivas 2018 | TCP overall | CIT | 60 | NR | NR | NR | Patients administered rhIL-11 from C1C2 who developed TCP | PPT and TPT | 39 | 8 | 21 |
| Virgili 2015 | TCP overall | CIT | 1743 | NR | NR | NR | All (patients with MM and PC >100 × 10^9/L undergoing ASCT) | PPT and TPT | 1743 | 49 | 2.8 |
| Wang 2002 | TCP overall | CIT | 35 | NR | 296.01 (212.6)^{i} | 60.76 (13.9) | 19,598 (41.6) | All (patients with PC <100 × 10^9/L) | PPT and TPT | NR | 2.5 |
| Chan 2002 | TCP overall | HM | 33 | NR | 42 | 68 | 20 (60.6) | All (MDS patients with TCP) | PPT and TPT | 33 | 9 | 27 |
| Chem 2011 | TCP overall | HM | 76 | 26.5 (29.1) | 55.8 | 38 (50) | ICH patients with PC >50 × 10^9/L | PPT | 8 | 4 | 50 |
| Neukirchen 2009 | TCP overall | HM | 2900 | NR | 116 | 71 | NR (53) | PPT | 68 | 64 | 94 |
| Poordad 2011 | TCP overall | CLD (HCV patients) | 7905 | 112.9^{i} | 50 (7.8) | 221 (72.5) | Patients with TCP | NR | 305 | 26 | 8.5 |
| Antun 2013 | TCP overall | Mixed (patients receiving EACA) | 44 | NR | 8 | 61 | 29 (65.9) | All (TCP patients receiving EACA) | PPT | 44 | 7 | 16 |
| Birchall 2017 | TCP overall | Mixed (hematology patients) | NR | 47.8 (0.5) | 33.4 | NR | Patients with reversible BMF (2010) | PPT | NR | NR | 46 |
| Chandran 2015 | TCP overall | Mixed (ICU patients) | 40,693 | NR | 47.8 | 62 | 196 (66) | Patients with PC <100 × 10^9/L | PPT | 9158 | 2244 | 24.5 |
| Goel 2014 | TCP overall | Mixed (TTP, HIT and ITP) | NR | 47.8 (0.5) | 33.4 | NR | TTP hospitalizations | NR | 10,624 | NR | 10.2 |
| Goel 2015 | TCP overall | Mixed (TTP, HIT and ITP) | NR | 47.8 (0.5) | 33.4 | NR | HIT hospitalizations | NR | 1448 | NR | 15.6 |
| Guerrero 2014 | TCP overall | Mixed (IC) | 1341 | NR | NR | NR | PT administered for bleeding risk | PPT | 7401 PTs | 5479 PTs | 74.0 |
| Guerrero 2017 | TCP overall | Mixed (IC) | 2572 | 64.2 (13.7) | 182 (60.3) | NR | PT administered for therapeutic indication | TPT | 208 PTs | 1340 PTs | 2.8 |
| Habr 2015 | TCP overall | Mixed (patients receiving PT) | 296^{m} | 29 | NR | NR | All (ICH patients) | PPT | 904 PTs | 300 PTs | 33.2 |

(Continued)
| Article | PICOS classification | TCP etiology grouped | Overall study population | Mean baseline PC × 10^9/L, (SD)a | Age (Years), mean (SD)a | Male, n (%)a | TCP population / subgroup | PT type (PPT or TPT) | Number with TCP | Number with PT | % of those with TCP receiving PT |
|---------|---------------------|----------------------|--------------------------|-------------------------------|-------------------|-----------------|--------------------------|---------------------|--------------|--------------|-------------------------|
| Jones 2016 [183] | TCP overall | Mixed (patients with postpartum hemorrhage) | 347 | 192\[2\] | 29\[2\] | 0 (0) | All (patients with postpartum hemorrhage) | TPT | 347\[4\] | 12\[4\] | 3.5\[4\] |
| Meehan 2000 [102] | TCP overall | Mixed (patients receiving PT) | 245\[5\] | NR | 49 (19.9) | 124 (50.6) | Patients receiving 1 platelet unit | NR | 245\[6\] | 77 | 31.4\[6\] |
| Qureshi 2007 [206] | TCP overall | Mixed (patients receiving PT) | 4421\[7\] | NR | NR | NR | Patients receiving PT with documented reason | PPT and TPT | 100 P Ts\[7\] | 2388 | 58.2\[7\] |
| Rabon 2018 [207] | TCP overall | Mixed (patients receiving LZD) | 118 | 89\[8\] \[9\] | NR | NR | Patients with LZD-associated TCP | PPT and TPT | NR | 45 | 69 |
| Rao 2002 [211] | TCP overall | Mixed (ICU patients) | 1247 | 54.5\[10\] | NR | NR | All (ICU patients) | PPT and TPT | 1247\[10\] | 202 | 16.2\[10\] |
| Roubinian 2016 [213] | TCP overall | Mixed (hospitalized patients) | 13,276\[11\] | 22\[12\] | 62\[12\] | NR (57) | Hospitalizations in 2009 | NR | NR | NR | 1.7\[12\] |
| Samuelson 2016 [214] | TCP overall | Mixed (patients with CRT) | 41 | NR | 50 | 21 (51) | All (patients with PC <50 × 10^9/L) | NR | 41 | 36 | 88 |
| Akpunonu 2014 [160] | TCP overall | Other (secondary to rattlesnake envenomations) | 159\[13\] | NR | 39.5 | 101 (87) | Patients with TCP (PC <100 × 10^9/L) | NR | 116 | 11 | 9 |
| Feliciano 2016 [175] | TCP overall | Other (myelofibrosis patients) | 1658 | NR | 66\[14\] | NR (50) | Patients with anemia and TCP | NR | NR | NR | 23 |
| Gerber 2007 [178] | TCP overall | Other (GBM patients treated with TMZ plus radiation) | 52 | NR | 52\[15\] | 28 (54\[15\]) | Patients with PC <50 × 10^9/L | NR | 10 | 5 | 50 |
| Niwa 2009 [201] | TCP overall | Other (patients treated with LZD) | 42 | 244 (110)\[16\] | 59.6 (12.8) | 31 (73.8) | Patients with a ≥ 25% decrease in PC and final PC <100 × 10^9/L | NR | 7 | 2 | 29 |
| Otrock 2015 [222] | TCP overall | Other (TTP patients undergoing plasma exchange) | 110 | 19\[17\] | 39\[17\] | 9 (39\[17\]) | Patients with ADAMTS13-deficient TTP | PPT and TPT | 55 | 23 | 42 |
| Sekeres 2010 [217] | TCP overall | Other (MDS patients receiving azacitidine) | 417 | NR | 75\[18\] | NR | Patients with primary MDS | NR | 380\[18\] | 140\[18\] | 13\[18\] |
| TESSIER 2015 [222] | TCP overall | Other (patients treated with LZD) | 693 | NR | 51.2 (12.7) | 62 (56.4) | Patients with secondary MDS | NR | 110\[19\] | 36 | 33\[19\] |
| Wandt 2006 [51] | TCP overall | Other (patients receiving ABR SCT) | 106 | NR | 54\[20\] | 68 (64.2) | Non-transplant cohort | NR | 572\[20\] | 110 | 19.2\[20\] |
| Yoshii 2014 [126] | TCP overall | Other (patients with TMA) | 1211 | NR | NR | NR | All transplantations | PPT or TPT | 235 P Ts | 81 P Ts | 65.5\[20\] |
| Jubelirer 2011 [184] | TCP and elective invasive procedure | ITP | 51 | NR | NR | NR | Patients with acquired idiopathic TTP | NR | 263 | 48 | 18.3 |
| Tada 2018 [220] | TCP and elective invasive procedure | ITP | 32 | 44 | 33 (23) | 8 (36.4) | Patients with ITP (PC <100 × 10^9/L) | PPT | 10 | 5 | 50 |

(Continued)
| Article            | PICOS classification | TCP etiology grouped | Overall study population | Mean baseline PC × 10^9/L (SD)a | Age (Years), mean (SD)a | Male, n (%)a | TCP population / subgroup | PT type (PPT or TPT) | Number with TCP | Number with PT | % of those with TCP receiving PT |
|-------------------|----------------------|----------------------|--------------------------|---------------------------------|-------------------------|-------------|--------------------------|---------------------|-----------------|----------------|--------------------------------|
| Vecchio 2005      | TCP and elective invasive procedure | ITP                  | 40                       | 15 range 19–30 range 18–27     | 5 (25)                  | 5 (25)      | Patients with ITP undergoing OS | TPT                 | 20              | 20            | 100                                          |
|                    |                      |                      |                          |                                 |                         |             | Patients with ITP undergoing LS | TPT                 | 20              | 6             | 30                                           |
| Keulers 2018       | TCP and elective invasive procedure | HM                   | 1200                     | 18 range 19–30                  | 102 (56.35)             |             | Patients receiving TVAP implantations with PC <150 × 10^9/L | PPT                 | 181             | 68            | 38                                           |
|                    |                      |                      |                          |                                 |                         |             | Patients receiving TVAP implantations with PC 101–150 × 10^9/L | TPT                 | 55              | 0             | 0                                            |
|                    |                      |                      |                          |                                 |                         |             | Patients receiving TVAP implantations with PC 50–100 × 10^9/L | PPT                 | 58              | 0             | 0                                            |
|                    |                      |                      |                          |                                 |                         |             | Patients receiving TVAP implantations with PC <50 × 10^9/L | PPT                 | 68              | 68            | 100                                          |
| Singh 2012 [219]   | TCP and elective invasive procedure | HM                   | 63                       | NR range 66–99                  | 107 (39)                |             | Patients with TCP who underwent surgical procedure and received ROMI | PPT                 | 63              | 10            | 16                                         |
| Al-Samkari 2018    | TCP and elective invasive procedures | Mixed (patients treated with ROMI) | 288                      | 47.5 (5.8)                      | 61 (55)                |             | Patients with TCP who underwent surgical procedure and received ROMI | PPT                 | 47              | 3             | 6                                           |
| Delaitre 2000      | TCP and elective invasive procedures | Mixed (patients undergoing splenectomy) | 275                      | NR range 26–44                  | 107 (39)               |             | All (patients undergoing splenectomy) | NR                  | 275             | 23            | 8.4                                          |
| Dzierba 2016       | TCP and elective invasive procedures | Mixed (patients with severe ARDS with or without ECMO) | 85                       | NR range 50–69                  | NR                     |             | TCP patients with PC ≤50 × 10^9/L | TPT                 | 18              | 22            |                                             |
|                    |                      |                      |                          |                                 |                         |             | TCP patients with PC >50 × 10^9/L | TPT                 | 67              | NR            | 2                                            |
| Fillmore 2013      | TCP and elective invasive procedures | Mixed (patients undergoing dental extraction) | 68                       | 44.6 (2.6)                      | 53.3 (17.9)            |             | All (PC ≤100 × 10^9/L) | PPT                 | 68              | 32            | 47                                          |
|                    |                      |                      |                          |                                 |                         |             | Patients receiving 1 PT | PPT                 | 81              | 37            | 46                                          |
|                    |                      |                      |                          |                                 |                         |             | Patients receiving >1 PT | PPT                 | 81              | 44            | 54                                          |
| Hussein 1998       | TCP and elective invasive procedures | Mixed (BMT or AL patients receiving amphotericin-B and PT) | 81m                      | NR range 50–69                  | NR                     |             | Patients receiving 1 PT | NR                  | 81              | 37            | 46                                          |
| Kluge 2004 [186]   | TCP and elective invasive procedure | Mixed (patients undergoing percutaneous tracheostomy) | 42                       | 26.4 (11.9)                     | 50.2 (12.4)            |             | All (patients with PC <50 × 10^9/L) | PPT                 | 42              | 40            | 95                                          |
| Krishna 2014 [101] | TCP and elective invasive procedure | Mixed (patients undergoing endoscopy) | 395d                     | 29.4 (11.6)                     | 54.8 (15.8)            |             | All (patients with PC <75 × 10^9/L) | PPT                 | 481             | 329           | 68.4                                        |
| Limkemann 2015     | TCP and elective invasive procedure | Mixed (patients with SOT or HSCT) | 234                      | NR                              | NR                     |             | Patients treated with LZD | NR                  | 110             | 43            | 39                                          |
| Nandagopal 2016    | TCP and elective invasive procedure | Mixed (patients undergoing bronchoscopy and/or BAL) | 150                      | NR                              | 94 (63)                |             | Patients treated with DAP | PPT                 | 124             | 24            | 19                                          |
| Ramos 2016 [209]   | TCP and elective invasive procedure | Mixed (patients with GI bleeding undergoing endoscopy) | 49                       | 0.039 (0.9)                     | 57 (31)                |             | All (patients with PC <50 × 10^9/mL) | NR                  | 49              | NR            | 88                                          |
| Ramos 2018 [208]   | TCP and elective invasive procedure | Mixed (patients with GI bleeding undergoing endoscopy) | 144                      | 0.041 (5.9)                     | 59 (65)                |             | Patients with PC ≥20 to <50 × 10^9/mL, receiving post-procedural PT | NR                  | 144             | 63            |                                             |
|                    |                      |                      |                          |                                 |                         |             | Patients with PC ≥20 to <50 × 10^9/mL, receiving pre-procedural PT | NR                  | 55              | 38            |                                             |

(Continued)
| Article          | PICOS classification  | TCP etiology grouped                  | Overall study population | Mean baseline PC × 10^9/L (SD)* | Age (Years), mean (SD)* | Male, n (%)* | TCP population / subgroup | PT type (PPT or TPT) | Number with TCP | Number with PT | % of those with TCP receiving PT |
|------------------|-----------------------|----------------------------------------|--------------------------|--------------------------------|-------------------------|--------------|---------------------------|---------------------|----------------|----------------|--------------------------------|
| Ranucci 2017     | TCP and elective invasive procedure | Mixed (cardiac surgery patients)       | 589                      | 212†                             | 69†                     | 459 (78)     | Patients with ADPtest ≥ 30 U and PC < 150 × 10^9/L | PPT                 | NR             | 49             | NR 14                       |
|                  |                       |                                        |                          |                                 |                         |              | Patients with ADPtest < 30 U and PC ≥ 150 × 10^9/L |                     | 54             | NR             | 39                           |
|                  |                       |                                        |                          |                                 |                         |              | Patients with ADPtest < 30 U and PC < 150 × 10^9/L |                     | 26             | NR             | 50                           |
|                  |                       |                                        |                          |                                 |                         |              | Patients with PC ≤ 10 × 10^9/L | PPT                 | 376†††             | NR             | 3*                         |
|                  |                       |                                        |                          |                                 |                         |              | Patients with PC 11–20 × 10^9/L |                     | NR             | 23*                        |
|                  |                       |                                        |                          |                                 |                         |              | Patients with PC 21–30 × 10^9/L |                     | NR             | 27*                        |
|                  |                       |                                        |                          |                                 |                         |              | Patients with PC 31–40 × 10^9/L |                     | NR             | 11*                        |
|                  |                       |                                        |                          |                                 |                         |              | Patients with PC 41–50 × 10^9/L |                     | NR             | 6*                         |
|                  |                       |                                        |                          |                                 |                         |              | Patients with PC 51–75 × 10^9/L |                     | NR             | 3*                         |
|                  |                       |                                        |                          |                                 |                         |              | Patients with PC ≥ 76 × 10^9/L |                     | NR             | 8.3                        |
| Schmidt 2018     | TCP and elective invasive procedure | Mixed (patients receiving PT prior to IP) | 376 (22.5)               | 48.0 (23.2)                     | 226 (60)              |              | Patients with PT | PPT                 | 860             | 71             | 9.9                         |
|                  |                       |                                        |                          |                                 |                         |              | Patients with PC ≤ 100 × 10^9/L |                     | 2060            | 203            | 6.8                         |
|                  |                       |                                        |                          |                                 |                         |              | No preoperative PT; peri-procedural PT |                     | 1857            | 127            | 6.8                         |
|                  |                       |                                        |                          |                                 |                         |              | Patients with PC ≤ 100 × 10^9/L |                     | 203             | 46             | 22.7                        |
|                  |                       |                                        |                          |                                 |                         |              | Preoperative PT; peri-procedural PT |                     | NR             | 25             |                             |
| Warner 2016      | TCP and elective invasive procedure | Mixed (patients undergoing noncardiac surgery) | 13,978                  | 49.0††                     | 63††                    | 43 (61)*     | Patients with PC ≤ 100 × 10^9/L receiving preoperative PTs | PPT and/or NR       | 2060            | 203            | 9.9                         |
|                  | TCP and elective invasive procedure | Mixed (patients undergoing interventional radiology procedures) | 18,204                  | NR                         | NR                     | NR           | All patients with PC ≤ 100 × 10^9/L receiving preoperative PTs |                     | 1857            | 127            | 6.8                         |
|                  |                       |                                        |                          |                                 |                         |              | No preoperative PT; peri-procedural PT |                     | 203             | 46             | 22.7                        |
|                  |                       |                                        |                          |                                 |                         |              | Preoperative PT; peri-procedural PT |                     | NR             | 25             |                             |
| Duffy 2013       | TCP and elective invasive procedures | Other (patients undergoing catheterization attempts) | 55                      | 26†                             | NR                     | NR           | All (presumed TTP patients) | PPT                 | 55              | 14             | 25                          |
| Benson 2011      | CLD TCP and elective invasive procedure | CLD (patients undergoing liver transplantation) | 525                     | NR                         | NR                     | NR           | All (liver transplant patients) | NR                 | 525†††           | NR             | 64*                         |
|                  |                       |                                        |                          |                                 |                         |              | Patients with ESLD, PC > 60 × 10^9/L |                     | 8               | 5               | 63                          |
| Napolitano 2016  | CLD TCP and elective invasive procedure | CLD (cirrhotic patients scheduled for IP) | 363                     | 94.1 (NR)                  | 67 (NR)               | 5 (62.5)    | Cirrhotic patients undergoing IP with PC < 150 × 10^9/L | PPT                 | 30              | 6              | 60                          |
|                  |                       |                                        |                          |                                 |                         |              | – postprocedural bleeding |                     | 30.8            | 6.4            | 60                          |
|                  |                       |                                        |                          |                                 |                         |              | Cirrhotic patients undergoing IP with PC < 150 × 10^9/L |                     | 10              | 6              | 60                          |
|                  |                       |                                        |                          |                                 |                         |              | – no postprocedural bleeding |                     | NR              | 6              |                             |
| Pillarsetti 2011 | CLD TCP and elective invasive procedure | CLD (patients with ESLD undergoing cardiac catheterization) | 86                      | 86.8 (66)                  | 56.8 (8.5)           | NR (72)     | All patients with ESLD, PC > 60 × 10^9/L | PPT                 | 43†††           | 5               | 12*                         |
|                  |                       |                                        |                          |                                 |                         |              | Patients with ESLD, PC < 60 × 10^9/L |                     | 31              | 0               | 0                            |
|                  |                       |                                        |                          |                                 |                         |              | Patients with ESLD, PC < 60 × 10^9/L |                     | 12              | 5               | 42                          |

(Continued)
Table A6. Continued.

| Article | PICOS classification | TCP etiology grouped | Overall study population | Mean baseline PC × 10^9/L (SD)a | Age (Years), mean (SD)a | Male, n (%)a | TCP population / subgroup | PT type (PPT or TPT) | Number with TCP | Number with PT | % of those with TCP receiving PT |
|---------|----------------------|----------------------|--------------------------|---------------------------------|------------------------|-----------|--------------------------|---------------------|----------------|----------------|---------------------------------|
| Giannini 2010 [54] | CLD TCP and elective invasive procedures | Mixed (patients evaluated for orthotopic liver transplant) | 102 | 79.0 (31.0) | 56 (9) | 67 (66) | Patients with PC <100 × 10^9/L | PPT | 50 | 7 | 14 |
|  |  |  |  | 50.2 (12.3) | 56 (9) | 8 (80) | Patients with PC <75 × 10^9/L undergoing IP |  | 10 | 4 | 40 |
|  |  |  |  | 50.6 (14.9) | 58 (8) | 14 (64) | Patients with PC <75 × 10^9/L undergoing IP – no procedure-related bleeding |  | 22 | 3 | 14 |

ADP Test = testing of platelet P2Y12 receptor activity; AL = acute leukemia; APBSCT = autologous peripheral blood stem cell transplantation; ARDS = acute respiratory distress syndrome; ASCT = autologous stem cell transplantation; BAL = broncho-alveolar lavage; BMF = bone marrow failure; BMF = bone marrow transplant; C1C1 = course 1 cycle 1; C1C2 = course 1 cycle 2; CAG = coronary artery bypass grafting; CIT = chemotherapy-induced thrombocytopenia; CLD = chronic liver disease; CRIT = catheter-related thrombosis; DAP = daptomycin; EACA = epsilon aminocaproic acid; ECMO = extracorporeal membrane oxygenation; EPAG = eltrombopag; ESLD = end-stage liver disease; GBM = glioblastoma multiforme; GI = gastrointestinal; HCV = hepatitis C virus; HIT = heparin-induced thrombocytopenia; HM = hematological malignancy; HSCT = hematopoietic stem cell transplantation; ICH = intracranial hemorrhage; ICU = intensive care unit; IP = invasive procedure; ITP = immune thrombocytopenia; LS = laparoscopic splenectomy; LZD = linezolid; MDS = myelodysplastic syndrome; MM = multiple myeloma; NR = not reported; OS = open splenectomy; PC = platelet count; PPT = prophylactic platelet transfusion; PT = platelet transfusion; rhIL-11 = recombinant human interleukin-11; RITUX = rituximab; ROMI = romiplostim; SD = standard deviation; SOT = solid organ transplant; TCP = thrombocytopenia; TIVAP = totally implantable venous access ports; TMA = thrombotic microangiopathy; TMZ = temozolomide; TPT = therapeutic platelet transfusion (for active bleeding); TTP = thrombotic thrombocytopenia purpura; U = units.

aFor overall study population or subgroup, unless otherwise stated.
bData analyzed from 120 hospitalizations, corresponding to 106 patients.
cValue presented as median.
dThe total number of patients reported is 570, however a total of 590 patients results from the sum of the 3 sub-groups (320, 220 and 50).
eValue corresponds to patients ever transfused with blood or platelets.
fValue prior to LZD therapy; mean PC of 17.8 × 10^9/L during LZD therapy.
g60.7 (19.9) for TCP patients.
hTransfusion reported, but not specified whether platelet or other.
iValue corresponds to total in this subgroup; number with TCP not reported.
j41.0% of patients developed Grade 3–4 TCP.
kValue corresponds to percentage in this subgroup receiving PT (not necessarily with TCP).
l45.2% of patients developed Grade 3–4 TCP.
mAll patients in the overall study population received PTs.

nValue corresponds to percentage of PTs administered to patients in this subgroup out of total PTs administered.

The article stated that 5 patients received 0 PT and that 42 patients did receive PT. However, the article also stated that all patients with PC <20 × 10^9/L received PT and that 43 patients had PC <20 × 10^9/L. The abstract reported that all patients required at least one PT.

pValue for patients receiving PT.

qValue at nadir.
r43,995 patients with a PC were evaluated.
s43% of patients had a PC <100 × 10^9/L.
tValue corresponds to percentage of patients in this subgroup (not necessarily with TCP) requiring PT more than once a month.
uValue for TCP patients only.

6 patients administered PT had TCP before hemorrhage.

From 2570 bites identified.

56c for TCP patients. The text of the publication reports the overall cohort age as 52c, while Table 1 of the publication reports the overall cohort age as 57c.

14 (40) for TCP patients.

167 (38) for TCP patients.

11% of patients had adverse events of TCP.

27% of patients had adverse events of TCP.

Data analyzed from 140 transplantations, received by 106 patients.

Value at initiation of ROMI; 164c at time of surgery for TCP patients only.

31.1 for patients receiving PT.

Data analyzed from 481 patient encounters.

60 patients had PC <150 × 10^9/L at start of treatment.

76 patients had PC <100 × 10^9/L at start of treatment.

PC reported as 39 × 10^9/mL.

PC reported as 41 × 10^9/mL.

Of the 90 patients who received pre-procedural PT, 19 also received PT during procedure.

12c for patients receiving PT.
Table A7. Summary of the primary endpoints of remaining 21 platelet intervention studies.

| Article | Primary endpoint | Treatment/subgroups | Result | P       |
|---------|------------------|---------------------|--------|---------|
| Khalaflah 2013 [157] | 1 h platelet increment (mean change, × 10^9/L) | FFGM vs Gemini pump | 21.8 vs 21.7 | 0.90 |
|         |                  | FFGM vs Graseby pump | 21.8 vs 21.0 | 0.77 |
|         |                  | FFGM vs Baxter pump | 21.8 vs 21.0 | 0.03 |
| Habibi 2011 [156] | Platelet count 1 h post-transfusion (× 10^9/L) | Slow vs standard infusion rate | 30.9 vs 47.5 | 0.011 |
| Preparation |         |         |        |         |
| de Wildt-Eggen 2000 [78] | Reactions (% patients) | Plasma vs PAS-2 | 12 vs 3.3 | <0.05 |
|         | CCI 1 h | Untreated in plasma vs untreated in PAS vs PCT in PAS | 43.5 vs 45.3 vs 47.9 | NR |
| Goodrich 2010 [79] | WHO Grade 2–4 bleeding (% patients) | PRT vs reference | 11,725 vs 16,939 | <0.0001 |
| Heddie 1999 [88] | Reactions (% patients) | Post-storage WBC-reduced vs plasma-depleted | 25.8 vs 17.0 | <0.008 |
| Heddie 2002 [89] | Reactions (% patients) | Plasma-removed vs random donor WBC-reduced | 21.3 vs 11.4 vs 13.3 | 0.384 |
| Janetzko 2005 [82] | CCI 1 h (× 10^9/L) | PCT vs reference | 11.6 vs 15.1 | 0.11 |
| Johansson 2012 [75] | Relative MA 1 h (mm) | PRT vs reference | 0.30 vs 0.38 | n.s. |
| Johansson 2013 [76] | Change in MA 1 h | PRT vs reference | 10.6 vs 14.3 | 0.20 |
| Kerkhoffs 2010 [80] | CCI 1 h | Plasma vs PAS III with PRT | 17.1 vs 11.4 | <0.0001 |
|              |                  | Plasma vs PAS III without PRT | 17.1 vs 15.3 | n.s. |
| Lozano 2011 [81] | CCI 1 h (mean) | PCT vs conventional | 8163 vs 9383 | 0.007 |
| McCullough 2004 [62] | WHO Grade 2 bleeding (% patients) | PCT vs control | 58.5 vs 57.5 | <0.01b |
| Simonsen 2006 [83] | CCI 1 h | PCT vs reference (combined treatment periods) | 6587 vs 8935 | 0.547c |
| Slichter 2006 [159] | Bleeding time (minutes) | PCT vs reference | 19.3 vs 14.3 | 0.25 |
| van Rhenen 2003 [84] | 1 h platelet count increment (× 10^9/L) | PCT vs conventional | 27.5 vs 35.8 | 0.03 |
| Vadhna-Raj 2002 [85] | CCI 1 h | PCT vs conventional | 13,100 vs 14,900 | 0.11 |
| Van Der Meer 2017 [90] | WHO Grade 2–4 bleeding (% patients) | PRT vs control | 15.7 vs 19.8 | 0.398 |
|              | Time to initiate clotting (minutes)a | Per-protocol analysis | 52 vs 44 | 0.19d |
| Zhu 2014 [86] | Angle of clot formation (°)a | Gamma irradiated vs non-irradiated | 8.30 vs 8.41 | 0.930 |
|              | MA (mm)a | 49.55 vs 52.34 | 0.148 |
|              | CCI 1 h | 47.81 vs 49.26 | 0.397 |
|              |                  | 11.6 vs 12.8 | 0.171 |
| Storage |         |         |        |         |
| Diedrich 2009 [87] | CCI 1 h | 1–5 day PT vs 6–7 day PT | 10.4 vs 7.4 | <0.001 |
| MacLennan 2015 [158] | % of successful transfusions | 2–5 day PT vs 6–7 day PT | 71 vs 69 | 0.625 |

CCI = corrected count increment; CI = confidence interval; FFGM = free flow gravity method; MA = maximum amplitude; NR = not recorded; n.s. = not significant; PAS = platelet additive solution; PCT = photochemically treated; PRT = pathogen reduction technology; PT = platelet transfusion; WBC = white blood cell; WHO = World Health Organization.

*aWith a pre-protocol population with a pre-specified margin of 12.5%, non-inferiority was not achieved for PCT in PAS vs untreated in plasma (4.4%; 95% CI, −4.1% to 12.9%), but was achieved for PCT in PAS vs untreated in PAS (2.6%; 95% CI, −5.9% to 11.1%).

*bBased on a non-inferiority test with a non-inferiority margin of 0.125 (one-sided 95% CI of difference: −1, 0.07), p value <0.05 indicates that PCT was not inferior to control.

*cMean difference in CCI was 2400±4301 (one-sided non-inferiority test, upper bound of one-sided 95% CI of CCI, 4040). Specified non-inferior margin was 2200, indicating that the study failed to show non-inferiority within this specified margin of inferiority.

*dNon-inferiority criterion was met for the intention-to-treat analysis (indicating that PCT was not inferior to control), but not for the per-protocol analysis.

*eAll measured at 1 h post-transfusion.
### Table A8. Summary of the effectiveness and safety from real-world evidence studies – change in platelets counts.

| Article | PCOS classification | Treatment/subgroup | N of patients<sup>a</sup> | Baseline PC (<i>x</i>10<sup>9</sup>/L) (SD) | Time of post-transfusion readout | Post-transfusion readout | PE |
|---------|---------------------|---------------------|---------------------------|---------------------------------|-------------------------------|------------------------|----|
| Alikia 2017 [162] | TCP and elective invasive procedure | PT | 35 | 4.4 (7.1) | Day 1 | PC of 59.5 (8.2) | NR |
| Arnold 2006 [99] | TCP overall | PT | 27 | NR | 5.2<sup>b</sup> | Change in PC of 14 (−2−30)<sup>b</sup> | NR |
| Benke 2017 [113] | TCP overall | PT | 44 | 26 (18−34)<sup>b</sup> | 24 h | PC of 52 (39−76)<sup>b</sup> | NR |
| Bhat 2016 [165] | TCP overall | PT/ non-responders (CCI ≥5) | 159 | 15 (12–20)<sup>b</sup> | 4 h | PC of 41 (30−52)<sup>b</sup>, CCI 18 | For both change in PC and CCI P < 0.001 |
| Callow 2002 [139] | TCP overall | PT | 15 | NR | 24 h | Improvement in PC in 78% | NR |
| Charbonnier 2014 | TCP overall | TPT | 884 | NR | NR | PC of 98.9% patients non-refractory | NR |
| Chen 2011 [114] | TCP and elective invasive procedure | PT, PC <10 × 10<sup>9</sup>/L | 10 | 5.7 (3.1) | PC readout Day 1 | PC of 73 (54), CR in 89%<sup>c</sup> |
| Chopra 2011 [120] | TCP overall | PT | 76 | 26.5 (29.1) | 36 h | PC of 51.6 (32.8) | NR |
| Chien 2014 [169] | TCP overall | PT | 159 | NR | 16–24 h | PC increment in 64%, 36% refractory<sup>d</sup> |
| Dufty 2013 [115] | TCP and elective invasive procedure | Pre-procedure PPT | 14 | Median: 12 (range 1–34)<sup>b</sup> | NR | Median PC of 50 (range 11–100)<sup>b</sup> |
| Fujimura 2002 [177] | TCP overall | PT | 64 | <10 in 50% of patients | 1 and 24 h | Early platelet yield effective in 81%, based on CCI | NR |
| Habr 2015 [50] | TCP overall | PT | 296 | 29 (15−54)<sup>b</sup> | NR | Change in PC of 10 (2−25)<sup>b</sup> | NR |
| Hussein 1998 [182] | TCP overall | PT with no AMB | 39 PTs | NR | 10 min | CCI of 9300 |
| Kander 2014 [185] | TCP and elective invasive procedure | Pre-procedure PT | 39 | 24 (18−32)<sup>b</sup> | 1 h | PC of 42 (31−50)<sup>b</sup> | P < 0.0001 from baseline |
| Krishna 2014 [101] | TCP and elective invasive procedure | PT | 481 patient encounters | 29.4 (11.6) | Post-transfusion | PC of 36.7 (12.4) | NR |
| Lee 2016 [119] | TCP overall | PT | 486 | 14 (7−19)<sup>b</sup> | Next day | Change in PC of 8 (−6−43)<sup>b</sup>, Time for PC ≥50 3 (1−5) | For both change in PC and time for PC ≥50 P < 0.0001 |
| Levin 2003 [189] | TCP overall | PT | 97 | Median: 11 range (4–60) | 1 and 16 h | 40% of 181 PTs had a <20% recovery at 1 h and 37% of 181 PTs had a <10% recovery at 16 h. | NR |
| Lye 2009 [120] | TCP overall | PPT | 188 | 15 (7−19) 5th/95th | 24 h | Change in PC of 7 (−7−50) 5th/95th, Time for PC ≥50 3 (1−4) | Change in PC, P = 0.26, time for PC ≥50 P = 0.59 |
| McDonald 2012 [193] | TCP overall | PT | 22 | NR | 24 h | PC response in 64%<sup>b</sup> | NR |
| Meehan 2000 [102] | TCP overall | PT/292 study admissions | 245 | NR | NR | In 78% of admissions, patients were non-refractory | NR |
| Mohd Hayat 2016 [194] | TCP overall | PT/All | 80 | NR | NR | Good increment in 67%<sup>c</sup> | NR |

<sup>a</sup> N of patients: number of patients included in the study.  
<sup>b</sup> Baseline PC: baseline platelet count.  
<sup>c</sup> Time of post-transfusion readout: time of post-transfusion readout.  
<sup>d</sup> Post-transfusion readout: post-transfusion readout.  
<sup>e</sup> PE: P value.  

(Continued)
| Article                  | PICOS classification | Treatment/subgroup | N of patients | Baseline PC [×10⁹/L] (SD) | Time of post-transfusion readout | Post-transfusion readout | P       |
|-------------------------|----------------------|--------------------|---------------|---------------------------|---------------------------------|--------------------------|---------|
| Nandagopal 2016 [196]   | TCP and elective invasive procedure | PT/poor increment⁷ | NR            | NR                        | NR                              | CCI of 1571              | NR      |
|                         |                      | Pre-procedural PT  | 58            | <50                       | NR                              | PC >50 in 33%              | NR      |
| Ning 2016 [100]         | TCP overall          | PT                 | 4467          | 87 (57–130)b              | 7 h⁸                           | Change in PC of 23 (7–48)⁹ | PC increment ≥ 5 × 10⁹/L in 78.2% of PTs | NR      |
| Norol 1998 [202]        | TCP overall          | Medium dose PT/adults | 69           | 19                        | 12 h post-transfusion           | 33 (22)                  | NR      |
|                         |                      | High dose PT/adults |              |                           |                                 | 51 (29)                  | P < 0.01 vs medium |
|                         |                      | Very high dose PT/adults |             |                           |                                 | 62 (34)                  | P < 0.01 vs high |
| Schmidt 2018 [128]      | TCP and elective invasive procedure | Pre-procedural PPT | 376           | 32.6 (22.5)               | Post-procedure                  | PC of 56.9 (36.4)         | NR      |
| Schuh 2013 [216]        | TCP overall          | PT                 | 50            | 9.000/muL (6.000–15.000)b | 1 h                            | CCI of 6.500              | NR      |
|                         |                      |                    |               |                           |                                 | 24 h                      | NR      |
|                         |                      |                    |               |                           |                                 | CCI of 2.146              | NR      |
|                         |                      |                    |               |                           |                                 | 1 h                       | NR      |
|                         |                      |                    |               |                           |                                 | Good response in 44%⁶      | NR      |
|                         |                      |                    |               |                           |                                 | 24 h                      | Good response in 39%⁹ | NR      |
|                         |                      |                    |               |                           |                                 | Change in PC of 62.8 (39.9)| p = 0.000 |
| Sethi 2017 [123]        | TCP overall          | PPT                | 209           | NR                        | 48 h or discharge               | Change in PC of 101.7 (49.9) | NR      |
|                         |                      | No PPT             | 430           | NR                        |                                 |                           | NR      |
| Spahr 2008 [107]        | TCP overall          | Concurrent IVig and PT | 40           | 10                        | 24 h                            | PC of 55                  | NR      |
|                         |                      |                    |               |                           |                                 | 48 h                      | PC of 69 | NR      |
|                         |                      |                    |               |                           |                                 | 24 h                      | Good response in 48%⁶ | NR      |
| Wallace 2003 [127]      | TCP and elective invasive procedure | PT               | 50            | 17                        | 1–24 h                          | Change in PC of 101.7 (49.9) | NR      |
| Wandt 1998 [104]        | TCP overall          | PPT, PC <10 × 10⁹/L | 58           | NR                        | 0% patients non-refractory due to alloimmunization | NR      |
|                         |                      | PPT, PC ≥20 × 10⁹/L | 47            | NR                        | 0% patients non-refractory due to alloimmunization | NR      |
| Wu 2012 [229]           | TCP and elective invasive procedure | Pre-operative PT  | 10            | 9.4 (8.7)                 | Non-pre-operative PT            | PC of 272.3 (126.9)       | PT vs no PT p = 0.096 |
|                         |                      |                    |               |                           |                                 | PC of 387.8 (191.1)        | NR      |
| Rehrman 2002 [230]      | TCP overall          | PT                 | 20            | 12.6 (8.2)                | Non-preoperative PT             | PC of 387.8 (191.1)       | NR      |
| Zhou 2017 [232]         | TCP and elective invasive procedure | Pre-procedural PT  | 120           | <60                       | NR                              | Increase in PC in 89%     | NR      |
|                         |                      |                    |               |                           |                                 |                           | NR      |

**Notes:** CCI = corrected count increment; AMB = amphotericin B; CCI = corrected count increment; CLD = chronic liver disease; CR = complete response; ER = effective rate; HLA = human leukocyte antigen; IP = invasive procedure; IVIg = intravenous immunoglobulin; NR = not reported; PC = platelet count; PICOS = population, interventions, comparators, outcomes, study design; PPT = prophylactic platelet transfusion; PT = platelet transfusion; TCP = thrombocytopenia; TPT = therapeutic platelet transfusion.

*Table A8. Continued.*
### Table A9. Summary of the effectiveness and safety from real-world evidence studies – bleeding.

| Article | PICOS classification | Treatment/subgroup | N^a | Bleeding |
|---------|----------------------|--------------------|-----|---------|
| Al Zaabi 2014 [161] | TCP and elective invasive procedure | Pre-procedure PPT | 58 | Post-procedural WHO bleeding Grade 2–4 (29%) and within 72 h (24%) |
| C allow 2002 [139] | TCP overall | PT | 98 | 271 bleeding episodes according to WHO criteria |
| Charbonnier 2014 [103] | TCP overall | TPT | 884 | Death due to hemorrhage (2.4%) |
| Chen 2011 [114] | TCP and elective invasive procedure | PPT | 524 | Death due to hemorrhage (0.4%) |
| Duffy 2013 [115] | TCP and elective invasive procedure | Pre-procedure PPT | 14 | Minor bleeding complications (36%) |
| Fillmore 2013 [130] | TCP and elective invasive procedure | PT | 32 | Bleeding complications (29%) |
| Frigaa 2015 [176] | TCP overall | PT | 64 | Hemorrhagic syndrome (level 02; 63%) |
| Giannini 2010 [54] | CLD TCP and elective invasive procedure | PPT | 7 | Bleeding (57%) |
| Goel 2015 [21] | TCP overall | PPT | 25 | Bleeding (14%) |
| Habr 2015 [50] | TCP overall | PT | 279 | WHO bleeding Grade 3 and 4 (14.3%) |
| Jubelirer 2011 [184] | TCP and elective invasive procedure | No PT | 21 | Excessive bleeding complications (9%) |
| Kander 2014 [185] | TCP and elective invasive procedure | PPT | 39 | 4 CTCAE Grade 1 bleeding events |
| Keulers 2018 [129] | TCP and elective invasive procedure | Pre-procedure PT | 68 | Bleeding complications (0%) |
| Krishna 2014 [101] | TCP and elective invasive procedure | Pre-procedure PT, PC ≤ 50 × 10^9/L | 329^c | OR (95% CI) 1.02 (0.98, 1.05) of bleeding with PT |
| Lawrence 2001 [188] | TCP overall | PPT, threshold PC < 20 × 10^9/L | 64 | Minor and major bleeding on 70% and 18% of patient-days, respectively |
| Lee 2016 [119] | TCP overall | PT | 486 | Bleeding (23.5%) |
| Li 2018 [110] | CLD TCP and elective invasive procedure | Pre-procedure PT | 4^* | Major bleeding (25%) |
| Lye 2009 [120] | TCP overall | PPT | 188 | Major bleeding (2.1%) |
| Nevo 2007 [198] | TCP overall | PPT, threshold PC < 20 × 10^9/L | 68 | Bleeding (3%) |
| Park 2015 [111] | CLD TCP and elective invasive procedure | Pre-procedure PT | 61 EBL sessions | Bleeding (5%) |
| Ramos 2018 [208] | TCP and elective invasive procedure | PT | 144 | Recurrent bleeding rate of 22% at 30 days and 30% at 1 year |
| Samuelson Bannow 2017 [106] | TCP overall | AII^d | 82 | WHO bleeding Grade 2–4 (37%); fatal bleeding (4.9%) |
| Schmidt 2018 [128] | TCP and elective invasive procedure | Pre-procedure PPT | 376 | Bleeding (0%) |
| Sethi 2017 [123] | TCP overall | PPT | 209 | Modified WHO bleeding Grade 1 (31.1%) |
| Spahr 2008 [107] | TCP overall | Concurrent IVIg and PT | 40 | Death due to a massive intracranial bleed (3%) |
| Swisher 2009 [105] | TCP overall | PT | 33 | Death due to hemorrhage (3%) |
| Toor 2000 [108] | TCP overall | PT | 39 | Death due to or in part due to hemorrhagic complications (15%) |
| Vijenthalira 2017 [226] | TCP overall | TXA alone | 28 | WHO bleeding Grade 4 (11%) |
| Virgili 2015 [227] | TCP overall | PT | 49 | Grade IV hemorrhagic episodes in 3 patients (6%) |

^a N: Number of patients.

(^Continued)
Table A9. Continued.

| Article            | PICOS classification | Treatment/subgroup | N \(^{a}\) | Bleeding                                      |
|--------------------|----------------------|--------------------|-----------|-----------------------------------------------|
| Wandt 1998 [104]   | TCP overall          | PPT, threshold PC <10 \(\times 10^9\)/L | 104        | WHO bleeding Grade 2–4 (33%)                 |
|                    |                      | No PPT             | 302       | WHO bleeding Grade 3–4 (15%)                 |
|                    |                      |                   | 2270      |                                               |
| Ypma 2012 [109]    | TCP overall          | PT                 | 64        | WHO bleeding Grade 1–4 (89%), Grade 3–4 (8%), death due to bleeding complication (2%) |

\(^{a}\)Confidence interval; CI = confidence interval; CLD = chronic liver disease; CTCAE = Common Terminology Criteria for Adverse Events; EBL = endoscopic variceal band ligation; FFP = fresh frozen plasma; HIT = heparin-induced thrombocytopenia; HR = hazard ratio; ITP = immune thrombocytopenia; IVIg = intravenous immunoglobulin; OR = odds ratio; PC = platelet count; PICOS = population, interventions, comparators, outcomes, study design; PPT = prophylactic platelet transfusion; PT = platelet transfusion; TCP = thrombocytopenia, TPT = therapeutic platelet transfusion; TTP = thrombotic thrombocytopenia purpura; TXA = tranexamic acid; WHO = World Health Organization.

\(^{b}\)N of patients unless otherwise stated.

\(^{c}\)There were 43 catheterization attempts in 41 patients.

\(^{d}\)A total of 617 procedures were performed in 395 patients. PTs were administered within 24 h preceding the procedure in 329 patient encounters.

\(^{e}\)Clinical bleeding except petechiae.

\(^{f}\)Only 204 of the 874 patients had severe thrombocytopenia. 10 of 21 patients with bleeding had TCP. 194 of 853 of patients without bleeding had TCP.

\(^{g}\)Patients received a median of 6 PTs (range 0–61).

Table A10. Summary of the effectiveness and safety from real-world evidence studies – safety.

| Article            | PICOS classification | Treatment/subgroup | Number of patients | Safety                                      |
|--------------------|----------------------|--------------------|--------------------|---------------------------------------------|
| Arnold 2016 [112]  | TCP overall          | PT                 | 5621               | 10.7% of patients with PT had died and 6.5% of patients without PT had died, HR (95% CI) 0.66 (0.46, 0.96) for mortality with PT, \(P = 0.028\) |
|                    |                      | No PT              | 37,613             |                                              |
| Aubron 2017 [17]   | TCP overall          | PT                 | 2250               | Infection: 7.7% of patients with PT, 1.4% of patients without PT, \(P < 0.01\); Bacteremia: 4.4% of patients with PT, 0.5% of patients without PT, \(P < 0.01\); Bacteremia: 4.0% of patients with PT, 1.9% of patients without PT, \(P < 0.01\); OR (95% CI) 2.56 (1.98, 3.31) with PT, \(P < 0.01\). |
|                    |                      | No PT              | 16,715             |                                              |
| Beneke 2017 [113]  | TCP overall          | PT                 | 44                 | 0% of patients with PT had died, 2.6% of patients without PT had died, \(P = \text{ns}\) |
|                    |                      | No PT              | 206                |                                              |
| Benson 2011 [52]   | CLD TCP and elective invasive procedure | PT                  | 336                | OR (95% CI) 1.11 (0.92, 1.34) for post-operative infection with PT, \(P = 0.28\), OR (95% CI) 1.44 per PT unit (1.12, 1.87) for TRALI, \(P < 0.01\) |
|                    |                      | No PT              | 189                |                                              |
| Callow 2002 [139]  | TCP overall          | PT                 | 98                 | 4% of patients had died within 3 months |
| Chandran 2015 [44] | TCP overall          | PPT                | 1792               | 22.5% of patients with PPT had died within 1 month, 14.3% of patients without PPT had died within 1 month, OR (95% CI) 1.8 (1.5, 2.1) for mortality with PT, \(P < 0.001\) |
|                    |                      | No PPT             | 1792               |                                              |
| Charbonnier 2014 [103] | TCP overall | TPT               | 884               | 7 patients had died at a median of 12 days after diagnosis, 1 patient had died 16 days after diagnosis |
| Chen 2011 [114]    | TCP and elective invasive procedure | PT, PC <10\(^a\)/L | 10                | 0% of patients had died within 5 days |
|                    |                      | No PT, PC <10\(^a\)/L | 20                | 0% of patients had died within 5 days |
|                    |                      | No PT, PC 10–30\(^a\)/L | 24                | 0% of patients had died within 5 days |
|                    |                      | No PT, PC ≥30\(^a\)/L | 27                | 0% of patients had died within 5 days |
| Chern 2011 [168]   | TCP overall          | PT                 | 68                 | OR (95% CI) 7.49 (1.3, 42.0) between responders and non-responders for mortality, \(P = 0.022\) |
| Davasaambuu 2013 [171] | TCP overall | PT             | 41                | 7% of patients had died |
| Duffy 2013 [115]   | TCP and elective invasive procedure | Pre-procedure PPT | 14                | 43% of patients had died |
|                    |                      | No PPT             | 41                | 5% of patients had died |
| Eder 2013 [174]    | TCP overall          | PT                 | NR                 | Rate of TRALI: 7.3 per million distributed components in 2008–2011 |
| Engele 2016 [131]  | TCP and elective invasive procedure | PT              | 621               | 25.3% of patients had nosocomial infection, OR (95% CI) 2.53 (2.0, 3.2) for infection with PT, \(P < 0.001\); HR (95% CI) 1.46 (1.2, 1.8) for infection with PT, \(P < 0.001\) |
| Fillmore 2013 [130] | TCP and elective invasive procedure | PT, Local hemostatic measures | 32                | 3% of patients had infection |
|                    |                      |                   | 26                | 0% of patients had infection |
| Goel 2014 [116]    | TCP overall          | TTP hospitalizations, PT | NR | OR (95% CI) 2.02 (1.26, 3.22) for mortality with PT, \(P < 0.001\) |
|                    |                      | TTP hospitalizations, no PT | NR |                                              |
|                    |                      | HIT hospitalizations, PT | NR | OR (95% CI) 4.72 (1.53, 14.53) for mortality with PT, \(P < 0.01\) |
|                    |                      | HIT hospitalizations, no PT | NR |                                              |
|                    |                      | ITP hospitalizations, PT | NR | OR (95% CI) 1.06 (0.79, 1.42) for mortality with PT, \(P = 0.07\) |
|                    |                      | ITP hospitalizations, no PT | NR |                                              |
| Guerrero 2017 [117] | TCP overall          | PT                 | 302               | OR (95% CI) 1.39 (1.19, 1.94) for mortality with PT within 3 months, \(P = 0.050\) |

(Continued)
| Article | PICOS classification | Treatment/ subgroup | Number of patients | Safety |
|---------|---------------------|-------------------|-------------------|--------|
| Habr 2015 [50] | TCP overall | PT | 296 | 37.8% of patients had died, there were 5 serious adverse events reported |
| Keulers 2018 [129] | TCP and elective invasive procedure | No PT, mild TCP | 55 | 4% of patients had infection |
| | | No PT, moderate TCP | 58 | 9% of patients had infection |
| | | TCP PT, severe TCP (PC <50) | 68 | 10% of patients had infection |
| Kuter 2017 [118] | TCP overall | All | 442 | HR (95% CI) 2.81 (1.54, 5.12) for mortality after PT, P < 0.001 HR (95% CI) 1.77 (1.07, 2.89) for composite endpoint<sup>a</sup> after PT, P = 0.022 |
| Lawrence 2001 [188] | TCP overall | PPT, threshold PC <20<sup>a</sup> | 64 | 14% of patients treated with PPT for a PC <20 had died within 6 months and 18% of patients treated with PPT for a PC <10 had died within 6 months, P = 0.9 |
| Lee 2016 [119] | TCP overall | PPT | 486 | 0.2% of patients with PPT had died and 0.0% of patients without PPT had died, P = 0.43 |
| Lye 2009 [120] | TCP overall | PPT | 188 | 0.5% of patients with PPT had died and 0% of patients without PPT had died, P = 1.00 |
| Makroo 2014 [121] | TCP overall | PT | 30 | 60% of patients had died |
| | | No PT | 21 | 10% of patients had died |
| Nevo 2007 [198] | TCP overall | PPT (threshold PC <20<sup>a</sup>) | 211 | 10% of patients treated with PPT for a PC <20 and 7.1% of patients treated with PPT for a PC <10 had died within 100 days of HSCT, P = 0.31 |
| Nevo 2001 [200] | TCP and elective invasive procedure | Bleeding | 321 | 42.4% of patients had died within 100 days after BMT |
| Ning 2016 [100] | TCP overall | PT | 7073 | 12.5% of patients had died within 100 days after BMT |
| Otrock 2015 [122] | TCP overall | PT | 23 | 13% of patients with PT had died within 30 days and 3% of patients without PT had died within 30 days, P = 0.30 |
| Palo 2010 [203] | TCP overall | PT | 32 | 9.5% of patients had died within 24 months |
| Ramos 2018 [208] | TCP and elective invasive procedure | PT | 632 | 19% of patients had died within 1 month and 37% within 12 months |
| Raval 2015 [22] | TCP overall | PT | 225 | 1 event of septic transfusion reaction within 30 days, 2 events of allergic reactions, TACO occurred in 2 patients (0.9%), with a TACO to PT unit rate of 1:167 |
| Samuelson Bannow 2017 [106] | TCP overall | All<sup>b</sup> | 82 | 13% of patients experienced transfusion reactions, 37% of patients had TACO-volume overload within 30 days |
| Samuelson 2016 [214] | TCP overall | PPT | 36 | 14% of patients had a transfusion reaction, 44% of patients had TACO-volume overload within 30 days |
| Schmidt 2018 [128] | TCP and elective invasive procedure | Pre-procedural PPT | 376 | 16.0% of patients had died within 1 month, of which 29 patients (48%) died from septic shock/SIRS |
| Sethi 2017 [123] | TCP overall | No PPT | 209 | 1.9% of patients with PT had died and 0.2% of patients without PT had died, P = 0.024 |
| Singh 2012 [219] | TCP and elective invasive procedure | PT | 10 | 50% of patients had died within 12 months |
| Spahr 2008 [107] | TCP overall | Concurrent IVlg and PT | 40 | 5% of patients had died within 72 h, no side effects of combined treatment were noted |
| Swisher 2009 [105] | TCP overall | NT | 33 | 24% of patients with PT had died (2 patients died from sepsis) and 24% of patients without PT had died, P = 0.97 |
| Tran 2010 [124] | TCP overall | PT/Major bleed | 21 | 12% of patients with PT had died and 9% of patients without PT had died, P = 0.12 |
| Vigil-De Gracia 2006 [225] | TCP overall | Dexmethasone | 26 | 23% of patients had complications, 0% of patients had died |
| | | Dexmethasone + PT | 20 | 50% of patients had complications, 0% of patients had died |
| Wallace 2003 [127] | TCP and elective invasive procedure | PT | 50 | 26% of patients had died within 1 month, 9 patients died from infection/sepsis |
| Wandt 1998 [104] | TCP overall | PPT, PC <10<sup>a</sup> | 58 | 4% of patients had died, 9% of patients had serious infections and sepsis |
| Warner 2017 [46] | TCP and elective invasive procedure | Pre-procedural PT | 203 | 21.7% of patients with PT had died and 9.8% of patients without PT had died, OR (95% CI) 2.55 (1.76, 3.64) for mortality with PT, P < 0.001 |
| Warner 2016 [125] | TCP and elective invasive procedure | Pre-procedure PT | 71 | 27% of patients with PT had died and 10.1% of patients without PT had died, OR (95% CI) 3.20 (1.80, 5.67) for mortality with PT, P < 0.001 |
| Yoshii 2014 [126] | TCP overall | PT | 48 | 23% of patients with PT had died and 17.7% of patients without PT had died, P = ns |

<sup>a</sup>Platelet counts are presented with the units x 10<sup>9</sup>/L.

<sup>b</sup>The composite endpoint comprised death, limb amputation/gangrene, and new thrombosis.

<sup>c</sup>Patients received a median of 6 PTs (range 0–29).

**BMT** = bone marrow transplant; **CI** = confidence interval; **CLD** = chronic liver disease; **HIT** = heparin-induced thrombocytopenia; **HR** = hazard ratio; **HSCT** = hematopoietic stem cell transplantation; **IVlg** = intravenous immunoglobulin; **NS** = not significant; **NR** = not reported; **OR** = odds ratio; **PC** = platelet count; **PICOS** = population, interventions, comparators, outcomes, study design; **PPT** = prophylactic platelet transfusion; **PT** = platelet transfusion; **SIRS** = systemic inflammatory response syndrome; **TACO** = transfusion-associated circulatory overload; **TCP** = thrombocytopenia, **TTP** = thrombotic thrombocytopenia purpura.