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REVIEW

TRANSFUSION

Prophylactic platelet transfusions versus no prophylaxis in hospitalized patients with thrombocytopenia: A systematic review with meta-analysis

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1 | INTRODUCTION

Thrombocytopenia is a common condition in several populations of hospitalized patients, including those with hematological and solid tumor cancer,[1,2] those with chronic liver disease,[3] and critically ill neonates[4] and adults,[5] and it has been associated with increased rates of bleeding, transfusion requirements, and mortality.[6–9] Prophylactic platelet transfusions are often recommended in patients with severe thrombocytopenia, but the supporting evidence is primarily derived from trials in hematological patients[10–12] and clinical practice varies considerably.[13–15] Prior to prophylactic platelet transfusion, the risk of bleeding and the beneficial effects of transfusion must be viewed in light of the potentially harmful effects, which, although rare, include serious and potentially life-threatening reactions, such as anaphylaxis, transfusion-transmitted infections, and transfusion-related acute lung injury.[16] Harm from platelet transfusions has been observed in randomized clinical trials (RCTs) among preterm infants[17] and patients with intracerebral hemorrhage.[18] Therefore, we aimed to assess the benefits and harms of prophylactic platelet transfusions versus no prophylaxis on patient-important outcomes in hospitalized patients with thrombocytopenia. We hypothesized that the evidence base for non-hematological patients would be sparse and uncertain.

2 | METHODS AND ANALYSES

2.1 | Study design

This systematic review with meta-analyses and trial sequential analyses (TSA) was registered in the International Prospective Register of Systematic Reviews

(PROSPERO; CRD42021236014) and conducted in accordance with a published protocol.[19] We followed the recommendations by the Cochrane Collaboration,[20] the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[21] approach and the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (checklist available in Supplement S1).[22]

2.2 | Study selection

All RCTs and cluster RCTs comparing prophylactic platelet transfusion in any dose versus no prophylaxis or placebo in non-bleeding hospitalized patients with thrombocytopenia (as defined in the trials) were eligible for inclusion without restriction regarding age, diagnoses, or settings. Cohort studies, case–control studies, reviews, quasi-randomized trials, and crossover trials were excluded. We did not allow concomitant use of other interventions unless they were used in both allocation groups.

2.3 | Outcomes

2.3.1 | Primary outcome

1. All-cause mortality at longest follow-up.

2.3.2 | Secondary outcomes

1. The proportion of participants with at least one episode of clinically important bleeding.
2. Days with clinically important bleeding.
3. The proportion of participants with at least one nosocomial infection.
4. The proportion of participants with at least one venous or arterial thromboembolic event.
5. The proportion of participants with at least one transfusion-related adverse event.
6. Days alive without life support.
7. Length of hospital stay.
8. Health-related quality of life.

Clinically important bleeding, nosocomial infection, venous or arterial thrombo-embolic, and transfusion-related adverse events were defined in the included trials. The unit of analysis was randomized patients, and all outcomes were assessed at the longest follow-up.[19] Additional details are available in the protocol[19] and Supplement S3.

2.3.3 | Process variables

We collected data on the number of units of platelets, red blood cells (RBC) and fresh frozen plasma (FFP) transfused per participant.

2.4 | Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, and Epistemonikos and searched for ongoing trials in the U.S. National Library of Medicine (ClinicalTrials.gov), EU Clinical Trials Register, and the World Health Organization (WHO) International Clinical Trials Registry. The searches were conducted without restrictions on language or publication status on March 29, 2021 and updated in PubMed on February 3, 2022 (Supplement S4).

2.5 | Data collection and analysis

2.5.1 | Study selection

All records were independently screened for eligibility by two authors (CTA, AG, PS, and NZ). Potential eligible articles were assessed in full text by two authors (CTA, AG, PS, and NZ). We resolved disagreements by discussion and consulted a third author (MHM and LR) if needed. We used Covidence (https://www.covidence.org; Veritas Health Innovation, Melbourne, Australia) to facilitate the study selection.

2.5.2 | Data extraction and management

Two authors independently (CA and AG) extracted data from the included studies. We extracted data on trial characteristics, population characteristics, interventions, co-interventions, outcomes, and process variables as specified above (Supplement S5). We contacted the corresponding authors at least twice for clarifications and unpublished or missing outcome data, if applicable. We resolved disagreements by discussion and involved a third author (MHM and LR) if needed.

2.5.3 | Risk of bias in included trials

Two authors independently (CA and PS) assessed the risk of bias using the Risk of Bias 2.0 tool.[23] We assessed the risk of bias on the outcome level within all five domains: "bias arising from the randomization process," "bias due

to deviations from intended interventions," "bias due to missing outcome data," "bias in measurement of the outcome," and "bias in selection of the reported result." For each outcome in each RCT, the overall risk of bias judgment was judged as low risk of bias if all domains were judged to be low risk of bias, as some concerns if at least one domain was judged to be of some concerns, and as high risk of bias if at least one domain were judged to be high risk of bias.[20,23] Disagreements were resolved by consulting a third author (AG or MHM). We planned to base our primary conclusions on results from RCTs with an overall low risk of bias,[19] but this was only feasible for the primary outcome as no trials were judged to be low risk of bias for the secondary outcomes.

2.5.4 | Measures of treatment effect

We calculated relative risks (RRs) with confidence intervals (CIs) for dichotomous outcomes and mean differences (MDs) with CIs for continuous outcomes. We contacted the corresponding authors for additional data if alternative statistical measures for continuous outcomes were reported.[19] We did not convert medians and interquartile range (IQR) to means and SDs, as correct conversion requires normally distributed data. Instead, we reported the results descriptively. Results are based on the analysis of intention-to-treat populations, and data was analyzed for superiority regardless of the original trial designs.

2.5.5 | Adjusting for multiple testing

We adjusted thresholds for statistical significance using a compromise between no adjustment and a complete Bonferroni adjustment.[24,25] We divided the pre-specified *p*-value (.05) with the value half-way between 1 (no adjustment) and the number of primary or secondary outcomes meta-analyzed (Bonferroni adjustment).[24,25] As we were able to meta-analyze the primary outcome and three secondary outcomes, the thresholds considered statistically significant were a *p*-value of <.05 and <.025, respectively. For outcomes that were not meta-analyzed, a *p*-value of <.05 were considered statistically significant. The reported CIs and TSA-adjusted CIs matched these significance thresholds.

2.5.6 | Assessment of heterogeneity and subgroup analysis

We assessed statistical heterogeneity by the calculation of inconsistency (I^2), diversity (D^2) statistics, and the χ^2 test for subgroup differences and considered a *p*-value of <.05 as statistically significant.[19] We report results from fixed effect models (FEM) if the $I^2 = 0\%$. If $I^2 > 0\%$ we used both FEM and random effects models (REM) and based conclusions on the most conservative estimate (highest *p*-value).[19] Results from both FEM and REM for the primary analyses are presented in Supplement S9.

We planned six subgroup analysis[19]:

1. Trials with overall low risk of bias versus trials with some concerns or high risk of bias.
2. Patients with hematological cancers versus patient with non-hematological cancers versus patients without cancer.
3. Medical versus surgical versus mixed patient populations.
4. Patients undergoing invasive procedures versus patients not undergoing invasive procedures.
5. Neonates (including preterm infants) versus pediatric patients versus adult patients.
6. Intensive care unit (ICU) patients (including high-dependency units) versus non-ICU patients.

Additional details and the a priori hypothesized directions of subgroup effects are available in the protocol[19] and in Supplement S6.

Clinical heterogeneity was assessed using the Clinical Diversity in Meta-analysis tool[26] and the credibility of the subgroup analyses were assessed using the Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) tool.[27]

2.5.7 | Assessment of small trial bias

We planned to assess small trial bias but as all analyses included fewer than 10 RCTs, this was not feasible.[19]

2.5.8 | Trial sequential analysis

We conducted TSA to assess the risk of random errors due to repetitive testing in cumulative meta-analyses.[28] In short, TSA estimates the required information size (RIS) needed for a conclusive meta-analysis to detect or reject a predefined effect size. When data are sparse and/or statistical diversity is present, the TSA will adjust (expand) the CIs to account for the uncertainty around the overall effect estimate.[28] We report TSA-adjusted CIs when feasible. We applied trial sequential monitoring boundaries according to 15% RR reduction for dichotomous outcomes and a MD of 1 day for continuous outcomes,

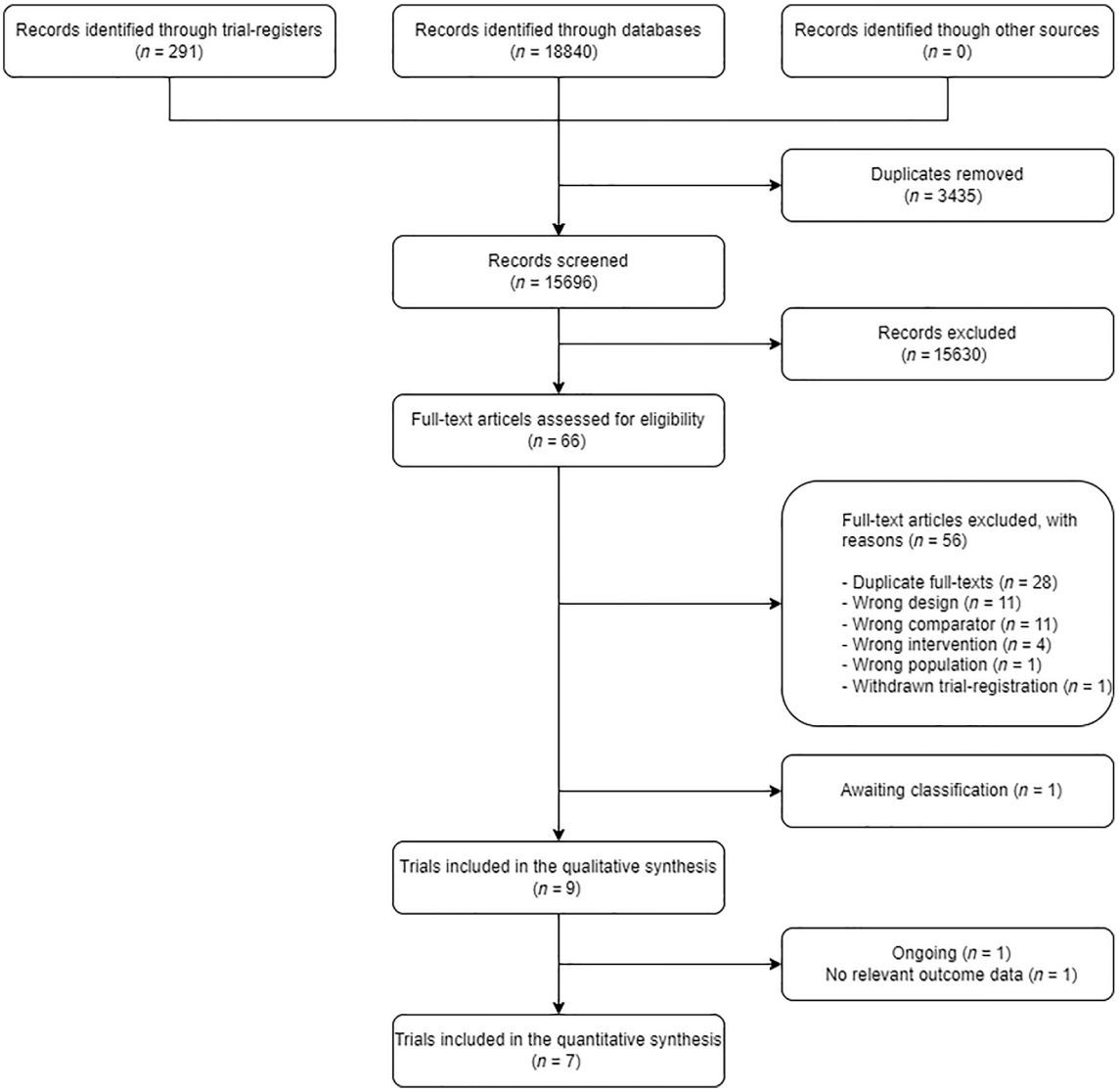

FIGURE 1 Flowchart of the trial selection process. One ongoing trial is awaiting classification due to insufficient information on the trial population.

an alpha of 5% and 2.5% for the primary and secondary outcomes, respectively, a beta of 10%, and a control event rate or variance suggested by the control groups in trials reporting on the outcome.[19] TSA is not feasible if the accrued information size was less than 5% of the RIS and in these circumstances, full TSAs were not presented.

2.5.9 | Data synthesis and software

Analyses were conducted using R version 4.1.0 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) with the "*meta*" package (version 5.1.0), and TSA was performed using the Copenhagen Trial Unit's TSA Software version 0.9.5.10b (available from http://www.ctu.dk/tsa).

2.5.10 | Sensitivity analysis

We conducted a sensitivity analysis on the primary and secondary outcomes.[19] We performed analyses that included all bleeding episodes (i.e., not restricted to clinically important bleedings) and analyses restricted to long-term all-cause mortality, defined as mortality beyond 90 days. The impact of missing outcome data was assessed by performing best-worst and worst-best (BW/WB) case analyses,[24] and the information from zero-event trials was accounted for by performing empirical continuity corrections.[29]

TABLE 1 Trial characteristics of the included trials

Author, year	Country centers setting	Inclusion criteria	Exclusion criteria	Randomized, *n* (P/no P)	Trial outcomes	Follow-up
Assir et al., 2013	Pakistan 1 Dengue HDU	Adults ≥ 14 years, dengue fever or dengue hemorrhagic fever, platelet counts < 30×10^9/L, no or mild bleeding (WHO grade 1 or 2)	Other causes of thrombocytopenia, chronic ailments, history of platelet transfusion, severe bleeding (WHO grade 3 or 4)	48[a] (21/24)	*Primary*: • Post-transfusion platelet increments at 1 h (for the treatment group) and at 24 h and 72 h for both groups *Secondary*: • Progression to severe bleeding (WHO grade 3 and 4) • Any new onset bleeding • Time to cessation of bleeding • Adverse events including death	72 h for the primary outcomes. Follow-up for secondary outcomes unclear.
Grossman et al., 1980	Canada 1 Hospital ward	Patients with amegakaryocytic thrombocytopenia, platelet counts less than 50×10^9/L	Refractory to platelet transfusions, not candidate for aggressive therapy, thrombocytopenia not expected to last for more than 7 days	100 (49/51)	*Primary*: Not specified *Secondary*: • Mild and severe bleeding episodes • Number of platelet transfusions received • Platelet increments 1 h post transfusion • Incidence of platelet refractoriness (alloimmunization) • Mortality due to bleeding	Unclear. Patients were followed throughout their initial hospital stay and all subsequent admissions, (mean length of follow-up was 42.7 days in the P-group and 41.6 days in the no P-group).
Lye et al., 2017	Singapore, Malaysia 5 Hospital ward[b]	Patients ≥ 21 years, probable or confirmed dengue (WHO 1997 or 2009 criteria), platelet count ≤20×10^9/L	Platelet count > 20×10^9/L, signs of clinical bleeding, pregnancy, lactating women, history of severe reactions to blood product transfusion, prior platelet transfusion within the same illness episode, patients likely to die within 48 h, history of peptic ulcer within 3 months, anticoagulants' use within 4 weeks, chronic liver disease, chronic renal failure or dialysis, active hematological or autoimmune disease, non-availability of platelet supply from local blood bank, consent unobtainable	372 (188/184)	*Primary*: • Clinical bleeding (excluding petechiae) *Secondary*: • Rate of change of platelet count at 1 h, 12 h and 24 h post transfusion (transfusion group only) • Median time to sustained platelet count >50×10^9/L • Clinical bleeding excluding petechia within 21 days of randomization • Plasma leakage • Dengue hemorrhagic fever or dengue shock • Admission to intensive care unit • Death • Secondary bacterial infection • Median length of hospital stay • Adverse events from platelet transfusion • Severe bleeding	21 days

(Continues)

TABLE 1 (Continued)

Author, year	Country centers setting	Inclusion criteria	Exclusion criteria	Randomized, *n* (P/no P)	Trial outcomes	Follow-up
Murphy et al., 1982	USA 1 Hospital ward[b]	Children with previously untreated acute leukemia	Not reported	56 (35/21)	*Primary*: Not specified *Secondary*: • Number, dates, and durations of serious bleeding episodes • Number of days in which bleeding was present • Platelet transfusion requirements within the first 10 months of follow-up	Unclear. Patients were followed from study entry until death or study closure (mean length of follow-up was 19.9 months in the P-group and 20.4 in the no P-group).
Sintnicolaas et al., 1981	Netherlands 1[b] Hospital ward[b]	Patients with acute leukemia and severe thrombocytopenia	Not reported	12[c] (?/?)	*Primary*: Not specified *Secondary*: • -Serological studies • Morbidity • Death due to bleeding • Refractory to random donor platelets	Unclear
Solomon et al., 1978	USA 1[b] Hospital ward[b]	Patients with previously untreated non-lymphoblastic acute leukemia	Promyelocytic leukemia	31 (19/12)	*Primary*: Not specified *Secondary*: • Deaths (per chemotherapy course) • Deaths due to bleeding (per chemotherapy course) • Transfusion requirements (per chemotherapy course) • Complete remission rates • Complete and partial remission rates	Within 1 month of chemotherapy course
Stanworth et al., 2013	United Kingdom, Australia 14 Hospital ward	Patients ≥ 16 years, undergoing chemotherapy or stem-cell transplantation to treat a hematological cancer, platelet count $< 50 \times 10^9$/L or expected to be so for at least 5 days, able to comply with treatment and monitoring	Previous WHO grade 3 or 4 bleeding, WHO grade 2 bleeding during current admission, inherited hemostatic or thrombotic disorder, requirement for therapeutic doses of anticoagulant agents, acute promyelocytic leukemia, known HLA antibodies, pregnancy, prior randomization into the trial	600 (299/301)	*Primary*: • Proportion of patients with a WHO Grade 2, 3, or 4 bleeds *Secondary*: • Proportion of patients with a WHO Grade 3 or 4 bleed • All cause mortality • Time to first WHO Grade 2, 3 or 4 bleeds • The rate of Grade 2, 3, or 4 bleeds • Proportion of patients who receive at least one platelet transfusion • Number of platelet transfusions • Number of platelet units transfused • Total number of red blood cell transfusions	30 days

TABLE 1 (Continued)

Author, year	Country centers setting	Inclusion criteria	Exclusion criteria	Randomized, *n* (P/no P)	Trial outcomes	Follow-up
					• Total number of red blood cell units transfused • Time from randomization to recovery of thrombocytopenia • Number of days with platelet count less than 20×10^9/L • Number of days in hospital	
Wandt et al., 2012	Germany 8 Hospital ward	Patients 16–80 years, undergoing intensive chemotherapy for acute myeloid leukemia or autologous haemopoietic stem-cell transplantation for hematological cancers	Refractory to platelet transfusions, previous major bleeding, plasmatic coagulopathy, pulmonary or cerebral lesions (stem-cell transplantations only)	396 (197/199)	*Primary*: • Number of platelet transfusions given during a standardized observation time of 14 days per participant *Secondary*: • Clinically relevant bleeding (WHO Grade ≥ 2) per treatment cycle • Percentage of days in which participants had bleeds of WHO Grade 2 or higher, dependent on morning platelet count • Days with platelet counts less than 20×10^9/L • Side-effects of transfusions • Duration of hospital stay • Survival • Numbers of red blood cell transfusion	Unclear. The study was completed when the platelet count was self-sustaining at more than 20×10^9 per L for 2 days or a maximum of 30 days, at hospital discharge, when treatment failure was diagnosed, at death, or at study withdrawal, which ever occurred first.
NCT03713489 (Ongoing)	China 1 Unclear	Patients 18–60 years, diagnosed with acute-on-chronic liver failure and chronic hepatitis B infection and ADP inhibition of ≥70%	Other causes of chronic live disease than chronic hepatitis B infection, previous decompensation, intracranial hemorrhage, use of anti-platelet or anticoagulants therapy within 4 weeks, esophageal variceal bleeding within 1 week, platelet transfusion within 1 week, malignant disease, pregnancy or breastfeeding, severe chronic extra-hepatic disease. Considered not suitable for inclusion by researchers.	Estimated enrolment: 20	*Primary*: • 28-day transplant free mortality *Secondary*: • transplant-free survival time	28 days for the primary outcome. Unclear for the secondary outcome.

(Continues)

TABLE 1 (Continued)

Author, year	Country centers setting	Inclusion criteria	Exclusion criteria	Randomized, *n* (P/no P)	Trial outcomes	Follow-up
van de Weerdt et al. (Ongoing)	Netherlands 11 Hospital ward/ICU	Adult (≥18 years) hematologic or ICU patients with thrombocytopenia (10–50 × 10^9/L) scheduled for emergency or elective insertion or replacement of a central line and an expectation of the inserted line to be in situ for at least 24 h	Patients with a non-correctable INR < 1.5, history of congenital or acquired coagulation factor deficiency or bleeding diathesis, treatment with double platelet-aggregation inhibitors or therapeutic unfractionated heparin not discontinued at least 1 h prior to insertion	Planned enrolment: 392 (196/196)	*Primary*: • Procedure-related relevant bleeding, occurring within 24 h after the procedure *Secondary*: • Platelet transfusion requirements within 24 h of CVC placement • Number of RBC transfusions within 24 h of CVC placement • WHO grade-1 bleeding within 24 h of CVC placement • Hematoma size • Hemoglobin level at 1 h and 24 h after CVC placement • Platelet transfusion increment • HEME bleeding score • Allergic transfusion reaction within 24 h • Onset of acute lung injury within 48 h • Length of hospital stay • Mortality • Costs	28 days

Abbreviations: ADP, adenosine diphosphate; CVC, central venous catheter; HDU, high dependency unit; HEME, hemorrhage measurement; HLA, human leukocyte antigen; ICU, intensive care unit; INR, international normalized ratio; P, prophylaxis; RBC, red blood cells; WHO, World Health Organization.

[a]Eighty-seven patients were randomized but 39 patients had bleeding (WHO grade 1 or 2) at randomization and were ineligible for this review.

[b]Assumption; not clearly reported.

[c]Allocation to intervention groups not reported.

TABLE 2 Interventions and definitions and assessments of bleeding in the included trials

Author, year	Intervention (prophylaxis group)	Control (no prophylaxis group)	Bleeding scale	Definitions of bleeding	Assessment of bleeding
Assir et al., 2013	Platelet transfusion with 1 SD platelet unit ($\geq 5 \times 10^{11}$ platelets/unit) at study entry	No platelet transfusion	WHO Bleeding scale	*Clinically important bleeding*: "Severe bleeding" defined as WHO grade 3 and 4 *Any bleeding*: "New onset bleeding" defined as WHO grade 1–4	*Assessor*: Not reported *Assessment*: Patients were assessed for WHO bleeding ever 12 h
Grossman et al., 1980	Platelet transfusion with 1 unit of either SD (4.8×10^{11} platelets/unit) or RD ($4.8–6.4 \times 10^{11}$/unit) platelets to maintain platelet count above 20×10^9/L through all hospital admissions	Platelet transfusions were given for clinically significant bleeding and prior to invasive procedures	Study specific	*Clinically important bleeding*: "Severe bleeding" *Any bleeding*: "Mild bleeds" defined as bleeds not requiring active intervention	*Assessor*: The clinical team performed the assessment *Assessment*: Daily clinical assessment for signs of bleeding. Fundoscopic examination twice daily when the platelet count was $\leq 20 \times 10^9$/L.
Lye et al., 2017	Supportive care plus 4 units RD (platelets/unit not reported) platelets each day the platelet count was $\leq 20 \times 10^9$/L up until day 7 or discharge If bleeding occurred, platelet transfusions were given at the clinician's discretion in both groups	Supportive care	None	*Clinically important bleeding*: Defined according to the WHO 2009 dengue guidelines: gum, nose, hemoptysis, hematuria, hematemesis, melaena, melaena or hematemesis-not controlled by procedure, menorrhagia, menorrhagia or intermenstrual bleeding-not controlled by progesterone, intermenstrual, hematoma, menses, others *Definition of any bleeding*: Not reported	*Assessor*: Not reported *Assessment*: Daily clinical assessment from day 1 until day 7 or discharge and at day 21 (+/−3)
Murphy et al., 1982	Platelet transfusion with RD (4 units/m^2 body surface, platelets/unit not reported) platelets when platelet count was $<20 \times 10^9$/L irrespective of clinical events. The goal was to maintain a platelet count above 20×10^9/L throughout the patient's course.	Platelet transfusion were given for serious bleeding episodes	None	*Definition of clinically important bleeding*: Serious bleeding episodes (bleeds) was defined as nasal or oral bleeding requiring packing, gross gastrointestinal bleeding, gross genitourinary bleeding, any central nervous system bleeding, or bleeding requiring red blood cell transfusion. Uncomplicated dermal bleeding was not included. *Definition of any bleeding*: Not reported	*Assessor*: Not reported *Assessment*: Not reported
Sintnicolaas et al., 1981	Platelet transfusion (units/transfusion not reported) with either RD or SD platelets (4×10^{11} platelets/unit) were given to maintain a platelet count above 20×10^9/L. Duration unclear.	Platelet transfusion were given for hemorrhage only	None	*Clinically important bleeding*: Not reported *Any bleeding*: Not reported	*Assessor*: Not reported *Assessment*: Not reported

(Continues)

TABLE 2 (Continued)

Author, year	Intervention (prophylaxis group)	Control (no prophylaxis group)	Bleeding scale	Definitions of bleeding	Assessment of bleeding
Solomon et al., 1978	Platelet transfusion with RD platelet (units/transfusion and dose not reported) whenever platelet count was $<20 \times 10^9$/L and when clinically significant bleeding occurred throughout the patient's course	Platelet transfusion were given when clinically significant bleeding occurred or when a platelet count of $<20 \times 10^9$/L was preceded by a decline of 50% in the platelet count during the preceding 24 h	Bleeding was not assessed	*Clinically important bleeding*: NA *Any bleeding*: NA	*Assessor*: NA *Assessment*: NA
Stanworth et al., 2013	Platelet transfusion with 1 unit of primarily RD ($>240 \times 10^9$/L platelets/unit) platelets when platelet count was $<10 \times 10^9$/L and continued daily until the platelet count is greater than 10×10^9/L for 30 days Both groups were transfused with platelets if bleeding of WHO grade 2 or more occurred and prior to invasive procedures or surgery	Platelets transfusions were not prophylactically given irrespective of platelet counts	Modified WHO Bleeding scale	*Clinically important bleeding*: "Clinical bleeding" was defined as bleeding of a modified WHO grade 2 or higher *Any bleeding*: Not reported	*Assessor*: Local research nurse for inpatients and self-assessment for discharged patients (unblinded) *Assessment*: Daily standardized bleeding assessment forms were completed each day that the patient was in hospital. Self-assessed bleeding diaries were completed for patients who were discharged.
Wandt et al., 2012	Platelet transfusion with 1 unit SD ($200\text{-}400 \times 10^9$ platelets/unit) or RD ($>200 \times 10^9$/unit) platelets was given when platelet count was $\leq 10 \times 10^9$/L If bleeding continued despite one platelet transfusion, further transfusions was given at the discretion of the treating clinician in both groups	Stable patients were only given platelet transfusion when clinically relevant bleeding occurred. Unstable patients with platelet count was $\leq 10 \times \times 10^9$/L were given prophylactic platelet transfusions.	Modified WHO Bleeding scale	*Clinically important bleeding*: "Clinically relevant bleeding" was defined as a modified WHO grade 2 or higher *Any bleeding*: Not reported	*Assessor*: A physician or experienced nurse (unblinded). Two investigators masked to treatment strategy later transformed the bedside bleeding report into modified WHO categories. *Assessment*: Clinical bleeding assessments was performed twice daily
NCT03713489 (ongoing)	Platelet transfusion with 1 unit of SD (platelets/unit not reported) platelets 3 times for the first week after enrolment, then 2 times a week in the following 3 weeks	Standard care	Bleeding not planned to be assessed	*Clinically important bleeding*: NA *Any bleeding*: NA	*Assessor*: NA *Assessment*: NA
van de Weerdt et al., (ongoing)	Platelet transfusion with 1 unit of RD (platelets/unit not reported) platelets prior to placement of central catheters The proceduralist can administer rescue platelets at clinical indication in both arms in case of procedure related bleeding	No platelet transfusion	Modified WHO Bleeding scale	*Clinically important bleeding*: Modified WHO grade 2–4 *Any bleeding*: Not reported	*Assessor*: Not reported *Assessment*: Clinical bleeding will be assessed at 1 h and 24 h post-procedural. Clinical photos taken at 1 h and 24 h will be used to evaluate size of hematoma in a blinded fashion.

Abbreviations: NA, not applicable; RD, pooled random donor platelets/buffy coat; SD, single donor apheresis platelets; WHO, World Health Organization.

TABLE 3 Risk of bias in the included trials

Outcome and study	Risk of bias domain (assessment for the effect of assignment to intervention)					Overall risk of bias
	1. Randomization process	2. Deviations from intended interventions	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported result	
All-cause mortality						
Lye et al., 2017	Low	Low	Some concerns	Low	Low	Some concerns
Murphy et al., 1982	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Solomon et al., 1978	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Stanworth et al., 2013	Low	Low	Low	Low	Low	Low
Wandt et al., 2013	Low	Some concerns	Low	Low	Some concerns	Some concerns
Clinically important bleeding						
Grossman et al., 1980	High	Low	Low	High	Some concerns	High
Lye et al., 2017	Low	Low	Some concerns	High	Low	High
Murphy et al., 1982	Some concerns	Some concerns	Low	High	Some concerns	High
Stanworth et al., 2013	Low	Low	Low	Some concerns	Low	Some concerns
Wandt et al., 2012	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
Days with clinically important bleeding						
Murphy et al., 1980	Some concerns	Some concerns	Low	High	Some concerns	High
Stanworth et al., 2013	Low	Low	Low	Some concerns	Low	Some concerns
Nosocomial infection						
Stanworth et al., 2013	Low	Low	Low	Some concerns	Low	Some concerns
Transfusion related adverse events						
Lye et al., 2017	Low	Some concerns	Some concerns	Some concerns	Low	Some concerns
Stanworth et al., 2013	Low	Low	Low	Some concerns	Low	Some concerns
Wandt et al., 2012	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
Length of hospital stay						
Lye et al., 2017	Low	Some concerns	Some concerns	Some concerns	Low	Some concerns
Stanworth et al., 2013	Low	Low	Low	Some concerns	Low	Some concerns
Wandt et al., 2012	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
Any bleeding (sensitivity analysis)						
Assir et al. 2013	Some concerns	Some concerns	Low	High	Some concerns	High
Grossman et al., 1980	High	Low	Low	High	Some concerns	High
Lye et al., 2017	Low	Low	Some concerns	High	Low	High
Murphy et al., 1982	Some concerns	Some concerns	Low	High	Some concerns	High
Stanworth et al., 2013	Low	Low	Low	Some concerns	Low	Some concerns
Wandt et al., 2012	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns

(Continues)

TABLE 3 (Continued)

Outcome and study	Risk of bias domain (assessment for the effect of assignment to intervention)					Overall risk of bias
	1. Randomization process	2. Deviations from intended interventions	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported result	
Days with any bleeding (sensitivity analysis)[a]						
Murphy et al., 1980	Some concerns	Some concerns	Low	High	Some concerns	High
Stanworth et al., 2013	Low	Low	Low	Some concerns	Low	Some concerns
Long term all-cause mortality (>90 days) (Sensitivity analysis)						
Murphy et al., 1982	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns

[a]Wandt et al. (2012) did not report days with clinically important bleeding with individual patients as the unit of analysis and hence the study was not included in risk of bias assessment for that outcome.

2.5.11 | Grade assessment

The overall certainty of evidence was rated independently by two authors (CA and AG) using the GRADE methodology[21] and disagreements were settled by discussion. We rated the certainty for each outcome as high, moderate, low, or very low based on assessments of risk of bias, inconsistency, indirectness, imprecision, and small trial bias.

3 | RESULTS

3.1 | Results of the search

We screened 15,696 records, assessed 66 records in full text and included nine trials in the qualitative synthesis[30–38]; one trial did not report any relevant outcome data[34] and one trial was ongoing.[37] Hence, seven RCTs[30–33,35,36,38] enrolling a total of 1642 participants were included in the quantitative analysis (Figure 1).[39]

3.2 | Characteristics of included trials

The trials were published from 1980 until 2017.[30–36,38] Five trials were published as full reports,[30,32,33,36,38] one as a letter to the editor,[35] one as an abstract,[34] and one remained unpublished.[31] The smallest trial randomized 12 patients[34] whereas the largest randomized 600 patients.[36] Two trials were conducted at multiple centres[36,38] and all trials were conducted in hospitalized patients with hematological malignancies[31,33–36,38] or dengue fever.[30,32] One trial included pediatric (hematological) patients only,[33] and one was a non-inferiority trial.[36] Trial characteristics are presented in Table 1 and further detailed in the Supplement S7.

3.3 | Interventions

All trials assessed prophylactic platelet transfusion compared with no prophylaxis; however, in two trials, prophylactic platelet transfusions were also administered in the no prophylaxis group under specific circumstances with a perceived high risk of bleeding.[35,38] Two trials administered prophylactic platelets in both groups prior to invasive procedures or surgery[31,36] and most trials administered platelets in both treatment groups when bleeding occurred.[31,32,35,36,38] One trial used a platelet count $\leq 30 \times 10^9$/L as a threshold for prophylactic transfusion,[30] five trials used $\leq 20 \times 10^9$/L[31–35] and two trials used $\leq 10 \times 10^9$/L.[36,38] Duration of the intervention,

type of platelets, number of units administered per transfusion and platelets per unit varied between trials (Table 2).

3.4 | Assessment of bleeding, bleeding scales and definitions of clinically important bleeding

Two trials reported bleeding as the primary outcome.[32,36] Three trials explicitly described who performed the assessment of bleeding outcomes[31,36,38] and the method of bleeding assessment was described in five trials.[30–32,36,38] Newer trials typically used the WHO scale in the original[30] or a modified version[36,38] to grade bleeding severity whereas older studies either used a study specific bleeding scale[31] or none at all.[33,34] We used the trials' definitions of clinically important bleeding, which varied substantially (Table 2).

3.5 | Risk of bias in included trials

An overview of risk of bias for all outcomes are provided in Table 3, with supportive comments available in Supplement S8. For the primary outcome, one trial was judged as overall low risk of bias. The domains "bias due to deviations from intended interventions" and "bias in selection of the reported results" were generally of concern in the remaining trials. For the remaining outcomes, all trials were judged to be of "some concerns" or "high risk of bias" with the domain "bias in measurement of the outcome" representing concerns for subjective outcomes.

3.6 | Primary outcome

3.6.1 | All-cause mortality at longest follow-up in overall low risk of bias trials

One low risk of bias trial reported data on all-cause mortality at the longest follow-up ($n = 598$) and showed uncertain results (RR 0.81; 95% CI 0.22 to 2.97, $p = .75$).[36] TSA could not be performed as only 0.6% of the RIS of 102,293 patients had been accrued. The certainty of evidence was low (Table 4). The sensitivity analysis was consistent with the primary analysis (Supplement S13).

3.6.2 | All-cause mortality at longest follow-up in all trials

Five trials reported data on all-cause mortality at longest follow-up ($n = 1398$).[32,33,35,36,38] Conventional meta-analysis showed uncertain results (FEM, RR of 0.99; 95% CI 0.58 to 1.68, $p = .97$) (Figure 2). TSA could not be performed as only 2.0% of the RIS of 52,950 patients had been accrued. We observed no statistical heterogeneity ($I^2 = 0\%$; $p = .91$, $D^2 = 0\%$) and low clinical diversity (Supplement S10). The certainty of evidence was very low (Table 4).

Subgroup analyses did not indicate heterogeneity of the treatment effect (Supplement S11), but the credibility was rated as very low as the analysis of effect modification was based solely on a between-trial comparison and the number of trials was very low (Supplement S12). Sensitivity analyses for long-term all-cause mortality (>90 days) and empirical continuity correction were consistent with the primary analysis, but BW/WB case scenarios showed conflicting results (Supplement S13).

3.7 | Secondary outcomes

3.7.1 | Clinically important bleeding

Five trials reported data on clinically important bleeding ($n = 1276$).[31–33,36,38] The conventional meta-analysis indicated that prophylactic platelet transfusion may reduce the proportion of patients with at least one episode of clinically important bleeding (REM, RR 0.70, 97.5% CI 0.53 to 0.92, $p < .01$) (Figure 3), but the TSA showed that only 13.4% of the RIS of 9546 patients had been accrued (TSA adjusted CI 0.26 to 1.87) (Figure 4). We detected significant statistical heterogeneity ($I^2 = 59\%$; $p = .04$, $D^2 = 72\%$), partly explained by the moderate clinical diversity (Supplement S10). Despite this, all individual trial point estimates favored the prophylaxis group. The certainty of evidence was very low (Table 4). Data from a subgroup of patients with acute myeloid leukemia ($n = 190$) from one of the larger trials were not included, as they were reported per treatment cycle received, but showed fewer clinically important bleeding episodes in the prophylactic group ($n = 96$, 245 cycles) as compared to the therapeutic group ($n = 94$, 198 cycles); 24% (95% CI 18% to 30%) versus 51% (95% CI 43% to 59%).[38]

Sensitivity analyses were consistent with the primary analysis, but the results were no longer statistically significant for all bleeding episodes (i.e., not restricted to clinically important bleedings) and in BW/WB case scenarios (Supplement S13).

3.7.2 | Days with clinically important bleeding

Two trials reported data on this outcome ($n = 654$) but the available summary data did not allow meta-analysis.[33,36]

TABLE 4 Grading of Recommendations Assessment, Development and Evaluation evidence profile

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prophylactic platelet transfusion	No prophylaxis	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
All-cause mortality (low risk of bias trials only)[a]												
1	Randomized trials	Not serious	Not serious	Not serious	Very serious[b]	None	4/298 (1.3%)	5/300 (1.7%)	**RR 0.81** (0.22 to 2.97)	**3 fewer per 1.000** (from 13 fewer to 33 more)	⨁⨁◯◯ Low	Critical
All-cause mortality (all trials)[a]												
5	Randomized trials	Serious[c]	Not serious[d]	Not serious[e]	Very serious[f]	None	27/714 (3.8%)	21/684 (3.1%)	**RR 1.00** (0.59 to 1.69)	**0 fewer per 1.000** (from 13 fewer to 21 more)	⨁◯◯◯ Very low	Critical
Proportion of participants with at least one episode of clinically important bleeding[a]												
5	Randomized trials	Serious[g]	Serious[h]	Not serious[i]	Serious[j]	None	218/647 (33.7%)	284/629 (45.2%)	**RR 0.70** (0.53 to 0.92)	**135 fewer per 1.000** (from 212 fewer to 36 fewer)	⨁◯◯◯ Very low	Important
Days with clinically important bleeding[a]												
2	Randomized trials	Serious[k]	Serious[l]	Not serious[m]	Not serious[n]	None	Stanworth 2013 reported a MD (95% CI) in number of days with clinically important bleeding of 0.5 (0.1–0.9) days fewer in the prophylaxis group versus the no prophylaxis group. Murphy 1982 reported a mean of 1.9 days with clinically important bleeding in the prophylaxis group versus 2.2 days in the no prophylaxis group.				⨁⨁◯◯ Low	Important
Proportion of participants with at least one nosocomial infection[a]												
1	Randomized trials	Serious[o]	Not serious	Not serious[p]	Very serious[q]	None	14/466 (3.0%)	16/453 (3.5%)	**RR 0.89** (0.40 to 1.97)	**4 fewer per 1.000** (from 21 fewer to 34 more)	⨁◯◯◯ Very low	Important
Proportion of participants with at least one venous or arterial thromboembolism[a]**—not reported**												
—	—	—	—	—	—	—	—	—	—	—	—	Important
Proportion of participants with at least one transfusion-related adverse event[a]												
3	Randomized trials	Serious[r]	Serious[s]	Not serious[t]	Very serious[u]	None	35/660 (5.3%)	27/650 (4.2%)	**RR 2.54** (0.27 to 23.61)	**64 more per 1.000** (from 30 fewer to 939 more)	⨁◯◯◯ Very low	Important
Days alive without the use of life support[a]**—not reported**												
—	—	—	—	—	—	—	—	—	—	—	—	Important
Length of hospital stay[a]												
3	Randomized trials	Serious[v]	Serious[w]	Not serious[e]	Not serious[x]	None	We were able to meta-analyze data from Lye 2017 and Wandt 2012 which showed a MD (97.5% CI) in length of hospital stay of 0.23 days fewer (0.60 fewer to 0.13 more) in the prophylaxis group versus the no prophylaxis group. Stanworth 2013 reported the median (IQR) days to be 12 (9–18) versus 12 (9–18) in the prophylaxis group ($n = 298$) and no prophylaxis group ($n = 300$) respectively.				⨁⨁◯◯ Low	Important

TABLE 4 (Continued)

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prophylactic platelet transfusion	No prophylaxis	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Quality of life[a]—not reported												
—	—	—	—	—	—	—	—	—	—	—	—	Important

Abbreviations: CI, confidence interval; IQR, interquartile range; MD, mean difference; RR, relative risks.

[a]All outcomes were assessed at longest follow-up.

[b]Only one trial was included. There were very few events and CI around effect estimate includes substantial benefit and harm. Trial sequential analysis (TSA) could not be performed as the accrued information size (AIS) of 598 patients only corresponds to 0.59% of the required information size (RIS) of 102,293 patients. Thus, we rated down two levels.

[c]Effect estimates in trials at overall low risk of bias versus trials at some concerns or high risk of bias does not seem to differ. However, there are very few events and CI a broad making judgment difficult. Only one trial was at overall low risk of bias and trials at some concerns or high risk of bias contributed with 84% of the weight in the meta-analysis. Thus, we rated down one level.

[d]We detected no statistical heterogeneity, $I^2 = 0\%$ ($p = .91$), $D^2 = 0\%$. The Clinical Diversity in Meta-analyses (CDIM) score was 11 corresponding to "low" clinical diversity. Thus, we did not to rate down for inconsistency.

[e]Only trials conducted in the hematological and infectious disease ward setting contributed to the meta-analysis. Results may not be applicable to other hospitalized patient populations (i.e., surgical patients, critically ill patients, neonates), but as the all trials reported on the defined patient population, we did not to rate down for indirectness.

[f]The meta-analysis included very few events and the CI around both the relative and absolute effect estimates include substantial benefit and harm. TSA could not be performed as the AIS of 1398 patients only corresponds to 2.0% of the RIS of 52,950 patients. Thus, we rated down two levels.

[g]All trials were at some concerns or high for risk of bias. We chose to rate down one level as there is no information from low risk of bias trials and as it is thus impossible to estimate the effects of risk of bias.

[h]We detected substantial statistical heterogeneity; $I^2 = 59\%$ ($p = .04$), $D^2 = 72\%$. The CDIM score was 17 corresponding to moderate clinical heterogeneity. However, all effect estimates favored prophylaxis. Thus, we rated down one level.

[i]Only trials conducted in the hematological and infectious disease ward setting contributed to the meta-analysis. Results may not be applicable to other hospitalized patient populations (i.e., surgical patients, critically ill patients, neonates), but as all trials reported on the defined patient population, we did not to rate down for indirectness.

[j]TSA highlighted that the AIS of 1276 patients corresponds to 13.4% of the RIS of 9546 patients. The TSA adjusted CI: 0.26 to 1.87 includes both substantial benefit and harm corresponding to 334 fewer to 388 more per 1000 patients. As the $D^2 = 72\%$ is high, the TSA adjusted CIs are broadened when using a random effects model. As we already rated down one level for inconsistency, we chose to only rate down one level for imprecision.

[k]The trials was at some concerns or high risk of bias. We chose to rate down one level as there is no information from low risk of bias trials and as it is thus impossible to estimate the effects of risk of bias.

[l]The CDIM score was 15 corresponding to moderate clinical diversity. Considering this and the sparsity of data, we chose to rate down one level.

[m]The trials only reported on hematological patients for this outcome and results may not be applicable to other hospitalized patient populations (i.e., surgical patients, critically ill patients, children, neonates), but as the trials reported on the defined patient population, we chose not to rate down for indirectness.

[n]TSA (assuming alfa of 5% and a beta of 0.1 and a clinically relevant difference in means of 1 day) was redundant as more than 100% of the RIS of 261 had been obtained. Thus, we did not rate down.

[o]The trial was at some concerns for risk of bias. We chose to rate down one level as there is no information from low risk of bias trials and as it is thus impossible to estimate the effects of risk of bias.

[p]The trial reported on hematological patients for this outcome and results may not be applicable to other hospitalized patient populations (i.e., surgical patients, critically ill patients, children, neonates), but as the trials reported on the defined patient population, we chose not to rate down for indirectness.

[q]TSA (assuming alfa of 5% and a beta of 0.1 and a clinically relevant risk reduction or increase of 15%) could not be performed as only 1.23% of the RIS of 48,730 patients had been accrued Therefore, we rate down two levels.

[r]All trials were at some concerns for risk of bias. We chose to rate down one level as there is no information from low risk of bias trials and as it is thus impossible to estimate the effects of risk of bias.

[s]We detected substantial statistical heterogeneity; $I^2 = 60\%$ ($p = .08$), $D^2 = 94\%$. CDIM tool yielded a score of 13 corresponding to moderate clinical diversity. We chose to rate down one level.

[t]Only trials conducted in the hematological and infectious disease ward setting contributed to the meta-analysis. Results may not be applicable to other hospitalized patient populations (i.e., surgical patients, critically ill patients, neonates), but as all trials reported on the defined patient population, we did not to rate down for indirectness.

[u]This analysis included very few events and CI around both the relative and absolute estimates of effect include substantial benefit and harm. TSA could not be performed as the AIS of 1310 patients only corresponds to 0.2% of the RIS of 73,050 patients. We chose to rate down two levels.

[v]All trials were at some concerns for risk of bias. We chose to rate down one level as there is no information from low risk of bias trials and as it is thus impossible to estimate the effects of risk of bias.

[w]We observed no statistical heterogeneity $I^2 = 0\%$, $D^2 = 0\%$ in the meta-analysis which did not include the data from Stanworth 2013 because of different statistical summary data used (median, IQR). However, the CDIM tool yielded a score of 12 corresponding to moderate diversity. We chose to rate down one level.

[x]TSA could not be performed as the RIS of 238 patients had already been accumulated within any of the two included trials.

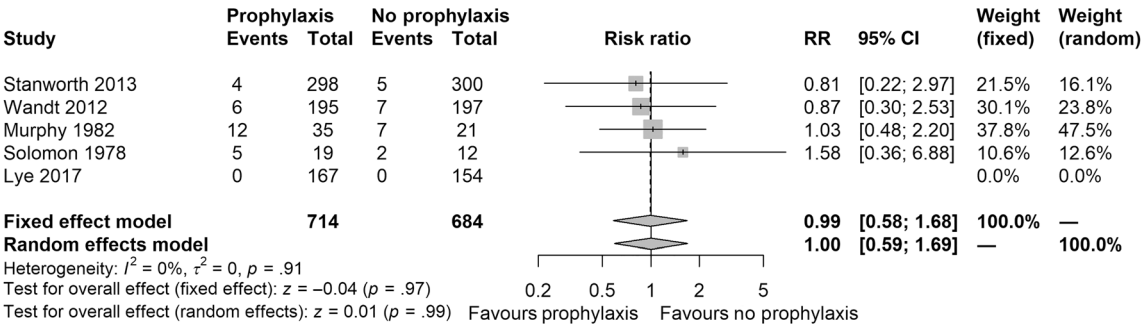

FIGURE 2 Forest plot for the primary outcome all-cause mortality at longest follow-up in all trials

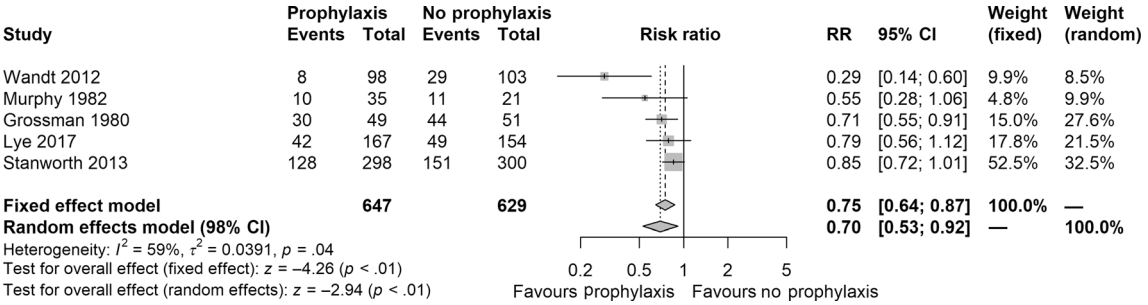

FIGURE 3 Forest plot for the secondary outcome clinically important bleeding (as defined in the included trials) at longest follow-up. Data from Wandt 2012 were reported per treatment cycle and only data for a subgroup of patients who had undergone autologous transplantation was extractable.

A smaller trial reported the mean number of days with clinically important bleeding to be 1.9 days in the prophylactic group versus 2.2 days in the no prophylaxis group[33] ($n = 56$) and a larger trial ($n = 598$) indicated that prophylactic platelet transfusions slightly reduced the number of days with clinically important bleeding (MD 0.5, 95% CI 0.1 to 0.9, $p = .01$). The TSA was redundant as more than 100% of the RIS of 261 had been accrued. We detected moderate clinical diversity (Supplement 10). The certainty of evidence was low (Table 4). Sensitivity analysis provided similar results (Supplement S13). A third trial[38] ($n = 396$) reported on the percentage of days with clinically important bleeding out of the total number of days on which a morning platelet count was available and found that the prophylactic strategy generally reduced the percentage of days with bleeding, with a larger effect on days with platelet counts $<10 \times 10^9$/L. As data was not reported with individual patients as the unit of analysis, the trial was not included in the meta-analysis, CDIM-evaluation, nor the GRADE evidence profile for this outcome.

3.7.3 | Nosocomial infection

One trial reported data on infections ($n = 598$) as part of serious adverse events, and we assumed that these infections were nosocomial.[36] The author did not have further details readily available. We found inconclusive results (RR of 0.94, 95% CI 0.46 to 1.91, $p = .86$) and TSA could not be performed as only 1.2% of the RIS of 48,730 patients had been accrued. The certainty of evidence was low (Table 4). Sensitivity analysis provided similar results (Supplement S13).

3.7.4 | Transfusion-related adverse events

Three trials reported data on this outcome ($n = 1310$).[32,36,38] The conventional meta-analysis showed inconclusive results (REM, RR 2.54, 97.5% CI 0.27 to 23.61, $p = .35$) (Supplement S9). TSA could not be performed as only 0.2% of the RIS of 73,050 patients had been accrued. There were considerable differences in the reported event rates between studies, and we detected statistical heterogeneity ($I^2 = 60\%$; $p = .08$, $D^2 = 94\%$) and moderate clinical diversity (Supplement S10). The certainty of evidence was very low (Table 4).

The empirical continuity correction agreed with the primary analysis, but the BW/WB case scenarios showed conflicting results (Supplement S13).

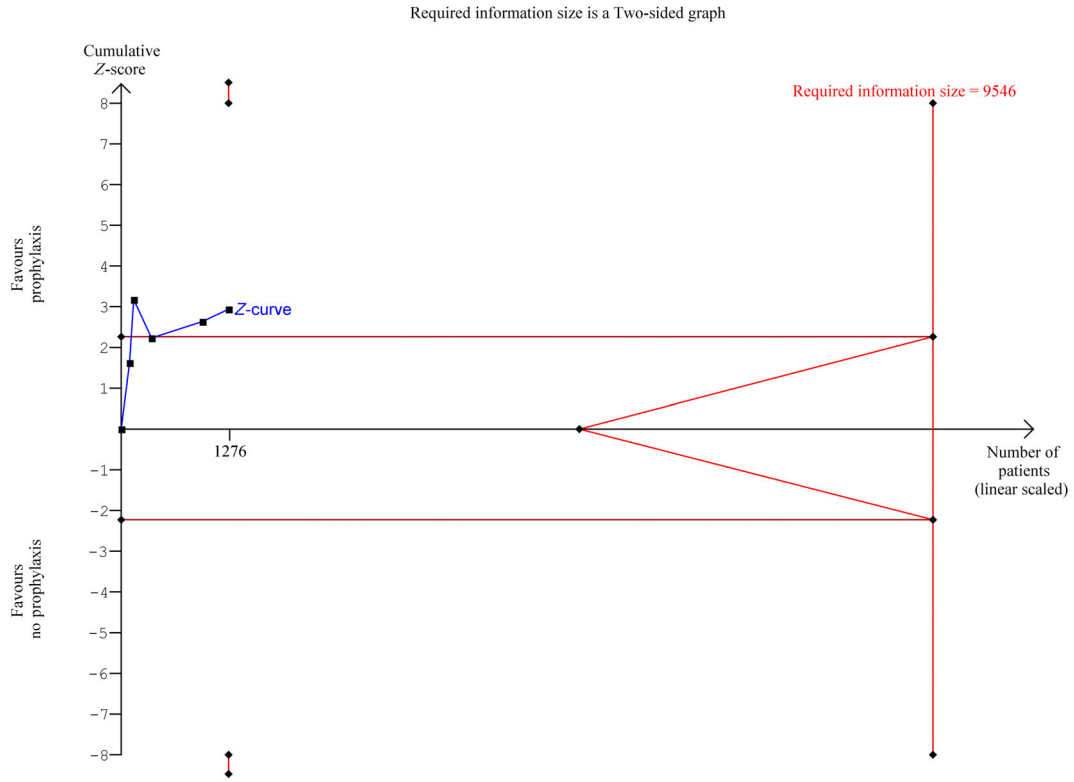

FIGURE 4 Trial sequential analyses (TSA) plot for the secondary outcome clinically important bleeding using a control event rate of 45.2% (from the included trials), a diversity D^2 of 72%, an alpha of 2.5%, a beta of 0.1 and a relative risk (RR) reduction of 15%. The meta-analytic RR was 0.70 with a TSA adjusted confidence interval of 0.26 to 1.87. The required information size was not reached (13.7% acquired) and the trial monitoring boundaries or futility boundaries were not crossed. Hence, the TSA highlights that the accrued information size was insufficient to reject or confirm a 15% reduction in RR. [Color figure can be viewed at wileyonlinelibrary.com]

3.7.5 | Length of hospital stay

Three trials reported data on this outcome ($n = 1310$)[32,36,38] but the statistical summary measures differed and only data from two trials were pooled.[32,38] These pooled results in the conventional meta-analysis suggested that the effect of the intervention may be of little to no clinical importance (FEM, MD −0.23, 97.5% CI −0.60 to 0.13, $p = .16$) (Supplement S9). The third study reported a median (IQR) length of stay of 12 (9–18) in both groups with no impact from prophylactic platelet transfusion.[36] We did not detect statistical heterogeneity ($I^2 = 0\%$; $p = .33$, $D^2 = 0\%$,) but found moderate clinical diversity (Supplement S10). The certainty of evidence was low (Table 4).

BW/WB case scenarios showed conflicting results (Supplement S13).

3.7.6 | Other secondary outcomes

No trials reported data on venous or arterial thromboembolic events, days alive without life support, or health-related quality of life.

3.7.7 | Process variables

Two studies reported the number of platelet units and red blood cell units transfused per participant ($n = 989$).[36,38] Conventional meta-analysis indicated that patients in the prophylaxis group received more platelet units as compared with the no prophylaxis group (REM, MD 1.00, 95% CI 0.53 to 1.47, $p < .01$, $I^2 = 57\%$) and possibly fewer red blood cell units (FEM, MD −0.25, 95% CI −0.58 to 0.07, $p = .13$, $I^2 = 0\%$) (Supplement S14).

4 | DISCUSSION

This systematic review identified seven RCTs with relevant outcome data comparing prophylactic platelet transfusion to no prophylaxis in 1642 hospitalized patients with thrombocytopenia.[30–33,35,36,38] We found uncertain results for all-cause mortality at longest follow-up between patients allocated to prophylactic platelet transfusion versus no prophylaxis when analyzing low risk of bias trials only and when incorporating data from all trials. The uncertainty about the effect is substantial since

the conventional CIs were wide and included both clinically relevant harm and benefit and less than 5% of the RIS had been accrued. The overall certainty of evidence was low or very low, respectively, indicating that the present evidence is insufficient to draw conclusions on the effect of prophylactic platelet transfusions on all-cause mortality.

The primary argument for the use of prophylactic platelet transfusions in patients with severe thrombocytopenia is to prevent bleeding.[10–12] We found that prophylactic platelet transfusion may reduce the proportion of patients with at least one episode of clinically important bleeding. However, less than 15% of the RIS has been accrued, the TSA-adjusted CI was wide and included clinically relevant benefit and harm, and the overall certainty of evidence was very low. We observed substantial statistical heterogeneity, partly due to clinical heterogeneity, as the included trials were conducted over a period of 37 years and had substantial differences in patient populations, interventions, timing of outcome measurement, and in definitions, assessments, and grading of clinically important bleeding. Despite the different pathophysiology and etiology of bleeding in patients with hematological malignancy and dengue fever,[40,41] all point estimates favored the prophylaxis group, indicating a similar effect of prophylactic platelet transfusion. Only two trials reported on the number of days with clinically important bleeding per participant, which was found to be slightly lower in the prophylaxis group. Taken together, the evidence suggests that prophylactic platelet transfusion may reduce the risk of clinically important bleeding, but uncertainty remains.

For the remaining secondary outcomes, we found substantial uncertainty around effect estimates for the proportions of patients experiencing at least one nosocomial infection or transfusion-related adverse event, and the evidence was too sparse to draw any meaningful conclusions. For the length of hospital stay, we found the difference between the allocation groups to be of little or no clinical importance, but the certainty of evidence was low. No trials reported on venous or arterial thrombotic events, days alive without life support or health-related quality of life.

Our findings concur with a previous systematic review in patients with hematological disorders treated with myelosuppressive chemotherapy or stem cell transplantation that also found high levels of heterogeneity in the timing of outcome measurements and in the definitions and assessment of bleeding and uncertainty around the effect on mortality and adverse events.[42] As our review had a wider scope, but still ended up including many of the same trials, it adds to the uncertainty around the effect of prophylactic platelet transfusions in patients outside the hematological setting.

This review has several strengths. We conducted the review in accordance with the protocol[19] and followed the recommendations by the Cochrane Collaboration[20] including independent selection of studies, data extraction, and assessment of risk bias using the ROB 2.0 tool.[23] We used TSA to estimate the RIS and calculate TSA-adjusted CIs where feasible.[28] We used the GRADE[21] approach to grade the overall certainty of evidence and we evaluated clinical diversity and subgroup credibility using the CDIM tool[26] and the ICEMAN tool,[27] respectively.

This review also has important limitations. First, due to the wide scope of the review, the included trials were heterogenous with respect to the populations, duration, and dose of the intervention, timing of outcome measurements and definitions, assessments, and grading of bleeding outcomes, which makes direct comparison uncertain. However, as we found only low to moderate clinical diversity for all outcomes and as the evidence base was sparse and event rates rare, conducting meta-analysis to answer the research questions seems justified. Further, we found no indications of very serious inconsistency in the results. Second, the number of patients and event rates were generally low, which led to imprecise results and increased risk of type two errors. In particular, omitting patients with acute myeloid leukemia from one of the larger trials due to the data format might have underestimated the effect of prophylactic platelet transfusions on clinically important bleeding as these patients in general are at increased risk of bleeding due to a longer duration of profound thrombocytopenia.[38] Third, newer trials defined clinically important bleeding as WHO grade ≥ 2,[30,36,38] which has been challenged as WHO grade 2 bleeding may not be considered clinically important.[43] Fourth, most outcomes were at risk of bias, which may decrease the overall validity of our results. Fifth, there was insufficient evidence to assess harm from prophylactic platelet transfusions; and sixth, the included patient populations were restricted to hematology-oncology patients and dengue fever patients, limiting the generalizability to other hospitalized patient populations with different reasons for thrombocytopenia, such as neonates, surgical patients, and ICU patients.

In conclusion, prophylactic platelet transfusion may reduce clinically important bleeding in hospitalized patients with hematological malignancy or dengue fever, but the evidence is very uncertain, and the generalizability to other patient populations is unclear. The effects on mortality and adverse events are uncertain and data from non-hematological settings are sparse. To move forward, RCTs are warranted to test the benefits and harms of platelet transfusion in diverse hospitalized populations with thrombocytopenia.

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CONFLICT OF INTEREST

The Department of Intensive Care at Rigshospitalet (CA, AG, PS, MHM, AP, and LR) has received funding for other projects from the Novo Nordisk Foundation, Pfizer, Sygeforsikringen "danmark" and Fresenius Kabi and conducts contract research for AM-Pharma. FP has received personal fees from Gilead and an institutional grant from Alexion for other projects. KP and NZ have no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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