Bleeding assessment and bleeding severity in thrombocytopenic patients undergoing invasive procedures

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Patients with a low platelet count (thrombocytopenia) have an increased risk of both spontaneous and post-procedural bleeding.[1,2] Platelet transfusions are therefore recommended in various guidelines,[3–5] either when the platelet count drops below a certain threshold or prior to invasive procedures. The clinical studies forming the basis of these guidelines are known to be of low quality,[3–6] essentially reducing the value of transfusion guidelines to the quality level of expert opinion.

Most studies designed to assess the optimal platelet transfusion trigger frequently include a clinical assessment of bleeding as outcome measure. A review of studies evaluating platelet transfusion triggers in patients with leukemia reported a spontaneous bleeding incidence that varied between 12 and 66%.[7] The authors concluded that this wide variance was more likely a reflection of different methods of bleeding assessment than an actual difference in the occurrence of bleeding. A recent review on coagulopathy prior to central venous catheter (CVC) placement by our group, also found a large variance in the incidence of bleeding.[1]

Several bleeding scales have been developed to help clinicians and researchers assess bleeding. The most widely used of these is the World Health Organization (WHO) bleeding scale,[8] which was created to standardize toxicity reporting in cancer treatment. The Society of Interventional Radiology (SIR) has developed standards for reporting post-procedural complications that includes a bleeding scale.[9] These bleeding scales are ordinal in nature.

An ordinal scale assigns grades to bleeding of increasing severity, whereas a singular definition gives criteria of bleeding to which the answer is either yes or no. In principle, an ordinal bleeding scale renders more details on bleeding complications than a singular definition, provided it is clear enough to allow unambiguous usage. The WHO bleeding scale in particular, is hampered by subjectivity and while none of the frequently used bleeding scales have ever been formally tested for reproducibility,[10] a study on adjudication of the WHO scale revealed high inter-observer variability.[11]

Another problem with designing adequate bleeding scales is their clinical relevance. Historically, many studies have used WHO Grade 2-4 bleeding complications as an outcome, while Grade 2 bleeding ("mild blood loss") is widely regarded as clinically irrelevant. Nonetheless, researchers often include grade 2 bleeding in order to capture enough endpoints. The incidence of grade 2 bleeding usually outweighs the incidence of grade 3-4 bleeding. Therefore, while such studies pretend to report clinically relevant bleeding, they mostly report "mild blood loss", in this case a surrogate outcome.[12]

In this systematic review, we expect to find different bleeding incidences depending on the assessment methods and bleeding definitions used, but also depending on the study design. Retrospective studies have been shown to be less accurate than prospective studies and heavily depend on chart review. Minor bleeding in particular is not regularly recorded in clinical practice, and may therefore be underreported.[7,13]

The primary objective of our study was to systematically review the methods and definitions used to assess bleeding severity in clinical research on invasive procedures. The secondary objective was to investigate the role of the study design in the variability in bleeding incidence.

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MATERIALS AND METHODS

Inclusion & exclusion criteria

We included clinical studies (randomized controlled trials [RCTs] and cohort studies), both prospective and retrospective, on the following invasive procedures: CVC placement, liver biopsy (LB), renal biopsy (RB), bone marrow biopsy (BMB), or lumbar puncture (LP). Included studies needed to have bleeding complications as their primary or secondary endpoint and had to include at least one thrombocytopenic ($<150 \times 10^9$/L) patient. An overview of thrombocytopenia and coagulopathy in each included study can be found in Appendix 1. Animal studies and case reports or series were excluded. Additionally, we excluded studies that were unavailable in English or Dutch.

Search

We conducted a MEDLINE search in May 2019, for which we used the search strategy that was previously described by the AABB, for the development of platelet transfusion guidelines.[3] The search was not limited in time. Two authors independently reviewed citations for eligibility (EvdW & FvB); if any disagreement occurred a third author adjudicated (BB). We manually checked platelet transfusion guidelines to identify missing articles.[3–5] The complete MEDLINE search terms are described in Appendix 2.

Assessment of risk of bias in included studies

For RCTs, the Cochrane Collaboration tool for the assessment of the risk of bias was used.[14] For observational studies, the Newcastle-Ottawa Scale was used.[15] Overall study quality was assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.[16] The quality assessment is provided in Appendix 3.

Statistical analysis

Continuous data was described as mean (SD) if normally distributed or as median (IQR) if not normally distributed. Categorical data was described as number (%). Non-normally distributed data was analyzed with Mann–Whitney U-tests, confidence intervals of bleeding incidences were calculated with the Wilson method[17] and all statistical analyses were performed using R-Studio (version 1.1.453).

RESULTS

Study selection and characteristics

Our MEDLINE search yielded a total of 2692 articles (1190 BMB, 211 CVC insertion, 1247 LB & RB and 44 LP), and the manual search of transfusion guidelines yielded another 472 articles. After removal of duplicates 3018 articles were left, of which 30 met the predefined inclusion and exclusion criteria (Fig. 1).

All studies were cohort studies, seven of which were prospective and 23 were retrospective. All studies had bleeding complications as their primary endpoint. There was reasonable variation in study types and populations studied (Table 1).

Differences in bleeding definitions

Overall, 11 studies used an ordinal bleeding scale, 13 used a singular bleeding definition and 6 reported no bleeding definition at all. Of the 24 studies with a bleeding definition, five used an existing ordinal bleeding scale (2) or

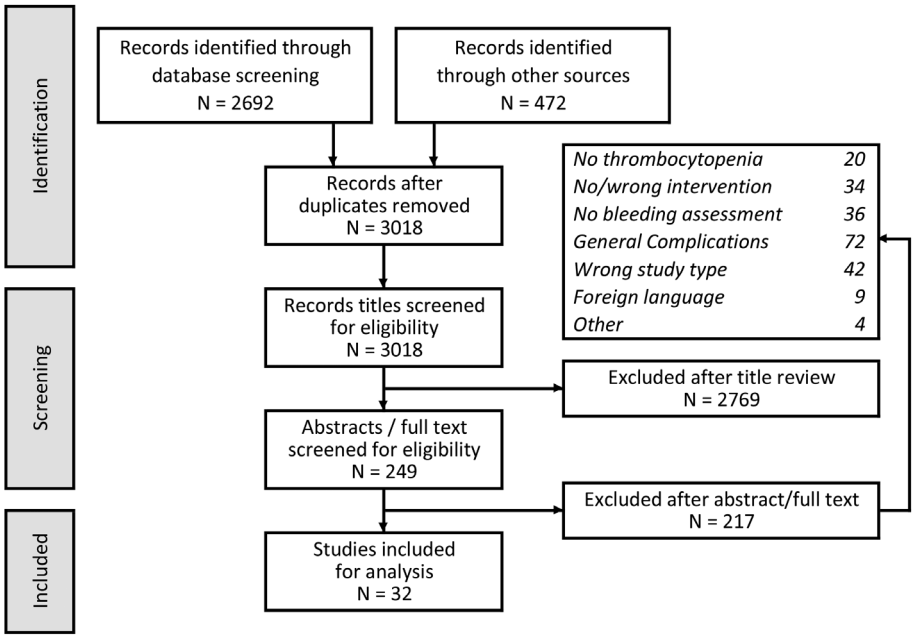

Fig. 1. Study flow.

incorporated elements of an existing ordinal bleeding scale in their singular definition (3). Nineteen studies used a bleeding definition (ordinal scale or singular definition) of the researchers' own design (Table 2). When investigators designed their own ordinal scale, it was always a two-point scale (major and minor bleeding).

The existing scales used in these studies included the SIR Technology Assessment Committee reporting standards[9] and the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE)[18] (Table 3). A detailed overview of bleeding definitions for all included studies can be found in Table 4.

Criteria used in bleeding definitions

The criteria used to define bleeding could be categorized into three distinct categories: symptoms, interventions, and laboratory results, which were all sometimes limited in time and/or size (Fig. 2). General symptoms included oozing, subcutaneous hematoma, and changes in hemodynamic function. Naturally, some symptoms differed between invasive procedures. Studies on CVC placement included hemothorax and mediastinal hematoma. Studies on LB included hemobilia, subcapsular liver bleeding, and hemoperitoneum. Studies on RB included (subcapsular) perirenal hematoma and hematuria. Studies on LP included spinal, subdural, subarachnoid, and epidural hematoma. The study on BMB did not include specific symptoms.

Common interventional criteria included erythrocyte (RBC) transfusion, surgical and/or radiological intervention to stop bleeding, which, together, often determined major bleeding, if such a distinction was made. Others included need for vasopressor or fluid therapy, extension of hospital stay, placement of suture ligaments, compression bandage, or manual pressure. Studies on CVC placement also included catheter removal, while one of the RB studies explicitly included angiographic embolization as a rescue intervention. Laboratory results used to define bleeding were a decrease in either hemoglobin (Hb) or hematocrit (Ht).

Some studies put size- or time-limitations on one or more of the prior criteria. Limitations in time were the most

TABLE 1. Study characteristics

Number of participants, median (IQR)	296 (108–1450)
Publication year, median (IQR)	2012 (2000–2016)
Design	
RCT	0 (0%)
Prospective cohort	7 (23%)
Retrospective cohort*	23 (77%)
Procedure type	
Central venous catheter*	12 (40%)
Liver biopsy (LB)	7 (23%)
Renal biopsy	6 (20%)
Lumbar puncture (LP)*	4 (13%)
Bone marrow biopsy (BMB)	1 (3%)
Population	
General population	12 (40%)
Advanced liver disease patients*	5 (17%)
Hemato- / oncology*	4 (13%)
Coagulopathic patients	3 (10%)
TTP patients	2 (7%)
Other	4 (13%)

* Also includes studies in children.
BMB = bone marrow biopsy; IQR = interquartile range; RCT = randomized controlled trial; TTP = thrombotic thrombocytopenic purpura.

TABLE 3. Bleeding scales used in studies of minimally invasive procedures

Scale	Items
SIR	A: no therapy, no consequence; B: requiring nominal therapy, no consequence, including overnight admission for observation; C: requiring therapy, minor hospitalization <48 hours; D: requiring major therapy, unplanned increase in level of care, prolonged hospitalization >48 hours; E: permanent adverse sequelae; F: death
CTCAE*	1: mild symptoms not requiring invasive intervention; 2: mild symptoms requiring minimally invasive interventions or aspiration; 3: event indicating transfusion, radiological or surgical procedure; 4: life-threatening consequences necessitating major urgent intervention; 5: death

* Zeidler et al used an adapted form of CTCAE that included prolonged compression as grade 2 bleeding.
SIR = Society of Interventional Radiology; CTCAE = Common Terminology Criteria for Adverse Events.

TABLE 2. Use of bleeding definitions in studies of minimally invasive procedures

		Categorical scale		Non-categorical definition		
Intervention	N	Existing bleeding scale	Researchers' own design	Incorporating existing scale	Researchers' own design	No definition
Total	**30**	**2 (7%)**	**9 (30%)**	**3 (10%)**	**10 (33%)**	**6 (20%)**
CVC placement	12	1 (8%)	5 (42%)	1 (8%)	3 (25%)	2 (17%)
Liver biopsy	7	1 (14%)	1 (14%)	0 (0%)	3 (43%)	2 (29%)
Renal biopsy	6	0 (0%)	3 (50%)	1 (17%)	2 (33%)	0 (0%)
Lumbar puncture	4	0 (0%)	0 (0%)	0 (0%)	2 (50%)	2 (50%)
BM biopsy	1	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)

BM = bone barrow; CVC = central venous catheter.

TABLE 4. Bleeding definitions and assessment methods for all included studies

Study	Year	Procedure	Bleeding definition* (Minor)	Bleeding definition* (Major)	Bleeding assessment / follow-up
Liu et al[31]	2017	Bone marrow biopsy	≥SIR grade C biopsy site bleeding, postprocedural imaging showing hematoma, >2g/dL Hb drop and requirement of vasopressors and/or inotropes		1st hour vital signs monitoring every 15 minutes, then medical record review at 48 hours.
Doerfler et al[32]	1996	CVC (Landmark)	-		Routine chest radiograph and nurses were instructed to report any evidence of bleeding or hematoma formation.
Fisher et al[33]	1999	CVC (Landmark)	Hemothorax or any other hemodynamically significant or life-threatening hemorrhage	Superficial oozing >24 hours without hemodynamic consequence, or superficial hematoma (visible or palpable)	Routine chest radiograph and daily inspection until catheter removal.
Foster et al[34]	1992	CVC (Landmark)	*Insertion site bleeding*: hemorrhage requiring removal of catheter or surgical intervention, including placement of suture ligatures, not including bleeding arrested with manual pressure; *Hemothorax*: pleural opacity on chest x-ray, confirmed by aspiration of blood on thoracocentesis; *Mediastinal hematoma*: collection of blood in mediastinum clinically evident from serial hematocrit concentrations, confirmed by appropriate density on chest x-ray or CT; *Subcutaneous hematoma*: subcutaneous bleeding at insertion site requiring surgical intervention to arrest bleeding or evacuate clot		-
Mumtaz et al[35]	2001	CVC (Landmark)	Intervention necessary to stop hemorrhage, hematomas increasing in size, hemothorax, hemomediastinum	Bleeding arrested with digital manual pressure for approximately 20 minutes	Routine chest radiograph. Medical record review at undetermined time.
Pandey et al[36]	2017	CVC (Landmark)	Requiring additional and non-expected hemostatic measures (compression bandage >15 minutes; blood transfusions) and bleeding causing extension of hospital stay		Routine chest radiograph and observation for 6 hours. Blinded assessor.
Zeidler et al[37]	2011	CVC (Landmark)	CTCAE		Daily inspection by specialized nurses.
Duffy et al[38]	2013	CVC (Mixed US-guided & landmark)	Requiring surgical intervention or causing significant morbidity/ mortality	Requiring minimal or no intervention	-
Ong et al[39]	2012	CVC (Mixed US-guided & landmark)	-		-
Vinson et al[40]	2014	CVC (Mixed US-guided & landmark)	1) New postprocedural fluid collection or enlargement in the pleural cavity, mediastinum or neck <24 hours of CVC; 2) line-related bleeding causing hemodynamic compromise requiring blood or fluid replacement, vasopressors or surgery	Oozing from a percutaneous puncture site or superficial hematoma <24 hours of CVC (includes use of manual pressure, no time-limit given); *Minor with procedural intervention*: requiring line removal, suture placement or administration of blood products	Medical record review at 48 hours with complication assessment by two investigators and a third arbitrator from a pool of four trained abstractors. Additionally, 5% randomly selected for independent review by a second investigator (97.8%-100% interrater agreement).
Haas et al[41]	2010	CVC (US-guided)	SIR, excluding minor oozing not requiring any intervention other than brief manual compression		-
Weigand et al[42]	2009	CVC (US-guided)	Drop in Hb >1,5g/dL within 24 to 36 hours		Routine chest radiograph and a laboratory test at least once within 24 to 36 hours.
Olivieri et al[43]	2016	CVC (Surgical)	Requiring surgical intervention or causing significant morbidity/ mortality	Requiring minimal or no intervention	Routine chest radiograph. Hemoglobin and platelet check within 24 hours. Medical record review at undetermined time.
McVay et al[21]	1990	LB (blind percutaneous)	Hb decrease >2,0g/dL	Hb decrease <2,0g/dL, but RBC-transfusion for hypovolemia given	Frequent monitoring of vital signs 1st 6 hours, routine hemoglobin check after 5 hours and often also the next day.

(Continues)

TABLE 4. Continued

Study	Year	Procedure	Bleeding definition* (Minor)	Bleeding definition* (Major)	Bleeding assessment / follow-up
Sharma et al[44]	1982	LB (blind percutaneous)	-		24 hours of bedrest. Frequent monitoring of vital functions for undetermined time.
Sandrasegaran et al[45]	2016	LB (Mixed blind & US-guided percutaneous)	Acute hemoperitoneum; drop in hematocrit >2g/dL, requiring inotropic or blood transfusion support or need for embolization of hepatic artery branches		Review of medical records at 4 weeks
Caturelli et al[46]	1993	LB (US-guided percutaneous)	-		Frequent monitoring of vital signs, routine hematological studies, clinical and ultrasound examination of the abdomen within 6 hours.
Kitchin et al[20]	2018	LB (US-guided percutaneous)	≥CTCAE grade 2	CTCAE grade 1	Two to four hours monitoring in nursing unit, next day telephone call and medical record review at 1 month by a single investigator.
Kamphuisen et al[47]	2002	LB (Plugged percutaneous)	Acute bleeding event requiring blood transfusion		Close monitoring and twice daily hemoglobin check until discharge (average 4 days).
Ahmed et al[48]	2016	LB (Transjugular)	Presence of an intraparenchymal liver hematoma, hemobilia, or subcapsular bleeding within 15 days following liver biopsy		Routine observation on nursing floor or interventional radiology recovery area for undetermined time. Review of records up to 15 days post-procedure.
Davis et al[49]	1995	RB (US-guided percutaneous)	Drop in hematocrit >6 within 6 hours of renal biopsy	Drop in hematocrit >4 or ultrasound evidence of new perirenal	Routine observation for 6 hours, with hematocrit check at 6 hours.
Islam et al[50]	2010	RB (US-guided percutaneous)	Hematuria, blood transfusion after biopsy or ultrasound-detected hematoma formation		Routine ultrasound both post-procedure and at discharge.
Soares et al[51]	2008	RB (US-guided percutaneous)	Requiring one or more major interventions, such as blood transfusion, hospital admission, or interventional or surgical procedure.	All other procedure-related bleeding not meeting the criteria for major bleeding	Routine ultrasound post-procedure, observation at least 6 hours and review of clinical notes at 1 week.
Sun et al[52]	2018	RB (US-guided percutaneous)	US or CT verified bleeding requiring blood transfusions, angiographic embolizations or surgical interventions.	Not requiring intervention.	Routine admission for one night with 6 hours of sandbag compression and imaging when signs of bleeding occurred.
Xu et al[53]	2017	RB (US-guided percutaneous)	Requiring intervention, including blood transfusion or invasive procedure (radiological or surgical) due to bleeding, within 1 week post-procedure		24 hours of bedrest, regular measurement of vital functions, imaging only on indication. Medical record review at undetermined time.
Monahan et al[54]	2019	RB (US- & CT-guided percutaneous)	≥ CTCAE grade 3, within 3 months of biopsy		Routine imaging directly post-procedure and when clinically indicated. A telephone call after 1, 2, or 3 days. Review of medical record at Days 1, 2, or 3 and after 3 months.
Estepp et al[55]	2017	Lumbar puncture	Objective confirmation on diagnostic imaging of a spinal hematoma, or a clinical suspicion leading to diagnostic imaging in a symptomatic patient		-
Foerster et al[56]	2015	Lumbar puncture	-		Chart review at undetermined time.
Horlocker et al[57]	1995	Lumbar puncture	-		Observation until discharge and hospital record review at 6 months.
Ning et al[58]	2016	Lumbar puncture	Spinal, subdural, subarachnoid and epidural hematomas		Review of medical records at 1 week.

* If two columns are used for bleeding definition, a distinction was made between minor and major bleeding. If one column was used, no such distinction was made.
CT = computed tomography; CTCAE = common terminology criteria for adverse events; CVC = central venous catheter; LB = liver biopsy; RB = renal biopsy; US = ultrasound.

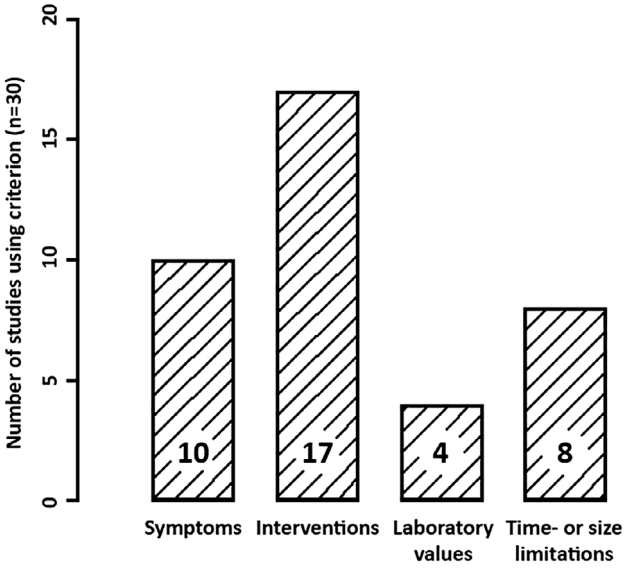

Fig. 2. Criteria used in bleeding definitions.

common, where the bleeding had to occur within a specified timeframe, varying between 24 hours and 3 months after the intervention. In other studies, symptoms and/or interventions needed a minimum duration, for instance manual compression for >15-20 minutes or oozing of >24 hours. Pertaining to size, one study defined major bleeding as hematomas increasing in size.

Differences in bleeding assessment

In five studies there was no mention of routine clinical post-procedural care. Routine care included post-procedural imaging, laboratory and clinical examinations, (overnight) admission, or observation. In 14 of 30 studies at least some data on bleeding assessment were described, in varying details, including chart review without further details on the procedure. Only one study used blinded bleeding assessors, although no details on the blinding procedure were given. Only one study used multiple trained bleeding assessors with an independent arbitrator. No other studies used trained bleeding assessors and/or arbitrators.

TABLE 5. Bleeding incidence per procedure type

Procedure	N	Bleeding incidence Median (IQR)
CVC	12	5.4 (0.2-13.5)
LB	7	2.2 (0.4-4.0)
RB	6	9.3 (3.3-24.1)
LP	4	0 (0-0)
BMB	1	0 (0-0)

CVC = central venous catheter placement; LB = liver biopsy; RB = renal biopsy; LP = lumbar puncture; BMB = bone marrow biopsy; IQR = interquartile range.

Variability in bleeding incidence

Although we restricted our study to five predefined invasive procedures, there was little overlap between studies, due to different subtypes of procedures and different study populations. We could identify 23 different combinations of patient populations and procedures, of which only five were represented by at least two studies. Bleeding incidences varied widely between groups (Table 5), but even within groups we found non-overlapping 95% confidence intervals (Fig. 3).

A significant difference in median bleeding incidence was observed between prospective studies (12.2% [8.1%-23.0%]) and retrospective studies (0.8% [0.0%-4.3], p = 0.02). We performed a *post-hoc* analysis on the ratio of major bleeding/minor bleeding for 10 studies that reported separate major and minor bleeding incidences. The median ratio was 0.1 (0.06-0.14) in prospective studies (n = 2), meaning that for every major bleeding there were 10 minor bleeding episodes, and 0.4 (0.2-1.2) in retrospective studies (n = 8), meaning five minor bleeding episodes for every two major episodes. This difference was not significant at p = 0.5.

DISCUSSION

In this study, we reviewed all studies on five frequently performed invasive procedures. We found a large variance in bleeding complications, even between studies assessing the same invasive procedure, mostly due to differences in the way clinical bleeding is assessed and defined, as suggested previously.[10,19]

The large proportion (19/30) of studies using a bleeding definition of investigators' own design forms a major problem, the impact of which is illustrated in the following example: a LB complicated by subcapsular bleeding requiring embolization and causing a 1 g/dL drop in Hb. This would be classified as major bleeding in one study (Kitchin et al[20]), but would not even be classified as minor bleeding in another study (McVay et al[21]). This illustrates that the difference in bleeding definitions should be taken into account when interpreting these results. Moreover, in the six studies without bleeding definition it is impossible to interpret the results.

Five studies fully or partly used an existing bleeding scale, which seems to increase the validity of these studies. However, even these scales suffer from subjective criteria and have never been tested for inter-observer variability. One of these bleeding scales was used in a different context than its intended use. The CTCAE scale was designed for toxicity reporting in cancer patients and it is therefore questionable to apply it in patients undergoing an invasive procedure. Moreover, the CTCAE scale has no predefined cut-off between minor and major bleeding. Since researchers mostly report minor and major bleeding as separate entities, a clear distinction is needed.

Besides the two bleeding scales encountered in this review, many other bleeding scales have been published

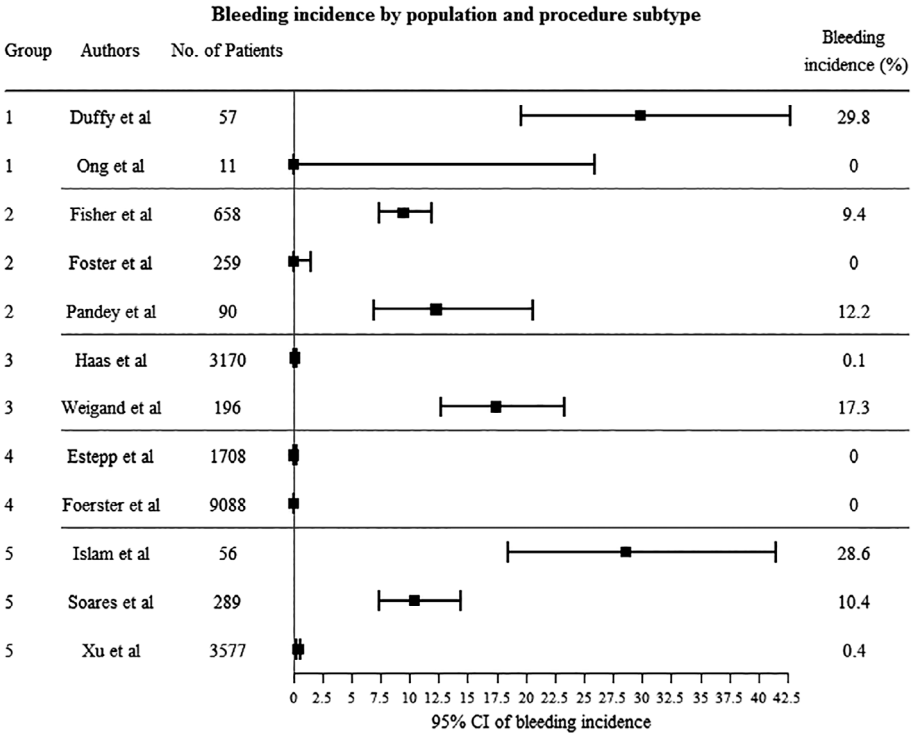

Fig. 3. Bleeding incidence by population and procedure subtype. CI = Confidence Interval. 1 = CVC placement (ultrasound-guided and landmark) in thrombotic thrombocytopenic purpura (TTP) patients, 2 = CVC placement (landmark) in advanced liver disease patients, 3 = CVC placement (ultrasound-guided) in general population, 4 = Lumbar puncture (LP) in pediatric cancer patients, 5 = Renal biopsy (RB) (ultrasound-guided percutaneous) in general population. Non-overlapping 95% CI in Groups 2, 3, and 5 signify difference in bleeding incidence within groups.

previously. Koreth et al[22] have already analyzed the majority of these scales, all of which are used in settings other than invasive procedures. Interestingly, the HEME bleeding assessment by Arnold et al,[23] which was specifically designed for critically ill patients, uses some objective criteria, like hemodynamic measures and specific bleeding sites, but retains subjectivity in defining major bleeding as bleeding requiring major therapeutic intervention. Another limitation of these interventional bleeding scales is the difference in the use of therapeutic interventions according to local clinical practice, as reported by Koreth et al.[22]

Methods of bleeding assessment varied also. Fourteen out of 30 reported their methods, which were mostly based on review of medical records, resulting in less accurate results than prospectively gathered data.[13] The amount of studies mentioning bleeding assessors was especially low (2/30), and none scored full marks with multiple trained, blinded bleeding assessors using independent adjudication. A systematic review on blinded versus non-blinded outcome assessors in RCTs showed that subjective binary endpoints suffer from bias when non-blinded assessors are used.[24] Furthermore, disagreement between two independent adjudicators using the WHO bleeding scale was as high as 31.2%.[11]

The necessity of adjudicating results has not been demonstrated in all situations. For instance, multicenter research seems to have more benefit than single center research, and vague, subjective endpoints need more adjudication than well-defined, objective endpoints.[25–28] Not all measures allow for adjudication: a trial on thromboprophylaxis in intensive care patients showed that attribution of bleeding to anticoagulant use was too hard for an arbitrating committee, when so many different causes of bleeding co-existed.[29]

Chart review is the predominant assessment method in retrospective studies. Our results show a significantly lower reported bleeding incidence in retrospective studies compared to prospective studies. This difference could be explained by the fact that in retrospective studies subtle positive outcomes (i.e., minor bleedings) are missed easily, since the assessment and documentation of minor bleeding is often not performed properly in general clinical practice.[7,13] The higher proportion of major bleeding that we found in retrospective studies further underlines this mechanism. However, due to the small number of prospective studies reporting minor and major bleeding, we were unable to demonstrate a statistically significant difference.

Our study is limited by heterogeneity of included studies (including the rate of thrombocytopenic patients), which is due to the broad range of patient populations undergoing different invasive procedures (as addressed in Fig. 3). Although this is a well-known limitation in transfusion medicine

research, current guidelines completely rely on these studies, so including them in this review is absolutely relevant.

Our results support the hypothesis that reported bleeding incidence depends more on methods of assessment and bleeding definition than on actual bleeding tendency. This is in line with earlier results concerning both SAE reporting and clinical bleeding.[1,7,30] Also, we have shown that the way of reporting bleeding assessment is often limited. The lack of this essential information reduces the validity and hampers the reproducibility of these studies. A major concern is that these studies form the basis of both current clinical guidelines and sample size calculations for future studies. Clinicians and researchers should be aware of the importance of outcome assessment and bleeding definition.

Future research should focus on developing such a uniform, objective, and practical bleeding definition. Through detailing current practices and common criteria in bleeding definitions, the results of this study could form the basis of such a uniform definition. We suggest a definition that is specific to each intervention, proposed by specialists in each field, and perhaps with the help of patient-advocates.[12] A specific definition could entail specific symptoms without relying on interventions or on subjective words like "significant morbidity" and "minimal intervention."

CONCLUSION

We demonstrate a high variability in definition and assessment of bleeding complications in studies on interventions in patients with thrombocytopenia. Hereby, interpretation and comparison of different study results is hampered. This has consequences for clinical practice (uncertainty about transfusion thresholds in guideline development) and clinical research (imprecise sample-size calculations and hampered comparison of studies). There is a dire need of a consensus procedure-related bleeding definition in the field of transfusion medicine, in patients undergoing invasive procedures.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest relevant to the manuscript submitted to Transfusion. This study is funded by ZonMW (Zorgonderzoek Medische Wetenschappen; part of the NWO [Nederlandse Organisatie voor Wetenschappelijk Onderzoek; the Dutch Organization for Scientific Research], Den Haag, The Netherlands), project number 843002625. The sponsors of this work were not involved in the study design, the collection, analysis, and interpretation of data, the writing of the report, or the decision to submit the manuscript for publication.

APPENDIX 1: OVERVIEW OF THROMBOCYTOPENIA AND COAGULOPATHY IN EACH INCLUDED STUDY

	Study	N	Platelets	Prothrombin time/INR	Activated partial thromboplastin time	Other
BMB	Liu et al[31]	981	<20: N = 33; 20-50: N = 187; >50: N = 761			
CVC	Doerfler et al[32]	104	Isolated <20: N = 11; 20-50: N = 30; 50-100: N = 22	Isolated 1.2-1.5 × ULoN: N = 12 >1.5 × ULoN: N = 6	Isolated 1.2-1.5 × ULoN: N = 4; >1.5 × ULoN: N=3	Combined PT & aPTT >1.5 × ULoN: N=3; PLT & coagulation abnormal: N = 13
	Fisher et al[33]	658	Median (IQR; range): Subclavian (n = 352) 81 (51-133; 9-1088) Internal Jugular (n = 306) 83 (53-133; 10-425)	Median (IQR; range): Subclavian (n = 352) 2.4 (1.7-3.9; 1-16) Internal Jugular (n = 306) 2,7 (1.8-4.7; 1-17)		
	Foster et al[34]	259	<80 (n = 122) Mean (range): 47 (8-79)	<40% (n = 122) Mean (range): 29% (39%-10%)	>77 (n = 3) Mean (range): 92 (78-100)	Normal coagulation: N = 57; 1) abnormal parameter: N = 160; 2) abnormal parameters: N = 40 3) abnormal parameters: N = 2
	Mumtaz et al[35]	2010	In 88 coagulopathic patients: Median (range): 95 (12-330)	In 88 coagulopathic patients: Median (range): 1.8 (1.2-3.5)	In 88 coagulopathic patients: Median (range): 54s (22-100)	1922 × normal (1680) or corrected (242) hemostasis

(Continues)

Appendix Continued

	Study	N	Platelets	Prothrombin time/INR	Activated partial thromboplastin time	Other
	Pandey et al[36]	90				PLT <150 and/or INR >1.5: N = 86
	Zeidler et al[37]	604	Mean: 48; <20: N = 14; 20-29: N = 48; 30-39: N = 56; 40-49: N = 52; 50-99: N = 140; >100: N = 272			
	Duffy et al[38]	57	Median (range): Overall (n = 57) 26 (3-128) Transfused (n = 14) 50 (11-100) Not transfused (n = 43) 25 (3-128)			
	Ong et al[39]	11	Median (range): 28 (7-129)			
	Vinson et al[40]	936	<20: N = 16; 20-50: N = 55; 50-75: N = 100; 75-100: N = 146	>3,0: N = 97; 2.0-3.0: N = 139; 1.5-2.0: N = 239; 1.3-1.5: N = 293	>50: N = 17; 35-50: N = 55	1) abnormal parameters: N = 732; 2) abnormal parameters: N = 187; 3) abnormal parameters: N = 17
	Haas et al[41]	3170	Isolated 3-19: N = 14; 20-24: N = 26; 25-29: N = 45; 30-34: N = 54; 34-39: N = 65; 40-44: N = 49; 45-49: N = 47	Isolated 1.5-1.6: N = 151; 1.7-1.8: N = 67; 1.9-2.0: N = 34; 2.1-2.2: N = 20; 2.3-3.8: N = 10		PLT < 50 & INR > 1,5: N = 44
	Weigand et al[42]	196	Isolated <50: N = 12	Isolated <50%: N = 32		Combined PLT < 50 & PT < 50%: N = 7
	Olivieri et al[43]	72	<50: N = 25 Mean (range): 251 (7-834)	Mean (range): 1.12 (0.96-1.76)	Mean (range): 30.5 (20.1-38.9)	All patients with PLT < 50 received PLT transfusion (1 unit/10kg).
LB	McVay et al[21]	177	<50: N = 2; 50-99: N = 18; ≥100: N = 157	13.6-15.7: N = 11; 11.6-13.5: N = 65; <11.5: N = 100	43.6: N = 14; 38.0-43.5: N = 23; 34.1-37.9: N = 37; <34: N = 103	
	Sharma et al[44]	87	30-60: N = 13; 60-90: N = 16; 90-120: N = 21; 120-150: N = 13; 150-180: N = 6; >180: N = 18			
	Sandrasegaran et al[45]	296	Mean: 205 In 7 transfused patients Range: 35-96	Mean: 1.17 In 11 transfused patients Range: 1.25-1.79		
	Caturelli et al[46]	85	Isolated <50: N = 36 Mean(range): 39.5 (18-49)	Isolated <50%: N =3 0 Mean(range): 44.3% 28%-49%)		PLT > 50 & PT < 50%: N = 19 Mean (range) PLT: 39.2 (22-49) Mean (range) PT: 42.6% (29%-49%)
	Kitchin et al[20]	1846	<50: N = 21 50-100: N = 110 >100: N = 1715 Mean (range): 219 (24-751)	>1.5: N = 40 1.0-1.5: N=755 <1.0: N=1051 Mean (range): 1.08 (0.8-2.7)		

(Continues)

Appendix Continued

	Study	N	Platelets	Prothrombin time/INR	Activated partial thromboplastin time	Other
	Kamphuisen et al[47]	36	In 27 patients with coagulopathy Mean (range): 53 (19-153)	In 27 patients with coagulopathy Mean (range): 16.3s (11.4-20.3)		
	Ahmed et al[48]	1600	BMT group (n = 183) Mean (sd; range): 88 (71; 5-336) Non-BMT group (n = 1417) Mean (sd; range): 174 (107; 8-1507)	BMT group (n = 183) Mean (sd): 1.2 (0.5) Non-BMT group (n=1417) Mean (sd): 1.2 (0.4)		
RB	Davis et al[49]	120	<150: N = 3	>13.6: N = 9	>36: N = 2	
	Islam et al[50]	56	Mean (sd; range): 260 (85; 107-442)	Mean (sd; range): 11.1s (1.2; 9.3-13.4)	Mean (sd; range): 26.5 (3.2; 21.7-37.1)	
	Soares et al[51]	289	Amyloidosis group (n = 101) Median (range): 282 (54-824) Control group (n = 188) Median (range): 265 (35-844)	Amyloidosis group (n = 101) Median (range): 0.9 (0.8-1.4) Control group (n = 188) Median (range): 0.9 (0.8-1.4)	Amyloidosis group (n = 101) Median (range): 26s (17-54) Control group (n = 188) Median (range): 26s (20-47)	
	Sun et al[52]	296	Mean: 248 <100: N = 6 (range: 75-94); 100-150: N = at least 5	Mean: 9.8	Mean: 26.1	
	Xu et al[53]	3577	Median (IQR): 226 (184-273)	Median (IQR): 10.1s (9.6s-10.7s)	Median (IQR): 31.3s (28.7-33.8)	
	Monahan et al[54]	2204	Median (IQR): 236 (182-297); <100: N=97; ≥100: N=1881	Median (IQR):1.0 (0.9-1.1)		
LP	Estepp et al[55]	1708	1-25: N = 40; 26-75: N = 236; 76-99: N = 111; ≥100: N = 1321			
	Foerster et al[56]	9088	<10: N = 25; 10-20: N = 67; 20-30: N = 88; 30-40: N = 92; 40-50: N = 107; 50-100: N = 729; >100: N = 7980			
	Horlocker et al[57]	1000	Mean (sd; range) 277 (84; 94-739)	Mean (sd; range): Bleeding group (n = 223) 12 (0.7; 9.8-13) Non-bleeding group (n = 777) 12.0 (1.1; 8.9-15.5)	Mean (sd; range): Bleeding group (n = 223) 29 (2.9; 22-37) Non-bleeding group (n = 777) 31 (8.4; 22-79)	
	Ning et al[58]	369	11-20: N = 3; 21-50: N = 17; 51-100: N = 40; 101-150: N = 52; >150: N = 242	All <1.5	All <40s	

aPTT = activated partial thromboplastin time; BMB = bone marrow biopsy; CVC = central venous catheter placement; INR = international normalized ratio; IQR = interquartile range; LB = liver biopsy; LP = lumbar puncture; PT = prothrombin time; PLT = platelet; RB = renal biopsy; ULoN = upper limit of normal.

APPENDIX 2 MEDLINE SEARCH (PUBMED)

- ("Platelet Count"[Mesh] OR "Platelet Count"[tiab] OR "Platelet Counts"[tiab] OR "Platelet Number"[tiab] OR "Platelet Numbers"[tiab] OR "Blood Platelet Disorders"[Mesh] OR "Blood Platelet Disorders"[tiab] OR "Blood Platelet Disorder"[tiab] OR "Thrombocytopenia"[tiab] OR "Platelet Storage Pool Deficiency"[tiab]) AND (("Bone Marrow"[Mesh] AND "Biopsy"[Mesh]) OR "Bone Marrow Aspiration"[tiab] OR "Bone Marrow Biopsy"[tiab] OR "Bone Marrow Biopsies"[tiab])
- ("Platelet Count"[Mesh] OR "Platelet Count"[tiab] OR "Platelet Counts"[tiab] OR "Platelet Number"[tiab] OR "Platelet Numbers"[tiab] OR "Blood Platelet Disorders"[Mesh] OR "Blood Platelet Disorders"[tiab] OR "Blood Platelet Disorder"[tiab] OR "Thrombo cytopenia"[tiab] OR "Platelet Storage Pool Deficiency"[tiab])AND("Catheterization, Central Venous"[Mesh] OR "Central Catheterization"[tiab] OR "Central Catheterizations"[tiab] OR "Central Venous Catheterization"[tiab] OR "Central Venous Catheterizations"[tiab] OR "CVC"[tiab] OR "CVL"[tiab] OR "CVCs"[tiab] OR "Central Vein Catheterization"[tiab] OR "Central Vein Catheterizations"[tiab])
- ("Biopsy, Needle/adverse effects"[MAJR] OR "liver biopsy"[tiab] OR "renal biopsy"[tiab] OR "kidney biopsy" AND ("Platelet Count"[Mesh] OR "Platelet Count"[tiab] OR "Platelet Counts"[tiab] OR "Platelet Number"[tiab] OR "Platelet Numbers"[tiab] OR "Blood Platelet Disorders"[Mesh] OR "Blood Platelet Disorders"[tiab] OR "Blood Platelet Disorder"[tiab] OR Thrombocytopenia [tiab] OR "Platelet Storage Pool Deficiency"[tiab])
- ("Platelet Count"[Mesh] OR "Platelet Count"[tiab] OR "Platelet Counts"[tiab] OR "Platelet Number"[tiab] OR "Platelet Numbers"[tiab] OR "Blood Platelet Disorders"[Mesh] OR "Blood Platelet Disorders"[tiab] OR "Blood Platelet Disorder"[tiab] OR Thrombocytopenia [tiab] OR "Platelet Storage Pool Deficiency"[tiab]) AND ("Puncture, Lumbar"[Mesh] OR "lumbar punct*"[tiab] OR "Spinal puncture"[Mesh])

APPENDIX 3: GRADE ASSESSMENT REGARDING BLEEDING INCIDENCE

Study	Year	Risk of Bias*	Inconsistency*	Indirectness*	Imprecision*	Publication bias*	Large effect†	Dose response‡	Residual confounding§	Overall study quality
Ahmed et al[48]	2016	−1	−1	−1	0	0	0	0	0	Very low
Caturelli et al[46]	1993	−1	0	−1	−1	0	0	0	0	Very low
Davis et al[49]	1995	−1	0	−1	0	0	0	0	0	Very low
Doerfler et al[32]	1996	−1	0	0	−1	0	0	0	0	Very low
Duffy et al[38]	2013	−1	0	0	0	0	0	0	0	Very low
Estepp et al[55]	2017	−1	0	0	0	0	0	0	0	Very low
Fisher et al[33]	1999	−1	0	0	0	0	0	0	0	Very low
Foerster et al[56]	2015	−1	0	0	−1	0	0	0	0	Very low
Foster et al[34]	1992	−1	0	0	−1	0	0	0	0	Very low
Haas et al[41]	2010	−1	−1	0	0	0	0	0	0	Very low
Horlocker et al[57]	1995	0	0	0	−1	0	0	0	0	Very low
Islam et al[50]	2010	−1	0	0	0	0	0	0	0	Very low
Kamphuisen et al[47]	2002	−1	0	0	−1	0	0	0	0	Very low
Kitchin et al[20]	2018	−1	0	0	−1	0	0	1	0	Very low
Liu et al[31]	2017	−1	0	0	0	0	0	0	0	Very low
McVay et al[21]	1990	−1	0	−1	−1	0	0	0	0	Very low
Monahan et al[54]	2019	0	0	0	0	0	0	0	0	Low
Mumtaz et al[35]	2001	−1	−1	0	−1	0	0	0	0	Very low
Ning et al[58]	2016	−1	0	0	0	0	0	1	0	Low
Olivieri et al[43]	2016	−1	0	0	−1	0	0	0	0	Very low
Ong et al[39]	2012	−2	0	0	−1	0	0	0	0	Very low
Pandey et al[36]	2017	−1	0	0	0	0	0	0	0	Very low
Sandrasegaran et al[45]	2016	0	0	0	0	0	0	0	0	Low
Sharma et al[44]	1982	−1	0	0	−1	0	0	0	0	Very low
Soares et al[51]	2008	−1	0	0	0	0	0	0	0	Very low
Sun et al[52]	2018	−1	0	0	0	0	0	0	0	Very low
Vinson et al[40]	2014	0	0	0	0	0	0	0	0	Low
Weigand et al[42]	2009	−1	0	−1	0	0	0	0	0	Very low

(Continues)

Appendix Continued

Study	Year	Risk of Bias*	Inconsistency*	Indirectness*	Imprecision*	Publication bias*	Large effect†	Dose response‡	Residual confounding§	Overall study quality
Xu et al[53]	2017	−1	0	0	−1	0	0	0	0	Very low
Zeidler et al[37]	2011	−1	0	0	0	0	0	0	0	Very low

Study quality can be "high," "moderate," "low," or "very low." Observational Studies start as low quality, there were no randomized controlled trials (RCTs) included. Each "-1" or "+1" makes the study fall or rise a quality level.
*Serious = −1, very serious = −2.
†Large effect = +1, very large effect = +2.
‡Evidence of gradient = +1.
§All plausible residual confounding would reduce demonstrated effect or suggest spurious effect if no effect was observed = +1.

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