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ORIGINAL ARTICLE

Predictors of bleeding complications following percutaneous image-guided liver biopsy: a scoping review

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PURPOSE
Percutaneous tissue biopsy is a mainstay of diagnostic and interventional radiology, providing a minimally invasive method for diagnosing malignant and benign disease. The purpose of this review was to collect and summarize the best available evidence regarding the risk factors associated with bleeding complications in image-guided liver biopsy.

METHODS
A literature review was performed, searching Medline, EMBASE, CINAHL, the Cochrane Library, the National Institute for Health and Care Excellence (NICE) and Canadian Agency for Drugs and Technology in Health (CADTH) databases for any studies evaluating bleeding complications in image-guided liver biopsy. A total of 68 articles, published between January 1994 and April 2015, were reviewed in full, with 34 ultimately eligible for inclusion in the review.

RESULTS
Bleeding of any kind occurred in up to 10.9% of image-guided liver biopsies, with major bleeding episodes ranging from 0.1% to 4.6% and minor bleeding events occurring in up to 10.9% of biopsies. The overall rate of bleeding was, however, found to be less than 2%. Several risk factors (patient, operator, and procedure-related) were identified as potentially indicative of an increased risk of post-biopsy bleeding. Patient-related risk factors included patient age (>50 years or <2 years), inpatient status (8/12 vs. 4/12, $P < 0.001$), comorbidities and/or concurrent diagnoses and coagulation status (rate of bleeding was 3.3% for international normalized ratio [INR] 1.2–1.5 vs. 7.1% for INR >1.5, $P < 0.001$). There was no consensus on impact of operator experience (>200 biopsies/year vs. <50/year) on post-biopsy bleeding rate. Procedure-related risk factors included needle size (cutting biopsy vs. fine needle aspiration, $P < 0.001$) and the presence of a patent track on post-biopsy ultrasound ($P < 0.001$). Lastly there was no difference found between targeted vs. nontargeted biopsies and number of needle passes.

CONCLUSION
Reported rate of post-biopsy bleeding ranges between 0% and 10.9%, although the vast majority of studies reported bleeding rates under 2%. Several patient, operator, and procedure-related risk factors are associated with a higher risk of bleeding following liver biopsy.

Percutaneous tissue biopsy is a mainstay of diagnostic and interventional radiology, providing a minimally invasive method for diagnosing malignant and benign disease commonly in an out-patient setting (1–3). In particular, percutaneous liver biopsies constitute a large portion of all biopsies and are being performed with an ever-increasing rate (4). The use of imaging guidance has improved biopsy accuracy and decreased the rate of overall complications (1). Despite these advances, complications do occur and could result in significant morbidity and mortality for the patient (1, 5, 6).

Post-biopsy hemorrhage (PBH) is the main source of mortality following liver biopsy and occurs in up to 10.9% of cases (7). The majority of PBH occur within the first 2–4 hours following the procedure (8), necessitating the need for close monitoring of the patient during this period. Several risk factors have been identified that contribute to the likelihood of bleeding complications following liver biopsy. These risk factors are categorized as either patient-related, operator-related, or procedure-related and range from coagulation status,

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comorbidities and operator experience to needle gauge and biopsy method. The purpose of this literature review is to compile the best available evidence for PBH and to evaluate the current consensus on methods to minimize risk for liver biopsy.

Methods

Research ethics board

Since this study did not directly involve patients or patients' clinical records, a Research Ethics Board approval was not required.

Terms and definitions

Image-guided biopsy was defined as obtaining tissue sample from a specific organ for diagnostic purposes using various needles under image guidance (5). Major bleeding complications were defined as a post-intervention event that were clinically relevant and required therapeutic intervention (e.g., blood transfusion, drainage, hospitalization). Minor bleeding complications were defined as post-intervention events that were not clinically relevant and did not require further medical attention (5).

Search strategy

Major medical databases were searched for studies summarizing risk factors for hemorrhage following percutaneous image-guided liver biopsy between January 1994 and April 2015. Databases included Medline, EMBASE, CINAHL and the Cochrane Library. We also searched for clinical guidelines and reviews in the UK National Health Service NICE and Canadian Agency for Drugs and Technology in Health (CADTH) databases. Searches were restricted to articles published in English, using the following subject headings and/or text words: hemorrhage, bleeding, complication, risk factor, liver biopsy, image-guided liver biopsy, and percutaneous. The reference lists from each article identified were cross-referenced and searched for additional eligible articles. All abstracts identified in the initial searches were reviewed for eligibility.

Main points

- Post-biopsy hemorrhage (PBH) occurs in less than 2% of patients undergoing liver biopsy (0%–10.9%).
- Several patient, procedure, and operator related factors could impact the rate of PBH.
- There is moderate level of evidence that utilization of image guidance has impact on the rate of PBH.
- There is weak evidence to support that age, coagulation status, patient comorbidity, needle size, and presence of a patent track correlate with PBH rate.

Selection of studies for inclusion

All abstracts were independently reviewed for relevance to the search criteria. Full-text article reviews were undertaken for any articles deemed to appropriately meet the essential inclusion criteria. Articles ultimately included in this review met the listed inclusion and exclusion criteria.

Inclusion and exclusion criteria

Eligible studies included clinical studies investigating complications associated with image-guided liver biopsy. Studies were limited to between Level Ib (randomized clinical trial) and Level III (retrospective observational study). Studies were eligible for inclusion, if they investigated or evaluated risk factors and/or complication rates for bleeding/hemorrhage in patients following image-guided percutaneous liver biopsy. No limitations were placed on the specific indication for biopsy, the nature of the biopsy (fine needle vs. tissue biopsy), the diagnosis, the patient age, concurrent conditions, diameter of biopsy needle or the method of biopsy. Studies were excluded if they met the following criteria: review studies, biopsy of other organs, blind liver biopsy or liver biopsy using a technique other than percutaneous techniques. Studies reporting bleeding complication rates without investigating potential risk factors were also excluded from the review.

Results

From an initial pool of 2910 of potentially eligible studies, 110 were selected for abstract review. Following exclusion of 42 of studies, 68 were reviewed as full-text articles, providing a total of 34 studies (3, 5, 9–40) for inclusion in this review (Fig.).

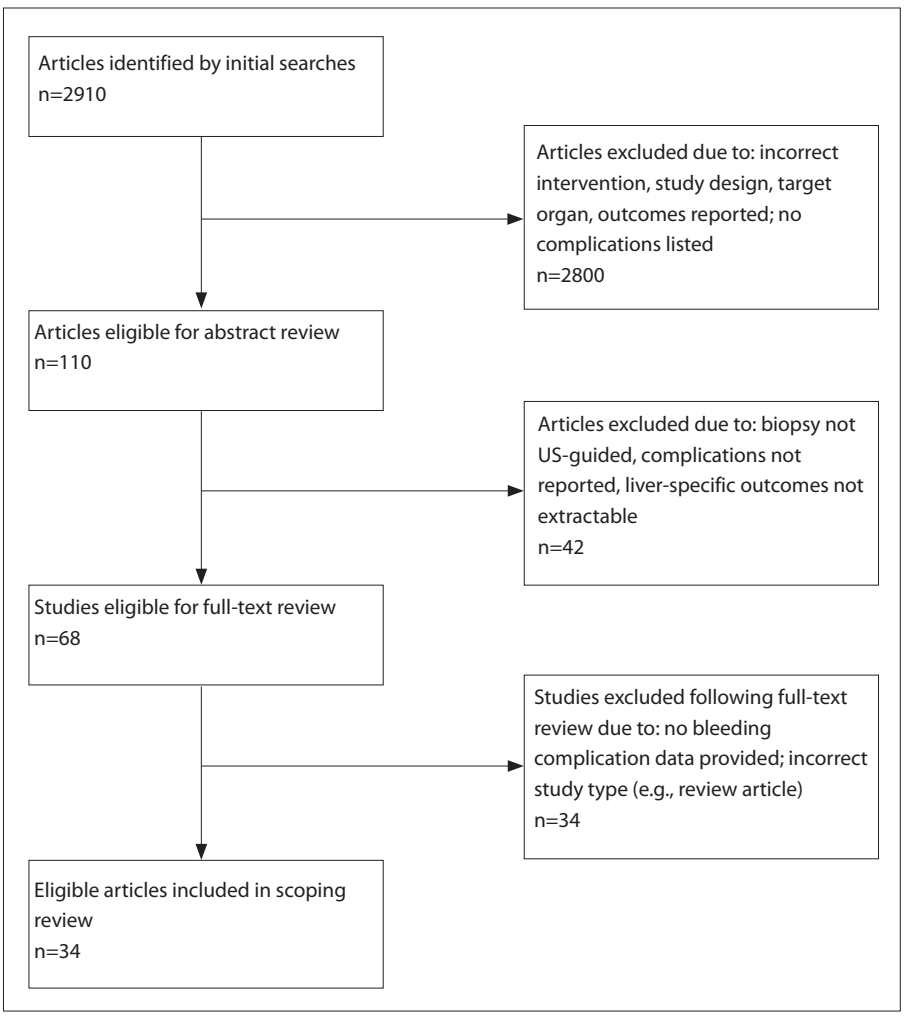

Figure. PRISMA flowchart summarizing study eligibility.

Table 1. Eligible study characteristics

Lead author	Pub date	Study type/LOE	Patient population (age range)	Number of patients	Number of biopsies	Key findings
Lindor	1996	Randomized, controlled trial, Level Ib	Adult (44.9–48.5 y)	836	836	Use of US-guidance associated with a lower rate of bleeding complications (2.2% vs. 1.1%)
Beddy	2007	Prospective, Level II	Adult (8–76 y)	500	500	Overall bleeding complication rate: 0.2%
Kim	2007	Prospective, Level II	Adult (16–83 y)	352	361	Presence of a "patent track" on post-biopsy US was highly indicative of bleeding complication ($P = 0.0008$)
Thanos	2005	Prospective, Level II	Adult (57±12 y)	767	767	18-gauge needles are safe and effective
Gunnesson	2002	Prospective, Level II	Adult (51.2±0.35 y)	708	1086	Hemothorax occurred in 0.1% of patients
Rossi	2001	Prospective, Level II	Adult (mean, 44.7 y; 18–85 y)	140	142	US-guidance recommended for percutaneous liver biopsy
Govender	2013	Retrospective, Level III	Pediatric (1 m to 21 y)	470	597	Major bleeding rate after biopsy: 1.3%
Short	2013	Retrospective, Level III	Pediatric (1 w to 22 y)	213	328	Younger age and lower preprocedural hematocrit predicted bleeding complications
Westheim	2013	Retrospective, Level III	Pediatric (1 m to 18 y)	214	311	Bleeding rates higher when operator was less experienced
Howlett	2012	Retrospective, Level III	Pediatric and adult	3473	3496	Rate of major bleeding complications: 0.11% (minor: 0.4%)
Matos	2012	Retrospective, Level III	Pediatric (1 w to 22 y)	213	328	Minor bleeding rate after biopsy: 5.5%
Mueller	2012	Retrospective, Level III	Adult (18–96 y)	1961	2229	Collected data on patient, operator, and procedure-related factors
Westheim	2012	Retrospective, Level III	Pediatric (5.8±5.2 y)	190	275	Focal lesions were associated with a significantly higher bleeding complication rate than other lesion categories
Potter	2011	Retrospective, Level III	Pediatric (8 d to 20 y)	249	294	Five patients (2%) required blood transfusions due to post-biopsy bleeding complications
Vijayaraghavan	2011	Retrospective, Level III	Adult (30–44 y)	n/s	776	Left-sided epigastric biopsy approach was associated with bleeding complications in 0.8% of cases
Atwell	2010	Retrospective, Level III	Pediatric and adult (15 d to 96 y)	3636	3636	Data collected on procedural (needle size, number of passes) and patient-related (INR, platelet count) factors
Seeff	2010	Retrospective, Level III	n/s	1385	2740	Low albumin, platelet count and INR associated with significantly greater bleeding rate
Sornsarkin	2010	Retrospective, Level III	Pediatric (6 m to 18 y)	67	120	Overall bleeding complication rate: 0.83%
West	2010	Retrospective, Level III	Adult (40–59 y)	61187	61187	Rate of major bleeding complication: 0.65%
Padia	2009	Retrospective, Level III	Adult (20–84 y)	350	539	Overall bleeding complication rate: 0.6%
Weigand	2009	Retrospective, Level III	Adult (47±15 y)	715	715	Major bleeding rate: 0.15%; minor bleeding rate: 0.3%

Table 1. Eligible study characteristics (cont'd)

Lead author	Pub date	Study type/LOE	Patient population (age range)	Number of patients	Number of biopsies	Key findings
Hatfield	2008	Retrospective, Level III	Adult (range not specified)	n/s	784	Compared coaxial biopsy technique with non-coaxial techniques with and without gelatin sponge: no significant differences in bleeding rate
Myers	2008	Retrospective, Level III	Adult (41–64 y)	3627	4275	Bleeding rate was associated with abnormal platelet counts and INR
Amaral	2006	Retrospective, Level III	Pediatric (7–348 d)	61	65	Major and minor bleeding rates were equivalent (4.6%)
van der Poorten	2006	Retrospective, Level III	Adult (18–88 y)	1398	1398	Collected data on patient, operator, and procedure-related factors
Azzam	2005	Retrospective, Level III	Pediatric (13–90 d)	63	66	Bleeding occurred in 4.5% of patients post-biopsy
Firpi	2005	Retrospective, Level III	n/s	n/s	3214	Hemothorax rate lower with US-guidance ($P = 0.1$)
Chevalier	2004	Retrospective, Level III	Adult (46±12 y)	600	600	Bleeding occurred in 0.16% of patients
Nobili	2003	Retrospective, Level III	Pediatric (2.5 m to 18 y)	140	144	Compared US-guided biopsy with blind biopsy and found no bleeding complications with US-guided (4.7% when blinded)
Terjung	2003	Retrospective, Level III	Pediatric and adult (12–88 y)	574	629	Collected data on various concurrent conditions and their effect on bleeding rate and complications
Reimann	2000	Retrospective, Level III	Pediatric and adult (6–81 y)	n/s	258	Major bleeding rate: 1.6%; minor bleeding rate: 0.4%
Scheimann	2000	Retrospective, Level III	Pediatric and adult (1 m to 39 y)	123	249	Compared needle diameter and found no significant difference in bleeding rates
Tham-panitchawong	1999	Retrospective, Level III	Pediatric and adult (15–85 y)	459	484	Lower platelet counts associated with significantly higher rate of post-biopsy bleeding ($P = 0.014$)
Gilmore	1995	Retrospective, Level III	Adult (60–69 y)	1890	1500	Higher INR (>1.5) and lower platelet counts associated with higher bleeding rates

Pub, publication; LOE, level of evidence (Introducing Levels of Evidence to The Journal, The Journal of Bone and Joint Surgery - jbjs.org, Volume 85A, Number 1, January 2003); US, ultrasonography; y, years; m, months; w, weeks; d, days; n/s, not specified; INR, international normalized ratio.

As image-guided biopsy is an established diagnostic method, there are very few randomized trials evaluating its effectiveness. Instead, there are a large number of retrospective analyses evaluating both the diagnostic accuracy and value of biopsy, plus a large number cataloguing the various risk factors associated with the procedure. Of 34 studies eligible for inclusion in this review, only one study (40) was a randomized controlled trial, while five were prospective, single-arm, uncontrolled studies (13, 17, 37–39). The remaining studies were all retrospective chart reviews, apart from two that were retrospective audits of healthcare systems (9, 15). A summary of the included studies is presented in Table 1. Ten studies evaluated a pediatric population while 24 studies evaluated an adult population. Bleeding complications were reported in 19 of 34 studies, ranging from 0% to 10.9%. Minor bleeding (i.e., requiring no clinical intervention) was reported in 11 of 34 studies and ranged from 0.3% to 10.9%. Major bleeding (i.e., requiring medical intervention) was reported in 14 of 34 studies and ranged from 0.1% to 4.6% (Table 2).

There was considerable heterogeneity in the outcomes reported in the eligible studies. We stratified the risk factors for PBH into one of three categories: risk factors related to i) the patient, ii) the procedure, or iii) the operator.

Patient-related risk factors include age, gender, status of coagulation factors and current coagulopathy status, inpatient versus outpatient status, concurrent disease (e.g., liver failure), and current medications (e.g., acetylsalicylic acid, low molecular weight heparin). Several patient-related risk factors were identified that increase the risk of a bleeding complication following liver biopsy.

Five studies (5, 25, 27, 30, 31) evaluated the impact of age on bleeding risk. Two of five studies demonstrated that a higher bleeding rate was associated with older patients. Specifically, patient age >50 years (31) and >70 years (5) were found to be associated with a

Table 2. Comparison of overall and bleeding complication rates in adult and pediatric patients

	All studies			Pediatric patients only (10 studies)			Adult patients only (24 studies)		
	No. of studies	Low (%)	High (%)	No. of studies	Low (%)	High (%)	No. of studies	Low (%)	High (%)
Any complication									
Overall	8	1.2	18	2	5	18	6	1.2	6.83
Minor	8	0	4.6	3	1	4.6	5	0.3	2.4
Major	7	2.4	25	3	4.6	25	4	2.4	22
Bleeding complication									
Overall	19	0	10.9	5	0	4.5	14	0.1	1.7
Major	14	0.1	4.6	3	1.1	4.6	11	0.1	4.5
Minor	11	0.3	10.9	4	4.6	10.9	7	0.3	1.0

significantly higher likelihood of post-biopsy bleeding (age >50 years, $P = 0.02$; age >70 years, $P = 0.04$). No significant change in hemoglobin levels pre- and post-biopsy were noted in these patient groups (25). In a pediatric population, younger age (1.8 months vs. 84 months) was found to be associated with a higher rate of bleeding complication ($P = 0.05$) (27).

The effect of gender on the rate of post-biopsy bleeding was evaluated in four studies (5, 25, 26, 30). No studies were able to identify a statistically significant difference in bleeding rate based on patient gender. Two studies (5, 26) observed slight trends towards increased bleeding rates in female patients, but these differences were not statistically significant.

Coagulation status as a risk factor for post-biopsy bleeding was evaluated in eight studies (5, 11, 15, 20, 26, 30, 31, 35). Several factors were evaluated in the eligible studies, including INR status, platelet count and overall coagulation status. An increased INR (>1.5) pre-biopsy was associated with a statistically significant increase in bleeding rate in four studies (11, 15, 20, 26). Four studies (11, 20, 26, 30) observed that decreased platelet counts were associated with a statistically significant higher rate of post-biopsy bleeding. There was considerable range in the platelet counts that were measured for each of these studies. Atwell et al. (11) noted a serum platelet count of 194×10^9/L in patients suffering a post-biopsy bleed versus 257×10^9/L in patients who did not ($P < 0.001$). Conversely, Thampanitchawong and Piratvisuth (30) noted a 25% bleed rate among patients with a platelet count below 70×10^9/L, compared to 4% in patients above this threshold ($P = 0.014$). Seeff et al. (26) found that a platelet count of $\leq$60 000 mm^3 was associated with a statistically significant increase in bleeding ($P < 0.0001$). Finally, Gilmore (15) noted that 2.9% of patients with a platelet count below 150×10^9/L experienced a postprocedure bleed, while only 1.6% with a platelet count greater than 150×10^9/L bled post-biopsy.

Coagulation parameters were measured in three studies (5, 30, 31). An incomplete coagulation criteria was associated with a higher bleed rate in one study (2/47 bleeds vs. 16/710, $P = 0.391$) (5), while van der Poorten et al. (31) found a 9.5% bleed rate in patients with abnormal coagulation. Thampanitchawong and Piratvisuth (30) evaluated prothrombin time (PTT) and found that a PTT of >3 s was associated with a 10.5% bleed rate. In the same study, they noted that a PTT >10 s was associated with a greater bleed rate (10.3%) than a PTT <10 s (3.8%), although this difference was not statistically significant ($P = 0.079$).

Albumin levels were evaluated in one study (26) and it was observed that a lower albumin level was associated with a significantly higher bleed rate (albumin level, 3.7 g/L vs. 3.9 g/L, $P = 0.02$). Bilirubin levels were evaluated by Gilmore et al. (15) who found that a raised level above "normal" was associated with a higher rate of post-biopsy bleeding (2.7% when above normal vs. 1.1% when below normal).

Two studies (11, 31) compared inpatient status versus outpatient status for patients undergoing liver biopsy. While van der Poorten et al. (31) found a higher rate of hemorrhage in inpatients who suffered bleeding complications than in outpatients (8/12 vs. 4/12, $P < 0.001$; 42.9% risk of hemorrhage), Scheimann et al. (25) noted no significant change in hemoglobin between inpatients and outpatients ($P = 0.69$).

The effect of concurrent conditions on post-biopsy bleeding rates was evaluated in six studies (3, 20, 27, 29, 30, 35). Of the six studies, only one (27) performed statistical analysis. It was observed that a lower hematocrit level (29.3 vs. 34.3, $P = 0.04$) and hypoxia caused by sedation during biopsy were associated with a significantly increased risk of bleeding (11.1% vs. 0.5%, P=0.001). The relative effects of concurrent conditions on the risk of bleeding post-biopsy is summarized in Table 3.

Two studies (5, 18) evaluated the relationship between procedure type and risk of bleeding. Mueller et al. (5) compared the cutting biopsy (CB), using a 1.2 mm needle, with both fine needle aspiration (FNAC, 0.7 mm needle) and the Menghini technique (ABM, 1.4 mm needle). They observed that, when compared to FNAC, CB was associated with a greater proportion of bleeding postprocedure (8/368, 2.7% vs. 0/585, 0%, $P < 0.001$). ABM was associated with a lower rate of bleeding when compared with CB (2/717, 0.3% vs. 5/279, 1.8%, $P = 0.026$). Hatfield et al. (18) compared coaxial techniques versus non-coaxial techniques, both with and without gelatin sponges. They found no statistically significant differences in bleeding rate for any of the comparisons.

Three studies (11, 25, 37) compared needle size and bleeding rates. Each found no statistically significant difference in bleeding rates related to needle gauge. Scheimann et al. (25) compared 16-gauge Jamshidi needles with 18-gauge Monopty, 15-gauge ASAP and 18-gauge ASAP needles. Using hematocrit as an outcome, they found no significant differences

Table 3. Post-biopsy bleeding rates associated with concurrent conditions and/or diagnoses

Post-biopsy bleeding rate (%)	Concurrent condition/diagnosis	Author
	Diagnosis	
50	Liver failure	Terjung
41.7	Liver failure	Westheim, 2012
34.4	Cirrhosis	Terjung
26.9	Cancer/malignancy	Terjung
25	Cirrhosis	Short
18.2	Cholestasis	Short
18.2	Metabolic disease	Short
12.5	Leukemia/lymphoma	Weigand
12.5	AIDS	Terjung
12.5	Ascites	Myers
9.7	Cancer/malignancy	Terjung
8.3	Mycobacteriosis	Terjung
1.6	Cancer/malignancy	Terjung
0.58	Liver disease	Weigand
0.45	Other	Weigand
	Prebiopsy testing	
34.3	Hematocrit	Short
11.1	General tests	Short
6.9	Anti-fibrinolytics	Terjung
0.22	Abnormal liver function tests	Weigand
	Coagulation	
26.4	Bilirubin >2 mg/dL	Terjung
18.1	Platelet count <100 g/L	Terjung
6.9	Prophylactic prebiopsy platelet submission	Terjung
5.8	Hereditary coagulopathies	Terjung
	Patient-related	
11.1	Hypoxia due to sedation	Short
9.7	Hemodialysis	Terjung
9.7	History of previous bleed	Terjung
	Pharmacological	
26.4	Corticosteroids	Terjung
13.9	Metamizole	Terjung
9.7	Beta-lactam antibiotics	Terjung
6.9	Cytostatic drugs	Terjung

($P > 0.05$ for all comparisons). Atwell et al. (11) compared various needles sizes in over 15 000 biopsies and found no significant difference in bleeding rate associated with needle gauge ($P = 0.88$). Thanos et al. (37) noted only 3 incidences of minor complications in 767 patients undergoing CT-guided liver biopsy with an 18-gauge needle. Only one of these complications was related to bleeding (0.13%).

Three studies (5, 11, 35) investigated the relationship between lesion type and bleeding complications. All studies compared parenchymal lesions with focal lesions; only one study noted a significant difference between the bleeding rates in patients with these lesion types. Westheim et al. (35) found that the rate of bleeding in focal lesions was significantly lower than that of other categories (focal: 25/275, 9.1% vs. other: 11/25, 44%, $P = 0.047$). Neither Mueller et al. (5) nor Atwell et al. (11) (focal: 10/1836, 0.5% vs. parenchymal: 7/1836, 0.4%) noted a significant difference between lesion type and bleeding rate.

Two studies (11, 31) evaluated the effect of multiple passes on bleeding complications, with inconclusive results. While Atwell et al. (11) found that fewer passes were associated with significantly fewer bleeding complications (2.4 vs. 3.0, $P < 0.001$), van der Poorten et al. (31) found no significant difference in the rate of major complications based on number of needle punctures ($P = 0.31$).

Four studies (36, 38–40) evaluated the overall impact of image-guidance during biopsy on bleeding complication rates. The use of ultrasonography (US) guidance was generally associated with a lower rate of bleeding complications. In the lone randomized, controlled trial eligible for this review, Lindor et al. (40) noted that the bleeding complication rate was cut by 50% after the introduction of US guidance (2.2% without US guidance vs. 1.1% with US guidance, $P = 0.08$). Another study found that the specific risk of hemothorax was decreased with US guidance ($P = 0.1$) (36). Kim et al. (39) investigated the predictive value of a so-called "patent track", detectable by post-biopsy US. The patent track refers to the linear colorflow signal that may be seen along the needle track immediately after withdrawal of the needle. The authors found that there was a statistically significant increase in the rate of post-biopsy bleeding in patients demonstrating the patent track on post-biopsy US ($P < 0.001$).

Table 4. Rate of bleeding complications as a function of operator experience (data from Westheim et al., 2013)

Period	Experience level of operator	Major bleed rate, n (%)	Minor bleed rate, n (%)	Results
Prior to study	≤10 biopsies	1 (2.2)	7 (15.2)	No statistically significant differences in bleeding rate
	>10 biopsies	2 (0.8)	27 (10.2)	
During study period	≤ 10 biopsies	0 (0)	0 (0)	No statistically significant differences in bleeding rate
	>10 biopsies	2 (0.9)	21 (9.7)	

Table 5. Clinical recommendations for the safe performance of image-guided liver biopsy

Recommendation	Author(s)	Strength of evidence	Comment
Always use image guidance	Lindor, Beddy, Gunnesson, Kim, Rossi, Firpi, Padia, Nobili	Moderate	Recommendation supported by Level Ib (RCT), II (prospective) and Level III (retrospective) evidence
Screen for pre-biopsy coagulopathy	Matos, Potter, Seeff, van der Poorten, Riemann, Thampanitchawong	Weak	Recommendation supported by Level III evidence (retrospective reviews only)
Be aware of potential risk factors, screen potential patients carefully	Westheim, West, Short, Terjung,	Weak	Recommendation supported by Level III evidence (retrospective reviews only)
Use 16- or 18-gauge needles	Matos, Vijayaraghavan, Chevalier, Thanos	Weak	Recommendation supported by Level III evidence (retrospective reviews only)
Minimize the period between INR assessment and biopsy	Howlett	Weak	Recommendation supported by only 1 Level III (retrospective) study
Schedule biopsy at least 10 days after last aspirin dose	Atwell	Weak	Recommendation supported by only 1 Level III (retrospective) study
In infants, mitigate risk with sedation with benzodiazepines	Azzam	Weak	Recommendation supported by only 1 Level III (retrospective) study
Consider transjugular biopsy in patients where the bleeding risk may outweigh the potential benefits	Terjung	Weak	Recommendation supported by only 1 Level III (retrospective) study

Two studies (11, 27) compared US versus computed tomography (CT) guidance in liver biopsy. Atwell et al. (11) found that the vast majority (95.7%) of biopsies were guided by US, with only 157 of 3636 liver biopsies guided by CT. Two bleeding complications occurred among the 157 CT-guided procedures (1.3%), a rate higher than that of the US-guided group, where 15 bleeding complications occurred (15/3479, 0.4%). Short et al. (27) found that US was chosen as the guidance imagery for a similarly high proportion of patients (>90%), although did not note a significant difference in the use of US-guidance in patients with (90.9%) or without (93.6%, P = 0.53) a bleeding complication.

Five studies (5, 15, 26, 31, 34) investigated the impact of operator experience on bleeding complications. The results of these comparisons are inconsistent, with only one study (5) illustrating a statistically significant difference in bleeding rate based on operator experience. Mueller et al. (5) found that experienced operators (those having performed greater than 150 liver biopsies) were more likely to have bleeding complications than less experienced operators (<150 biopsies) (bleed rate 0.7% for inexperienced vs. 2.0% for experienced, P = 0.01). Gilmore et al. (15) compared operators who had performed fewer than 20 biopsies with those who had performed >100 biopsies and found that, in contrast to Mueller, more experienced operators were less likely to be associated with bleeding complications (3.2% vs. 1.1%), although they did not perform any statistical analysis on these findings. Westheim et al. (34) compared bleeding rates in operators, using 10 biopsies as the threshold between experienced and inexperienced. While experienced operators had a generally higher rate of bleeding complications, there was no statistically significant difference when compared with less experienced operators (Table 4). Finally, van der Poorten et al. (31) and Seeff et al. (26) each found no significant differences between experienced and inexperienced operators but did not provide specific data. Furthermore, as outlined above, the definition of experienced versus inexperienced operators varied greatly between different studies, further adding to the heterogeneity of the studies.

There was a trend towards an increased rate of bleeding complications in centers where more biopsies were performed on a per-year basis. In the Mueller report (5), which reported that bleeding complications were more common in experienced clinicians, the large center studied performed an average of over 200 biopsies each year. In contrast, in centers where fewer than 100 biopsies are performed each year, there was either no significant difference between experienced and inexperienced operators (15, 26, 31), or inexperienced operators were associated with more bleeding complications (3.2% for inexperienced operators [<20 biopsies] vs. 1.1% for experienced operators [>100 biopsies]) (34).

Discussion

Adverse events following image-guided liver biopsy are not common but can pose substantial challenges for physicians and patients. While major bleeding risk is known

to increase in patients who are unable to cooperate (i.e., maintain specific position, respond to commands) (41), several other risk factors play important roles in the risk of bleeding complications following biopsy. In this review, we compiled the best available evidence to identify risk factors associated with hemorrhage with image-guided liver biopsy. The risk of bleeding complication was directly assessed in 19 articles, with 17 estimating the risk at less than 2%. This rate compares favorably to the rate of bleeding complications in transjugular liver biopsy, used most often in patients with ascites or potential coagulopathy, which has been estimated at 1%–3% (42, 43), and as low as 0.59% (44).

Risk factors were categorized as either patient-related, operator-related, or procedure-related. The preponderance of evidence is in the form of retrospective studies and the findings are somewhat heterogeneous; however, several risk factors were identified and should be considered by clinicians performing this procedure.

The current literature indicates several patient-related factors that contribute to the risk of bleeding complications, including needle size, use of cutting needles, and biopsy in highly vascular organs/lesions (i.e., renal and liver biopsies) (41). In our review, several patient-related factors were associated with bleeding following biopsy. While some factors such as gender showed no effect, others such as age or inpatient status were associated with bleeding risk. Several studies demonstrated that increasing age was associated with an increased risk of bleeding. There was also evidence to indicate that in a pediatric population, younger patients were generally at a higher risk of bleeding. Likewise, inpatient status was associated with a higher risk of biopsy-related bleeding than patients who underwent the procedure on an outpatient basis. Advanced age and inpatient status were associated with concurrent diagnoses such as hypertension or malignancy, as well as with an increased likelihood of prescription medication use, perhaps accounting for the higher rate of bleeding noted with these risk factors (Table 3). Patients presenting for biopsy with risk factors that may affect their ability to tolerate the procedure are more likely to experience bleeding complications than those with no such risk factors. This is supported by the evidence that indicates that coagulation profile is also a risk factor for biopsy-related bleeding. Our review found that an elevated INR (>1.5) was associated with an increased risk in bleeding, as was an incomplete coagulation profile and a decreased platelet count. The SIR and CIRSE guidelines currently classify biopsy procedures into low, medium and high risk for bleeding and recommend different preprocedure screening based on this risk stratification (45, 46). INR screening is recommended in all patients undergoing moderate or high-risk procedures and patients receiving warfarin or with suspected liver disease undergoing low-risk procedures. In all patients, PTT is only routinely required in patients receiving intravenous unfractionated heparin. Preprocedurally, platelet and hematocrit levels are only recommended in patients undergoing high-risk procedures (45). The evidence from our review suggests that clinicians should consider patients with elevated INR and/or decreased platelet counts to be at higher risk of biopsy-related bleeding and should take preprocedure precautions. Likewise, inpatients, those with concurrent diagnoses that may affect bleeding and/or coagulation, and those over 50 years of age (or infants) should be identified as potentially higher risk for bleeding and should be monitored accordingly.

Operator-related risk factors center largely on experience. The pooled findings are somewhat inconsistent, with some reports suggesting that experienced interventionists are associated with a higher risk of bleeding while others indicate that increased experience actually decreases the likelihood of bleeding. Biopsy, as with any physical procedure, is a learned skill and, as such, it would be expected that inexperienced physicians would be associated with more cases of adverse events and bleeding than experienced physicians. However, Mueller et al. (5) suggest that experienced physicians are often assigned the more difficult and/or potentially difficult cases, resulting in more bleeding complications due to the inherent obstacles presented by the patient or case, rather than the experience level of the operator. In a pediatric population especially, more experienced physicians are associated with greater rate of bleeding (34), although this is likely due to the difficulty associated with the procedure in an infant population, rather than the abilities of the operator.

Experienced physicians are likely to continue to be assigned challenging or potentially challenging cases. All clinicians, including the less experienced, should take as much care as possible when performing these procedures, mindful of the potential for biopsy-related adverse effects, taking whatever steps are available to minimize the inherent risk.

Several procedure-related risk factors were evaluated in the eligible studies. Previous studies have suggested that needle size and procedure type (cutting) are associated with higher risk of bleeding (41). Our findings support this observation, as we noted that, in a compilation of over 5000 biopsies, fewer needle passes was associated with a statistically significant decrease in bleeding rates. Similarly, while no statistical analysis was performed, cutting biopsy was associated with a greater percentage of bleeding complications when compared with fine needle aspiration (2.7% vs. 0%) and with the Menghini technique (1.8% vs. 0.3%). This is expected as cutting biopsies traverse more vascular solid tissue compared to fine needle aspiration of cystic fluid. Where our findings contradict those of previous studies is the effect of needle size on bleeding rate. Needle gauge was evaluated in a very limited number of studies as subset analyses. While logical, no significant difference in bleeding rate was noted with increased needle size. This counteracts previous studies that have indicated that larger needle gauge is associated with an increase in bleeding (41).

Lesion type was evaluated in over 6000 biopsies and, in the vast majority of these cases, was found not to be relevant to bleeding risk. Westheim et al. (35), in a relatively small study of 275 biopsies in a pediatric population, found that focal lesions were associated with a significantly lower rate of bleeding than other lesion types; however, bleeding complications in large adult populations were found not to differ based on lesion type (e.g., focal, parenchymal). Lesion size was evaluated in only one study of 2229 biopsies, with nearly identical rates of bleeding for all sizes of lesion. The combined evidence suggest that lesion characteristics play little role in the risk of bleeding following biopsy. Regarding procedure-related factors in general, the type of procedure employed appears to be the most important factor in determining the likelihood of bleeding complications and should be considered by clinicians in the preprocedure decision-making process.

Several recommendations were made by the various authors; these recommendations are summarized in Table 5. The most common recommendations center on proper prescreening of patients. Those with confirmed or suspected coagulopathy or comorbidities are the most at-risk for bleeding complications. A general recommendation was to use image-guidance for all biopsies, as it increases the accuracy and decreases the likelihood of complications. The use of 16- or 18-gauge needles was also recommended. The majority of these recommendations are supported by moderate-to-weak evidence. Retrospective reviews dominate the evidence available for this review, with only two prospective studies available for inclusion. The addition of prospective, observational studies to the literature would help to increase the strength of these recommendations and provide improved clinical guidance. With the increasing focus on healthcare costs in North America, there is a definite need to generate evidence through structured reports and quality assurance initiatives in order to support the efficacy and safety of interventional radiology procedures including biopsies (47).

Our study has some limitations. The vast majority of evidence detailing risk factors for post-biopsy bleeding, or complications in general, is retrospective and observational in nature. Only one eligible randomized controlled trial could be identified in our searches. We were only able to identify five prospective studies that evaluated patient safety and adverse effects of associated with liver biopsy. As a result, the vast majority of our evidence is from retrospective chart reviews. Although this type of evidence is of generally low methodological quality, the cohort nature of the studies provides the best available evidence outlining risk factors and adverse effects. As biopsy is a generally accepted method of diagnosis, it is not subject to randomized trials and adverse effects are generally captured as secondary outcomes in larger studies.

As with many systematic or scoping reviews, the heterogeneity of outcomes in the eligible studies is a limitation. Across the 34 eligible studies, no single risk factor was evaluated in more than 8 studies. Some risk factors were evaluated in only 2 of 34 studies. This lack of consistency through the studies limits the veracity with which conclusions can be drawn from the data. Similarly, studies reporting on a similar risk factor often defined that factor differently, adding to the heterogeneity of sample. "Experienced operator" was variably defined as a physician having completed anywhere from over 10 biopsies to over 100 biopsies (15). One study provided two separate definitions of "experienced operator" within the same study, depending on whether the operator's skill was evaluated prior to the study period or during the stud period (34). Similarly, platelet counts were identified as an important risk factor for consideration in five studies but each study reported varying ranges and units. Studies variably set thresholds for platelet counts at 70×10^9 platelets/L, 150×10^9 platelets/L and 200×10^9 platelets/L, with another study providing platelet counts as density (platelets/mm^3). Furthermore, the biopsies were not further categorized based on fine needle aspiration or tissue biopsy as most of the source studies did not specify this. This heterogeneity increases the difficulty in pooling data and compiling conclusions. Nonetheless, as with other heterogeneous outcomes, the available evidence provides sufficient evidence to support conclusions in a pragmatic and clinically-relevant sense and thus is of substantial value to clinicians.

In conclusion, this review found that image-guided liver biopsy is a safe and effective procedure, with bleeding complications occurring at a rate of between 0% and 25%, although the vast majority of studies reported rates for bleeding under 2%. Risk factors identified as potentially important when attempting to minimize the risk of bleeding during biopsy include patient age (either >50 years or <2 years), inpatient status, comorbidities or concurrent diagnosis, and coagulation status. Operator experience should be considered as a risk factor for bleeding although, paradoxically, the increased risk is associated with experienced clinicians being assigned to more challenging cases, a fact of the art of medicine that is inescapable.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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