Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review

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BACKGROUND: The literature was systematically reviewed to determine whether a prolonged prothrombin time or elevated international normalized ratio predicts bleeding during invasive diagnostic procedures.

STUDY DESIGN AND METHODS: MEDLINE and CENTRAL were searched through August 2004, with no language restriction, and reference lists were reviewed. For inclusion, articles must have reported on bleeding in more than five patients with abnormal test results undergoing diagnostic procedures.

RESULTS: One trial and 24 observational studies were included. In 2 studies of bronchoscopy, the bleeding rates were similar among those with normal and abnormal tests, with wide confidence intervals (CIs) around the risk differences. During central vein cannulation (3 studies), bleeding rates among those with abnormal tests was unlikely to exceed 2.3 percent. The largest of 3 studies of arteriography found equivalent bleeding rates in patients with and without abnormal tests (risk difference, 0%; 95% CI, –3% to 2%). In the 3 studies of liver biopsy with plugging, bleeding rates were 0, 4, and 5 percent with the upper bounds of the CI as high as 17 percent. In the largest study of transjugular biopsy, the bleeding rate was 1.5 percent (95% CI, 0.3%-4%) in patients with abnormal tests. The highest bleeding rate in the 3 studies of percutaneous liver biopsy was 5.3 percent (95% CI, 1%-13%), similar to the rate in patients with normal test results.

CONCLUSION: There is insufficient evidence to conclude that abnormal test results predict bleeding. Randomized controlled trials should be performed to provide stronger evidence for clinical decision making regarding preprocedure transfusion.

Each year more than 3 million units of fresh-frozen plasma (FFP) are transfused in the United States. Recent data demonstrate that annual FFP usage has been steadily rising and that the number of transfused FFP units, relative to red blood cells, is higher in the United States than in other countries with advanced medical care.[1] Much of the plasma that is administered in the United States is given for the purpose of "correcting" a perceived coagulopathy before performing an invasive diagnostic procedure. This practice appears to be common despite the fact that most consensus guidelines do not recommend FFP for this indication.[2-4] A recent 3-month audit of the use of FFP at the Massachusetts General Hospital demonstrated that 32 percent of all FFP units requested outside of the operating room were ordered "before a procedure with elevated INR [international normalized ratio]."[5] This practice exposes patients to blood products and is costly. Furthermore, it promotes the use of preprocedural laboratory testing, which also has costs and may unnecessarily delay procedures.

The supposition underlying these transfusions is that even a mildly elevated INR is associated with excessive

ABBREVIATIONS: INR = international normalized ratio; PT = prothrombin time.

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Supported by NHLBI Grant 5 U01 HL072268-02.

Received for publication January 11, 2005; revision received February 23, 2005, and accepted February 23, 2005.

doi: 10.1111/j.1537-2995.2005.00546.x

TRANSFUSION 2005;45:1413-1425.

bleeding in the setting of an invasive procedure and that an intervention is needed for safety. We suggest that the assumptions driving preprocedural use of FFP are that 1) elevation of the prothrombin time (PT) or INR will predict bleeding in the setting of a procedure, 2) preprocedure administration of FFP will correct the prolonged clotting time result, and 3) prophylactic transfusion results in fewer bleeding events.

A recent systematic review addressed the second and third of these assumptions by reviewing randomized controlled trials that tested the efficacy of FFP.[6] In that review, the authors reviewed trials with laboratory measurements as the outcomes, as well as trials having bleeding as the outcome. Our goal in this study was to systematically review the evidence for the first assumption. We aimed to determine whether abnormalities in the extrinsic clotting pathway, evident as a prolonged PT or elevated INR, predict excessive bleeding during invasive procedures.

MATERIALS AND METHODS

Literature search

We identified studies through August 2004 with MEDLINE (which included articles since 1966) as well as the Cochrane Library Controlled Trials Register.[7] We examined reference lists from retrieved articles and reference literature, queried experts in the field, reviewed articles from our files, and used the related articles feature of MEDLINE. The search strategy is detailed in Appendix 1. During the search, letters to the editor and editorials were excluded. The search was limited to studies involving humans, without an exclusion based on language of publication. The search terms included "blood coagulation tests," "INR," "prothrombin time," while excluding "heparin," "warfarin," "coumadin," "coumarin," and "acenocoumarol" and included terms for the procedures of interest. These were liver or kidney biopsy, nephrostomy tube placement, transhepatic biliary tube placement, epidural injection or lumbar puncture, central vein cannulation or implantation of a venous access device, angiography or venography or cardiac catheterization, thoracocentesis or paracentesis, or endoscopy.

Abstract review

An abstract review form was generated with which to review the identified abstracts. One reviewer excluded the abstract if there was not a measurement of PT or INR before the procedure, bleeding was not reported as an outcome, or the enrolled participants did not undergo 1 of 11 specified procedures. Additionally, if all included participants received an intervention to correct the coagulopathy before the procedure, the abstract was excluded.

Data abstraction

We retrieved the articles for the included abstracts and then used a more detailed inclusion screening process. We required that the study report outcomes for the subgroup of participants with a prolonged PT or INR and that at least five patients with abnormal test results were studied. We developed and pilot tested a content abstraction form and chose to use a previously validated quality assessment form that had been developed to be useful for various study designs.[8] We did not exclude studies based on the results of the quality assessment.

The content abstraction form included fields describing study design, years of data collection, location of study, patient inclusion and exclusion criteria, details about the intervention, laboratory measurements, description of outcomes, the number of participants having outcome events, and a statement of conclusions by the study authors. Where available, we abstracted data on patients with and without coagulopathies who were undergoing invasive procedures. It was anticipated that many of the studies would be case series enrolling only patients with abnormal test results, with no comparison group.

Article review process

One investigator reviewed each article (J.S.). The reviewer was not blinded to author or journal names because previous work has shown that blinding is unlikely to affect the results of the data abstraction.[9] Data from the content abstraction forms were used to populate evidence tables, which were reviewed for accuracy by a second investigator (W.D.).

Quantitative pooling and presentation of findings

We grouped the studies by diagnostic procedure and looked for qualitative heterogeneity between studies within groups. Because there was significant qualitative heterogeneity, we did not pool the results mathematically. In studies reporting a comparison group, we calculated the risk difference for bleeding outcomes among patients with abnormal coagulation test results relative to patients with normal results, along with the 95 percent confidence interval (CI) for the difference. Results for these studies were plotted, by procedure, on a forest plot. When reporting event rates, we calculated 95 percent CIs around the estimate assuming a binomial distribution.

RESULTS

We retrieved 682 abstracts. Of these, 75 passed the initial abstract screening; however, 50 were excluded upon review of the full article. Of these 50, eight were excluded for not having a measure of the relevant coagulation vari-

ables, 12 for not including a group with elevated INR or prolonged PT, 24 for not reporting the bleeding results separately for patients with abnormal test results, 3 for having fewer than five patients with abnormal coagulation test results, 1 for not reporting bleeding as an outcome, 1 in which all patients with abnormal test results received plasma or platelets (PLTs) before the procedure, and 1 not having a relevant procedure. Many articles were excluded for more than one reason, although we did not document all reasons for exclusion for each article.

Included studies

Only one of the included studies was a clinical trial—comparing transjugular liver biopsy to percutaneous liver biopsy with plugging.[10] The other studies were of two types. Either studies were case series in which patients having the procedure of interest were defined as the study population or they were case series in which the participants were enrolled on the basis of their having abnormal coagulation test results. In studies with the latter design, there was generally no comparison to patients with normal coagulation results. The definition of abnormal coagulation tests varied across studies, with only five of the studies with the INR.[11-15]

Two articles evaluated the safety of bronchoscopy;[16,17] 3 examined central vein cannulation;[11,18,19] 3 at femoral arteriography;[12,20,21] and 13 at liver biopsy of which 5 involved a transjugular approach and of which 2 used minilaparoscopy.[10,13,14,22-31] One studied paracentesis and thoracocentesis,[32] 2 renal biopsy,[15,33] and 1 a mix of invasive procedures.[34] Details of the study designs are given in Tables 1 and 2.

Study quality

The study designs were not strong. Of the 25 studies, only 1 was a clinical trial. All others were observational studies and only half of the studies had a comparison group of patients with normal coagulation test results. Inclusion and exclusion criteria for participants were often incompletely described. Generally, however, the included patients were appropriate for the studies and likely representative of this patient population. Surprisingly, in seven studies there was no report of the mean INR or PT (or range) of the included patients. In most studies, there was an effort to account for possible confounders in the study design or analysis, either by reporting results stratified by some patient characteristic (such as PLT count) or by excluding patients with potentially confounding comorbidities. In 7 of the studies, there was no report of the mean INR or PT (or range) of the included patients. There were rarely sample size calculations performed before the studies and rarely post hoc power calculations. The statistical analyses were minimal but generally appropriate with approximately half the studies stating the statistical test and providing p values and CIs. Attrition from the study was seldom commented upon although these were studies with short follow-up where losses are not generally expected.

Procedures

Bronchoscopy. Two large studies evaluated the safety of bronchoscopy with biopsy, in patients with and without abnormal coagulation test results.[16,17] The numbers of patients with abnormal tests in the two studies were small (fewer than 30 patients in each). The earlier of the two studies collected data retrospectively over 8 years (1983-1991),[16] whereas the more recent article collected data prospectively in the late 1990s.[17] In both studies, the incidence rates of procedural bleeding were similar in the group with normal and the group with abnormal preprocedure coagulation tests, with risk differences of –2 percent (95% CI, 14%-10%)[16] and –3 percent (95% CI, –17% to 11%)[17] with negative percentages favoring the group with abnormal test results. The wide CIs, however, suggest that this is weak evidence upon which to base recommendations regarding the safety of bronchoscopy in patients with abnormal coagulation tests.

Central vein cannulation. Three studies from the 1990s examined whether central vein cannulation can be safely performed in patients with abnormal coagulation tests.[11,18,19] All studies used 16- or 18-gauge needles. The largest study was by Fisher and Mutimer in 1999.[11] This group prospectively evaluated the outcomes of 580 patients with an INR greater than or equal to 1.5 who required central vein cannulation. Of these patients, 83 percent also had a PLT count of less than 150×10^9 per L. Only one patient had major bleeding after the procedure, for an event rate of 0.2 percent (95% CI, 0%-1%). This event was attributed to inadvertent arterial puncture. The other two studies corroborate these results.[18,19] Neither study had major bleeding in the combined 155 patients with abnormal preprocedure coagulation tests (upper bound of 97.5% CI, 2.3%). The authors of each report concluded that bleeding complications during central vein cannulation are rare and that experienced physicians can safely perform this procedure in patients with abnormal results of hemostasis tests. These conclusions appear to be supported by the evidence.

Femoral angiography. Three studies, two very small, have examined this procedure in patients with abnormal test results.[12,20,21] The largest study, from 1996, enrolled patients prospectively who were undergoing femoral angiography and who had coagulation measurements. Eighty-five patients of 1000 had a PT greater than 15 seconds, with the upper limit of normal being 13 seconds. The PT among patients in the study group ranged from 15 to 20.8 seconds. The authors defined

TABLE 1. Design of studies evaluating bleeding with invasive diagnostic procedures

First author, year	Procedure and years of data collection	Design	Patient inclusion/ exclusion criteria	Definition of abnormal test result	Number of abnormal test results	Additional patient data and details of procedure
Kozak, 1994[16]	Bronchoscopy, 1983-1991	Retro. series	Charts having data	PT > 11.5 sec or aPTT > 39 sec	28 patients	Wang or forceps biopsy
Zahreddine, 2003[17]	Bronchoscopy, 1998-1999	Prosp. series	Inclusion: >18 and <80 years; exclusion: planned interventional bronchoscopy	PT < 70%	14 patients	In whole group, 219 had bronchial biopsy and 93 had transbronchial biopsy
Foster, 1992[18]	Central vein cannulation, 1988	Retro. series	Inclusion: with liver allograft	PT < 40%	122 procedures	Many also thrombocytopenic; 16-gauge needle, internal jugular or subclavian
Doerfler, 1996[19]	Central vein cannulation, NR (1 years)	Retro. series	NR	PT > 1.2 times upper limit of normal	33 procedures	43/76 men; mean age 59 years, 7 patients on anticoagulants 18-gauge needle; 65% 1 attempt, 17% 4 or more attempts
Fisher, 1999[11]	Central vein cannulation, 1996-1997	Prosp. series	Inclusion: liver disease and coagulopathy; exclusion: cannulation during transplant	INR ≥ 1.5 and/or PLT count $<150 \times 10^9$/L	580 procedures with INR ≥ 1.5	18-gauge needle
Wilson, 1990[12]	Femoral arteriography, 1989	Prosp. and retro. series	NR	INR > 1.2	4 patients and 5 patients	Prospective—mean age 58 years, 4/5 were on warfarin
Darcy, 1996[20]	Femoral arteriography, NR	Prosp. series	Exclusion: catheter left in place	PT > 15 sec (normal range 10.7-13.0 sec)	85 patients	In whole study, 72% had 5 French catheter, 23% had 6-7 French, 5% had >7 French
MacDonald, 2003[21]	Femoral arteriography for cardiac catheterization, 1999-2001	Prosp. series	NR	High-risk group: PT = 1.5 times normal	10 patients	In 5, arterial closure device; in 5, manual compression; closure device: either 6 French Angio-seal or Perclose device
Ewe, 1981[22]	Laparoscopic liver biopsy, NR	Prosp. series	Exclusion: severe, obstructive jaundice	PT < 70% (or greater than 13.5 sec)	93 patients	133/200 men; mean age 50 years Menghini needle, diameter 1.8 mm; majority had 1 puncture; direct visualization with laparoscopy

TABLE 1. *Continued*

First author, year	Procedure and years of data collection	Design	Patient inclusion/ exclusion criteria	Definition of abnormal test result	Number of abnormal test results	Additional patient data and details of procedure
Denzer, 2001[13]	Laparoscopic liver biopsy, 1996-1999	Retro. series	Exclusion: cholestasis, bacterial peritonitis, intestinal obstruction	INR > 1.5	29 patients	25/50 men; age range 15-77 years Silverman or Menghini, direct visualization with laparoscopy; current coagulation or topical fibrin for persistent bleeding
Riley, 1984[23]	Liver biopsy, plugged, NR	Retro. series		PT > 3 sec above control (control = 13 sec)	20 patients	Tru-Cut, with plugging with Gelfoam
Tobin, 1989[24]	Liver biopsy, 1981-NR	Case series	Patients needing a histologic diagnosis	PT "above control"	100 patients	54/100 men, mean age 52 years; 16-gauge Tru-Cut, plugging of all tracks with gelatin sponge
McVay, 1990[25]	Liver biopsy, 1983-1987	Retro. series	Inclusion: >15 years old, inpatient, known Hb, chart available; exclusion: active bleeding, FFP	PT > 11.5 sec	77 patients	130/177 men, mean age 45 years; few with 22-gauge, most with Standard Klutskin or Tru-Cut
Caturelli, 1993[26]	Liver biopsy, 1988-1992	Retro. series	Inclusion: consecutive patients undergoing liver biopsy with PLT count $<50 \times 10^9$/L and/or PT < 50%	NR	a) 30 patients prolonged PT; b) 19 patients prolonged PT and low PLT count	Mean 1.7 punctures per patient "fine needle"—20-gauge or less, ultrasound guidance
Sawyerr, 1993[10]	Liver biopsy (transjugular or plugged), NR	Trial	Exclusion: gross ascites or requiring targeted biopsy	PT > 3 sec above control	a) 44 patients for transjugular; b) 56 patients for plugged percutaneous	a) 31/44 men, mean age 52 years, up to 3 punctures; b) 28/56 men, mean age 46 years, up to 2 punctures; a) 16-gauge modified Ross, plugging if capsular puncture; (b) 18-gauge Biopty-Cut, gelatin plugging, CT before procedure
Kamphuisen, 2002[27]	Liver biopsy, plugged, 1995-2000	NR	Inclusion: contra-indication for routine biopsy; exclusion: recent prothrombin complex or FFP	PT > 14 sec	27 patients (includes 5 patients with normal PT and thrombocytopenia)	19/36 men, mean age 60 years; 18-gauge True-cut, plugged with polyvinyl formaldehyde foam, ultrasound-guided
Steadman, 1988[28]	Transjugular liver biopsy, 1983-1987	Retro. series	Inclusion: ineligible for percutaneous biopsy; exclusion: cholangitis, hydatid cyst, mental/ cardiorespiratory status unlikely to tolerate procedure	PT above normal (normal range 14-16 sec)	67 patients	43/67 men, mean age 46 years, 17 percent with ascites; 16-gauge modified Ross Trans-septal; up to 10 punctures permitted

TABLE 1. *Continued*

First author, year	Procedure and years of data collection	Design	Patient inclusion/ exclusion criteria	Definition of abnormal test result	Number of abnormal test results	Additional patient data and details of procedure
Papatheodoridis, 1999[29]	Transjugular liver biopsy, 1995-1997	Retro. series		PT > 5 sec prolonged *or* PLT count $<50 \times 10^9$/L *or* gross ascites	112 patients with PT > 5 sec prolonged	89/145 men, mean age 45 years, 60/145 with ascites; Cooks-type or Quick-core Tru-cut
Choo, 2000[30]	Transjugular liver biopsy, 4 years	Retro. series	Inclusion: contra-indication for percutaneous biopsy	PT > 15 sec and PLT count $<60 \times 10^9$/L	18 patients	9/18 men, mean age 50 years; mean 2.4 punctures, 11- to 16-gauge modified Ross Trans-septal; 8- to 18-gauge Quick-Core
Bruzzi, 2002[14]	Transjugular liver biopsy, years NR	Retro. series		INR > 1.2	31 patients	33/50 men, mean age 52 years; 18-gauge Quick Core needle; mean 2.2 punctures
Smith, 2003[31]	Transjugular liver biopsy, 1995-2002	Retro. series		PT > 14 sec despite having received plasma	203 patients	207/371 men, mean age 48 years; 13 received plasma during procedure 18-gauge Quick Core
McVay, 1991[32]	Paracentesis or thoracocentesis, 1986-1989	Retro. series	Inclusion: ≥16 years, inpatient, blind procedure; exclusion: active bleeding	Multiple of midnormal PT (PT 1.5× is INR of 2.2, PT 2.0× is INR of 3.8)	a) 37 patients with PT 1.5-2.0× normal; b) 5 with PT > 2.0× normal	a) 34 para- and 3 thora-cocenteses; b) 5 paracenteses. Variable needles, some use of ultrasonography
Davis, 1995[33]	Renal biopsy, 1993-1994	Prosp. series	Exclusion: received FFP, hypertensive	PT > 13.6 sec	9 patients	98/120 on aspirin, 16-gauge Temno, with ultrasound guidance
Thompson, 2004[15]	Transjugular renal biopsy, 2000-2002	Retro. series	Inclusion: contra-indication to percutaneous biopsy	Elevated INR	10 patients	8/10 men, mean age 48 years, 4 on anticoagulant; 18- to 19-gauge Quick-core, mean 4.3 punctures per patients, coil embolization at discretion of operator
Friedman, 1989[34]	Mixed, years NR	Prosp. series	PT > 15 sec, not in shock	PT > 15 sec	30 patients, 51 procedures	33/39 men, mean age 51 years; 43 paracenteses, 3 lumbar punctures, 3 thoracocenteses, 2 central vein cannulations

Abbreviations: CT = computerized tomography; aPTT = activated partial thromboplastin time; NR = not reported; INR = international normalized ratio; Retro. = retrospective; Prosp. = prospective.

TABLE 2. Outcomes*

First author, year, procedure	Degree of test abnormality	PLT count in patients with abnormal test	Definition of major bleeding	Patients with abnormal test results with major bleeding	Patients with normal test results with major bleeding*
Kozak, 1994,[16] bronchoscopy	NR	NR	"Significant" > 100 mL; "moderate" 20-100 mL; "minimal" < 20 mL	3/28 (11%) (bleeding grade was not specified in patients with abnormal results)	28/218 (13%)
Zahreddine, 2003,[17] bronchoscopy	PT from 49% to 69%	NR	Bleeding volume > 50 mL	1/14 (7%)	43/412 (10%)
Foster, 1992,[18] catheterization	Mean PT 29% (range 10%-39%)	NR	Required catheter removal, hemothorax, mediastinal hematoma	0/122 attempts	0/57 attempts
Doerfler, 1996,[19] catheterization	Approx. 16 with PT 1.2-1.5× normal; 17 with PT > 1.5× normal	Mean 78×10^9/L in 12 procedures and $>100 \times 10^9$/L in 21 procedures	Intrathoracic bleeding seen on X-ray or unexplained decrease in Hct	0/33	NR
Fisher, 1999,[11] catheterization	NR	483/580 procedures with PLT count of $<150 \times 10^9$/L	Not described	1/580 procedures (arterial puncture, died of multisystem organ failure) (0.2%)	NR
Wilson, 1990,[12] angiography	NR	Prospective—normal PLT counts	Signs of hemorrhage or need for intervention	0/4 in retrospective; 0/5 in prospective	0/105 in retrospective; 0/195 in prospective
Darcy, 1996,[20] angiography	PT range 15-20.8 sec	NR	Groin hematoma > 4 cm	1/85 (1.2%)	15/915 (1.6%)
MacDonald, 2003,[21] angiography	All = 1.5× normal	Most $< 80 \times 10^9$/L	Hematoma > 3 cm, pseudoaneurysm, arteriovenous fistula, femoral artery occlusion	1/10 (in manual compression group)	NR
Ewe, 1981,[22] liver biopsy	PT range 10%-100%	NR	Directly visualized liver bleeding time, heavy is >12 min	4/93 (4.3%)	4/85 (4.7%)
Denzer, 2001,[13] liver biopsy	INR > 1.5	9 with $<50 \times 10^9$/L	Not specified	0/29	1/50 required topical coagulants
Riley, 1984,[23] liver biopsy	Mean PT 20 sec (range 16-30 sec)	Mean 58×10^9/L (range 20×10^9-78×10^9/L)	Intraperitoneal bleeding	1/20 (5%)	NR
Tobin, 1989,[24] liver biopsy	PT 6 sec above control (range 4-12 sec above)	55×10^9/L (range 20×10^9-75×10^9/L)	Decrease in Hct	1/100 (1%)	NR
McVay, 1990,[25] liver biopsy	65 with PT 11.6-13.5 sec; 11 with PT 13.6-15.7 sec	NR	Hb decrease of 2 g/dL	4/65 with mild coagulopathy; 0/11 with moderate coagulopathy (together 5.3%)	4/100 (4%)

TABLE 2. *Continued*

First author, year, procedure	Degree of test abnormality	PLT count in patients with abnormal test	Definition of major bleeding	Patients with abnormal test results with major bleeding	Patients with normal test results with major bleeding*
Caturelli, 1993,[26] liver biopsy	a) 44.3% of normal; b) 42.6% of normal	a) Normal; b) mean 39×10^9/L	Change in vital signs or hematologic variables or blood seen on ultrasound of abdomen	a) 0/30; b) 0/19	NR
Sawyerr, 1993,[10] liver biopsy	a) INR 1.8 ± 0.6; b) INR 1.7 ± 0.7	a) $111 \times 10^9 \pm 95 \times 10^9$/L; b) $114 \times 10^9 \pm 73 \times 10^9$/L	Requiring transfusion	a) 0/44; b) 2/56 (together 2%)	NR
Kamphuisen, 2002,[27] liver biopsy	PT 16.3 sec in 27 patients (range 11.4-20.3 sec)	Mean 53×10^9/L (range 19×10^9-153×10^9/L)	Acute bleeding requiring transfusion	0/27	0/9 patients with ascites and normal coagulation status
Steadman, 1988,[28] liver biopsy	Mean PT 23 sec (range 18-32 sec)	NR	Intraperitoneal bleeding	0/67	NR
Papatheodoridis, 1999,[29] liver biopsy	PT 23 ± 9 sec in whole group	$104 \times 10^9 \pm 99 \times 10^9$/L in whole group	Requiring transfusion	0/112	0/45 in patients with thrombocytopenia or gross ascites
Choo, 2000,[30] liver biopsy	All > 15 sec	All $< 60 \times 10^9$	Hemoperitoneum, puncture site hematoma	0/18	NR
Bruzzi, 2002,[14] liver biopsy	Mean INR 1.6 in 31 patients	Mean 66×10^9 in 50 patients	Undefined	0/31	0/19 in patients with thrombocytopenia or gross ascites
Smith, 2003,[31] liver biopsy	PT 14.1-15.0 sec in 81; PT > 15.1 sec in 122	NR	Intraperitoneal hemorrhage detected clinically and on CT	3/203 patients (1.5%)	0/168 patients
McVay, 1991,[32] mixed	NR	NR	Hb decrease of 2 g/dL after procedure	1/37 (paracenteses); 0/5 (together 2.4%)	10/352 paracenteses; 8/204 thoracocenteses (together 3.2%)
Davis, 1995,[33] renal biopsy	PT 13.9-14.7 sec	NR	Hct decrease of 6%	1/9 (11%)	33/110 (30%)
Thompson, 2004,[15] renal biopsy	INR 1.73 ± 0.35	Median 240×10^9/L	Clinical sequelae, transfusion, need for more embolization, surgery	2/10 (20%)	0/15
Friedman, 1989,[34] mixed	Mean PT 18 sec (range 15-29 sec)	43% with 50×10^9-100×10^9; 5% with $<50 \times 10^9$/L	Decrease in Hct	0/51 procedures	NR

* Patients may have thrombocytopenia with normal PT and INR.
Abbreviations: CT = computerized tomography; NR = not reported.

major bleeding as a groin hematoma greater than 4 cm. With this definition, major bleeding occurred in only 1.2 percent of the patients with abnormal preprocedure coagulation tests and 1.6 percent of the patients with normal clotting test results, for a risk difference of 0 percent (95% CI, –3% to 2%). The authors concluded that preprocedural testing of PT and activated partial thromboplastin time in asymptomatic patients without an overt bleeding history is unwarranted, although they limited this recommendation to patients expected to have a PT of less than 18 seconds. One smaller study had only 4 patients with abnormal clotting tests in their retrospective data and 5 in their prospective data.[12] These authors saw no signs of hemorrhage in these patients, nor in any of the 200 enrolled patients with normal tests, for a risk difference of 0 percent (95% CI, –14% to 14%). The other study prospectively evaluated 10 patients with end-stage liver disease having cardiac catheterization with an INR of greater than 1.5. In 5 patients, an arterial closure device was used, and the other 5 received manual compression of the artery. One patient developed a hematoma (in the manual compression group).

Liver biopsy. Two studies involved liver biopsies performed with a laparoscope through which bleeding from the liver could be directly visualized. The larger study was the earliest of all we reviewed (1981);[22] these authors measured the time that the liver biopsy site bled among 93 patients with a PT greater than 13.5 seconds. Four patients (4.3%) bled for longer than 12 minutes after biopsy, a similar proportion (4.7%) as bled in the group of patients with normal preprocedure PT results. Moreover, the authors could not demonstrate any correlation between preprocedure PT or preprocedure PLT count and the length of time the liver capsule was observed to bleed after biopsy. The other study with laparoscopy reported no prolonged bleeding among 29 patients with elevated clotting times, although bleeding was not clearly defined.[13]

Three additional liver biopsy studies investigated plugging the biopsy site of "high-risk" patients with foam or gelatin, intrahepatically.[10,23,27] One other study of this technique by Smith and colleagues[35] was excluded because it was not clear which patients had an isolated elevation of INR and which had associated thrombocytopenia. The trial by Sawyerr and associates[10] was the only trial that we identified. The authors of the trial randomized patients considered to be at high risk of bleeding to percutaneous biopsy with plugging or to transjugular biopsy. They found that 2 of the 56 patients who underwent plugging needed transfusion (4%; 95% CI, 0.4%-12%); a similar proportion to the 0 of 44 in the transjugular biopsy arm (0%; 97.5% CI, 0%-8%).[10] Another plugging study reported a 1 in 20 (5%; 97.5% CI, 0%-17%) incidence of intraperitoneal bleeding,[23] and the third reported that none of 27 patients (0%; 97.5% CI, 0%-13%) needed transfusion.[27] All concluded that this plugged approach is a safe approach for patients with abnormal coagulation tests in whom a percutaneous biopsy might ordinarily be considered too risky; however, we note that these CIs are wide.

Five studies evaluated transjugular liver biopsy,[14,28-31] plus the arm randomized by Sawyerr and coworkers.[10] There were no bleeding complications in any of the patients with elevated clotting tests except in the largest study by Smith and colleagues.[31] In that study, 3 of 203 patients (1.5%; 95% CI, 0.3%-4%) with abnormal coagulation test results had intraperitoneal hemorrhage detected clinically and with computerized tomography. These patients all had a PT of greater than 13 seconds despite having received plasma. There were no bleeding complications in the 168 patients with normal tests in that study. Finally, three other studies evaluated percutaneous liver biopsy.[24-26] The highest incidence of bleeding was 5.3 percent (95% CI, 1%-13%), in the study by McVay and Toy.[25] They defined bleeding as a fall in hemoglobin (Hb) level of 2 g per dL. This rate was not different from the 4 percent (95% CI, 1%-10%) hemorrhage rate in their patients whose coagulation test results were in the normal range. All three studies concluded that fine-gauge needles and possibly ultrasound guidance make this procedure safer than previously thought in patients with preprocedure elevated clotting tests.

Kidney biopsy. Only two studies evaluated kidney biopsy and in very few patients. One study evaluated the percutaneous approach,[33] and the other a transjugular approach.[15] In the percutaneous study, the complication rates were high with one of nine (11%) patients with abnormal clotting tests experiencing a hematocrit (Hct) decrease of 6 percent, although the rate was 30 percent among patients with normal test results, most of whom were taking aspirin.[33] Two of 10 patients in the transjugular study had clinical sequelae of bleeding.[15]

Other procedures. Two studies evaluated a mix of paracenteses, thoracocenteses, lumbar punctures, and central vein cannulations.[32,34] Friedman and Sussman[34] found no decrease in Hct in the 51 procedures they evaluated. McVay and Toy[25] found a Hb decrease of more than 2 g per dL in 2.4 percent (95% CI, 0%-12%) of patients with abnormal coagulation tests and in 3.2 percent (95% CI, 2%-5%) of those with normal test results.[32]

Risk differences

Fourteen of the studies reported on a comparison group of patients with normal test results. In Fig. 1 we show the absolute difference in the proportion of patients with major bleeding in the group with and without abnormalities of preprocedure coagulation tests. For most procedures, the differences were negligible. The CIs for the differences in the many of the studies are wide, however, as a result of the small numbers of patients studied.

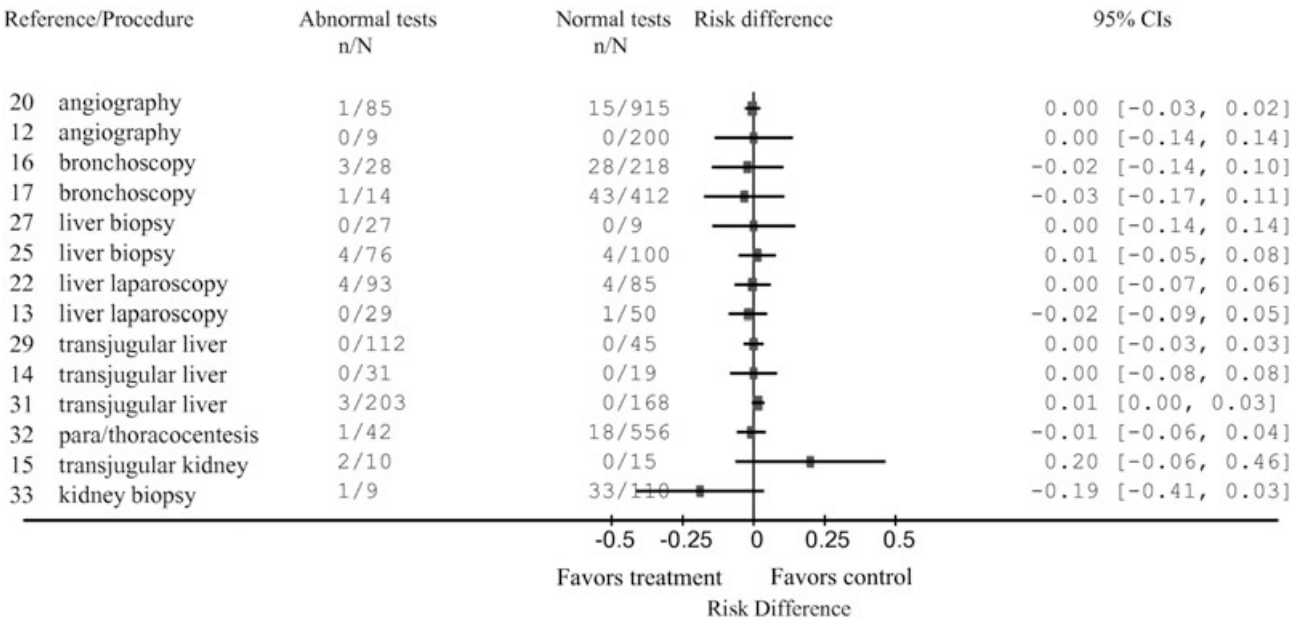

Fig. 1. Risk differences (and 95 percent CIs) between patients with abnormal and normal coagulation test results.

DISCUSSION

Our goal was to determine whether abnormalities of the preprocedure PT or INR were predictive of excessive bleeding during an invasive procedure. The 25 studies that we reviewed support the conclusion that an elevated INR is not predictive of periprocedural bleeding. We cannot conclude this definitively, however, because of the mixed quality of this evidence and the wide CIs surrounding the event rates and the risk differences. The majority of the studies were case series, most being retrospective reviews of patients having undergone the procedure of interest without a comparison group. Although many of the studies stated that consecutive patients were enrolled, there is little documentation of this in the studies. Furthermore, seven of the studies did not report the degree of test abnormality in their enrolled patients, so the results from these studies cannot easily be applied.

What can we learn from this literature? The evidence regarding the safety of central vein cannulation is fairly clear—an elevated INR is not predictive of bleeding from this procedure. The event rates among patients with normal and abnormal coagulation tests were so low that the difference in rates between groups is unlikely to be clinically important. The largest of the three studies demonstrating this was a moderately high-quality prospective study;[11] however, it did not report the degree of abnormality in the test results among their enrolled patients (INR was at least 1.5 for study inclusion). Therefore, the conclusion that this procedure is safe *cannot* be interpreted to mean that the procedure is safe in *all* patients regardless of the degree of abnormality. The evidence regarding bronchoscopy is weakly supportive of its safety in patients with an elevated INR, but does not allow definitive conclusions because fewer than 45 patients with abnormal clotting test results were studied. Femoral arteriography is likely not to be complicated with major bleeding in patients with moderately elevated PTs although this too is based on only one large prospective study, with support from two very small additional studies.

The studies of liver biopsy are a challenge to assimilate owing to the variety of techniques used. Studies of liver biopsy with plugging suggest that this is probably a safe procedure, with the strongest evidence coming from the randomized trial of this procedure. The other two studies had no comparison groups; the rates of bleeding were low, but the upper bounds of the CIs exceeded 10 percent in both studies. The data supporting the safety of transjugular liver biopsy are fairly strong with four of five studies having no bleeding events and the fifth study having bleeding in just 1.5 percent of those with abnormal test results.[31] Notably, however, these were all retrospective case series, although the study by Smith and colleagues[31] was fairly large. In the three studies of percutaneous liver biopsy, bleeding rates were higher than in studies with the transjugular approach, although abnormal coagulation test results did not definitively raise the risk of bleeding. Only one study had a CI about the risk difference that was narrow enough to provide evidence of the safety of this procedure in patients with abnormal test results.[25] There are too little data to draw conclusions about the safety (or lack therof) of kidney biopsy in patients with an elevated INR and too little data about the other procedures.

What future studies would contribute most to this literature? One cannot ethically devise a trial in which one randomizes patients to elevate their INR (such as with warfarin) or to maintain normal INRs and undergo an invasive procedure. This leaves well-designed observational trials, ideally with patients enrolled prospectively, with clear inclusion and exclusion criteria, and good documentation of the enrollment scheme to allow generalizability. It is also feasible to perform trials in which one randomly assigns patients either to receive therapy intended to correct an elevated INR or to receive no therapy and then performs invasive procedures as is required for their care. This could introduce a confounder because it would require the use of FFP or factor concentrates to lower the INR, and these may have hemostatic effects outside of what is measured by the INR. This, however, is the most clinically relevant study design, because this is the choice with which clinicians are faced.

Our study has some possible limitations. We may have missed some studies in our systematic search even though we tried to be comprehensive and used multiple sources, although EMBASE, the Excerpta Medica database, was not searched. Another limitation is a bias that we may have introduced by our study inclusion procedure. We included some studies which did not report separately the bleeding rates for patients with an elevated INR if no patient in the entire study had a bleeding event. In such studies, we had denominators for both groups and we also had numerators because both groups had zero events. We could not include studies in which bleeding occurred, however, but where the authors failed to report separately on the bleeding rates among patients with and without abnormal test results. In those studies, we could not know to which group to assign the bleeding events. Therefore, our collection of included studies is enriched with studies that had no bleeding events in either arm (with or without abnormal test results). The quality of the included studies was variable. Studies that did not report the mean INR or PT of the included patients are particularly hard to meaningfully interpret. Seven of the included studies fell into this category and information from these studies must be used cautiously.[11-13,16,21,30,32]

In conclusion, a systematic review of the published literature provides little evidence that preprocedure elevation of the INR or PT predicts an increased risk of bleeding at the time of an invasive diagnostic procedure. In particular, central vein cannulation and femoral arteriography are expected to be as safe in patients with an elevated INR as in patients with normal preprocedure test results, although the degree of INR elevation to which this applies is unclear. Transjugular liver biopsy may also be safe in patients with an elevated INR, and possibly also plugged liver biopsy, although there is much uncertainty surrounding the estimates of bleeding rates. Elevated coagulation test results also appear not to predict an increased risk of bleeding after percutaneous liver biopsy although the limited literature suggests that bleeding complications may be more frequent than with transjugular liver biopsy. Elevated clotting tests seem not to predict increased bleeding during bronchoscopy, although this conclusion is based on very limited data. Too few data exist to draw conclusions about paracentesis, thoracocentesis, lumbar puncture, or kidney biopsy. Prospective, randomized controlled trials can and should be performed to provide stronger evidence for clinical decision making. The Transfusion Medicine/Hemostasis Network is preparing a randomized trial testing use of FFP in patients with a prolonged PT referred for liver biopsy. Until such trials are reported, clinicians should not assume that mild to moderate prolongation of the INR or PT predicts a higher risk of bleeding or represents an indication for preprocedure transfusion of FFP or clotting factor concentrates.

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APPENDIX 1

Search strategy

- We searched allowing any study design (controlled trial, prospective or retrospective cohort study, case-control study, case series if more than five patients and consecutively enrolled). The study must have had a measurement of INR or PT, before the procedure. Bleeding must have been reported as an outcome.
- There was no age restriction.
- The procedure must have been one of the following: liver or kidney biopsy, nephrostomy tube placement, transhepatic biliary tube placement, epidural injection or lumbar puncture, central vein cannulation or implantation of a venous access device, angiography or venography or cardiac catheterization, thoracocentesis or paracentesis, or endoscopy.
- The initial search was in MEDLINE using PUBMED with the search terms as described below. This yielded 592 abstracts for review. The search of CENTRAL identified 230 titles. Title review identified two relevant clinical trials, both of which had already been identified in the search of MEDLINE.
- For each abstract identified as appropriate for inclusion, we performed a "related articles" search in MEDLINE and reviewed the first 20 abstracts appearing in the search. From this we identified 18 abstracts for closer review.
- We searched our personal files to identify additional articles appropriate for inclusion (reviewed six abstracts) and searched the bibliography of each included article to identify additional abstracts to review (four abstracts).
- We also reviewed the reference lists of key review articles to identify an additional 62 abstracts to review.

- Of the 682 abstracts reviewed, we retrieved 75 articles for closer review. Of these, 25 articles met all inclusion criteria and are included in this systematic review.

The specific search terms were as follows:

- In CENTRAL:

(((blood next coagulation next tests) or inr or (prothrombin next time)) and (not (heparin or warfarin or coumadin or coumarin or acenocoumarol)) and bleeding)

- In MEDLINE:

(blood coagulation tests OR INR OR prothrombin time) NOT (heparin OR warfarin OR coumadin OR coumarin OR acenocoumarol) AND (catheterization, central venous/*adverse effects OR cannulation/*adverse effects OR jugular vein) NOT letter NOT editorial. Limit: Human

(blood coagulation tests OR INR OR prothrombin time) NOT (heparin OR warfarin OR coumadin OR coumarin OR acenocoumarol) AND biopsy AND bleeding AND (liver OR hepat* OR transjugular OR transhepatic OR biliary) NOT letter NOT editorial. Limit: Human

(blood coagulation tests OR INR OR prothrombin time) NOT (heparin OR warfarin OR coumadin OR coumarin OR acenocoumarol) AND (thoracocentesis OR paracentesis) NOT letter NOT editorial. Limit: Human

(blood coagulation tests OR INR OR prothrombin time) NOT (heparin OR warfarin OR coumadin OR coumarin OR acenocoumarol) AND (endoscopy OR bronchoscopy OR transthoracic) NOT letter NOT editorial. Limit: Human

(blood coagulation tests OR INR OR prothrombin time) NOT (heparin OR warfarin OR coumadin OR coumarin OR acenocoumarol) AND (colonoscopy) NOT letter NOT editorial Field: All Fields. Limits: Human

(blood coagulation tests OR INR OR prothrombin time) NOT (heparin OR warfarin OR coumadin OR coumarin OR acenocoumarol) AND ((renal OR kidney) AND (biopsy OR nephrostomy)) NOT letter NOT editorial. Limit: Human

(blood coagulation tests OR INR OR prothrombin time) NOT (heparin OR warfarin OR coumadin OR coumarin OR acenocoumarol) AND (epidural OR lumbar puncture) NOT letter NOT editorial. Limit: Human

(blood coagulation tests OR INR OR prothrombin time) NOT (heparin OR warfarin OR coumadin OR coumarin OR acenocoumarol) AND (angiogra* OR venograph* OR cardiac catheterization) NOT letter NOT editorial. Limit: Human