



# The use of blood components prior to bedside procedures

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**Abstract:** A transition from liberal use of transfusions prior to invasive procedures to a thoughtful, restrictive approach to transfusion is underway. This shift is being driven by the publication of very large observational studies showing a very low incidence of bleeding complication from most common procedures (even in the presence of severe thrombocytopenia and abnormal tests of coagulation) in conjunction with an evidence-based 2019 guideline from the Society for Interventional Radiology recommending restrictive use of pre-procedure transfusion. Many common invasive procedures have a major bleeding risk well less than 1% with image-guided techniques. This is excellent for patient care, however prospective randomized trials of transfusion vs. no transfusion before invasive procedures are unattainable, given the studies would require an impracticable sample size due to low event rates and would expose the transfusion group to the harms of transfusion. Indeed, a recent pilot randomized trial not only found challenges with recruitment but high rates of transfusion complications suggesting that transfusion risks currently exceed bleeding risks. Utilization studies find approximately 25% of plasma and 10% of platelets are transfused to patients as prophylaxis for bleeding prevention prior to procedures. This suggests that adherence to restrictive practices could substantially reduce adverse reactions from transfusion, minimize blood product shortages, and minimize delays in procedures for transfusion. In addition to unnecessary transfusions, the unselected use of pre-procedure laboratory testing is unwarranted for all procedures. This testing is expensive, has a low positive predictive value for bleeding complications, and delays procedures unnecessarily. Numerous studies have also shown that the infusion of plasma for mildly elevated international normalized ratio (INR) test results (INR of 1.5–1.9) does not alter the INR and therefore is very unlikely to reduce the bleeding risk. Lastly, the INR does not predict the risk of bleeding and the coagulation status of patients with liver cirrhosis. Many large centers have successfully transitioned to a restrictive use of blood before procedures and published the safety of this approach. This review will provide the evidence to convince others to follow suit.

**Keywords:** Platelet transfusion; plasma transfusion; invasive procedure; coagulation; thrombocytopenia

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## Introduction

The incorrect transfusion management of patients undergoing invasive procedures is a longstanding problem that has frustrated interventional radiologists, other proceduralist physicians, laboratory physicians, and transfusion medicine technologists. The major knowledge gaps impairing the care of patients undergoing invasive procedures include the unnecessary use of unselected pre-transfusion laboratory testing prior to all procedures, the incorrect perception that bleeding after invasive procedures is common, the incorrect belief that plasma corrects mildly elevated international normalized ratio (INR) test results (let alone reduces the bleeding risk), the use of sub-therapeutic doses of plasma (1–2 units in adults), and the lack of awareness that the use of blood products before procedures is associated with adverse reactions. These challenges continue despite a comprehensive, recent, and evidence-based publication on the appropriate pre-procedure management by the Society for Interventional Radiology (SIR) (1). This article will provide clinicians with clarity on these issues to build our collective confidence in our ability to safely perform the vast majority of procedures without blood transfusion support. The focus of the review will be on the most common procedures performed at the bedside by clinicians or by interventional radiologists; the review will not discuss the use of blood products before operative procedures, which have been reviewed elsewhere (2,3). We will highlight the largest studies and most important work in this area, rather than providing an exhaustive review of every observational report for every procedure.

The first important concept is that pre-procedure coagulation testing does not predict which patients will have a bleeding complication. A systematic review performed by the British Committee for Standards in Haematology found the predictive value of unselected screening to be very poor (the positive predictive value ranged from 0.03 to 0.22) and rarely altered patient management (1% or less in all case series) (4). For low-risk procedures, the SIR guidelines recommended that performing a pre-intervention platelet count or INR is not required (1). It is also important to recognize that in patients with cirrhosis, the INR does not accurately reflect the coagulation status of the patient due to the test's inability to detect a fall in natural anticoagulants (5). Accordingly, the SIR provided different evidenced-based transfusion thresholds for procedures in patients with cirrhosis (1).

The second important concept is that bleeding with many invasive procedures is exceptionally rare. For example, a case series of 3,116 paracenteses in patients with liver disease observed a rate of bleeding of 0.19% despite no correction of abnormal laboratory tests with pre-procedure transfusion (6). Similarly, a case series of 436 thoracenteses, including 41 patients with a platelet count below  $30 \times 10^9/L$ , observed no serious bleeding complications (7). The very low rate of bleeding complications means that randomized clinical trials comparing a liberal to a restrictive transfusion strategy are not feasible (8). A study from the Netherlands highlights the insurmountable challenges to performing such a trial (9). This research team screened 6,825 patients to randomize 81 patients to plasma or no plasma before invasive procedures in the intensive care unit. The trial was stopped early due to poor enrollment. There was no difference in the rate of major bleeding, but the incidence of ventilator associated pneumonia and duration of mechanical ventilation were both greater in the plasma arm. Given event rates below 1%, it would be unethical to expose hundreds of additional patients to the risks of transfusion in the plasma arm knowing there is only the potential for benefit in a rare patient. A second pilot randomized controlled trial similarly found the rate of transfusion reactions to exceed the rate of bleeding (10).

The third important concept is that the infusion of plasma to patients with mildly elevated INRs, from 1.5 to 1.9, does not result in a reduction in the INR level post-transfusion. This has been verified in numerous observational studies (11,12) and led to a recommendation by the British Committee for Standards in Haematology to refrain from using plasma for mildly elevated INRs (1.5–1.9) (13).

The final concept is that the transfusion of platelets and plasma is not risk free. The most concerning risk from a platelet transfusion is bacterial sepsis, with a risk of bacterial contamination at 1 in 2,572 units (14). The use of pre-procedure platelet transfusions in propensity matched studies are associated with an increased risk of intensive care admission (15). The most concerning risk from plasma transfusion is transfusion-associated circulatory overload (TACO) experienced by 5% of recipients, a reaction now understood to be associated with mortality (16). The use of pre-procedure plasma transfusions in propensity matched studies are associated with an increased risk of intensive care admission and red cell transfusion rates (17). Lastly, the performance of baseline laboratory testing, pre-transfusion plasma and/or platelet transfusion, and then repeat

laboratory testing after infusion leads to considerable health care costs and delays in performing the procedure. The cost of platelet and plasma transfusions are estimated to be 1,360 and 1,608 USD per patient, respectively (18,19). This review provides evidence to support a shift from liberal to restrictive use of laboratory testing and transfusions prior to invasive procedures.

## Methods

A literature search was conducted on Medline and Embase and was limited to full length, English language articles published on human subjects between 1980 and March 30, 2021, meeting the study objective. The search was focused on interventional radiology procedures, bleeding complications and hematologic and coagulation parameters. Search terms included: platelet count; INR; platelet transfusion; thrombocyte transfusion; plasma; plasma transfusion; blood transfusion; central venous access; liver biopsy; transjugular liver biopsy (TJLB); lumbar puncture; paracentesis; thoracentesis; thyroid biopsy; bone marrow biopsy; lymph node biopsy; gastrojejunostomy tube insertion; gastrostomy tube insertion; deep abscess drainage; musculoskeletal procedure; percutaneous nephrostomy (PCN); percutaneous transthoracic lung biopsies; epidural; regional anesthesia; and radiofrequency ablation (RFA). An additional manual search was performed for each procedure on PubMed using the same inclusion criteria and search terms as listed above. Randomized controlled trials, observational studies, case series and review articles were selected and narratively reviewed in compliance with the Scale for the Assessment of Narrative Review Articles (SANRA) narrative review checklist (20).

## Results

### *Low-risk procedures*

The SIR has an extensive list of procedures considered at a low-risk of associated bleeding (*Table 1*) (1). For these low-risk procedures, the evidence supports the safe performance of these procedures when the INR is below 2.0 to 3.0 and the platelet count is  $20 \times 10^9/L$  or higher. However, the SIR guidelines and the evidence also support foregoing routine laboratory screening altogether. We reviewed the most important evidence for many of the procedures listed in the guidelines as low-risk, concentrating on commonly performed procedures.

### **Lumbar puncture**

There is a large body of evidence from observational studies in patients with malignancy that lumbar punctures for diagnostic and therapeutic reasons (i.e., intrathecal chemotherapy) can be performed safely despite severe thrombocytopenia. The three largest studies identified detailed 8,070 lumbar punctures in adults and children, including 1,079 patients with a platelet count below  $50 \times 10^9/L$  in which not a single bleeding complication was observed (21-23). The largest study evaluated 5,442 lumbar punctures in 958 children at St. Jude Children's Hospital (22). Overall, 941 (17%) were performed without bleeding complications despite a platelet count below  $50 \times 10^9/L$ ; where 199 (4%) of those procedures were performed with a platelet count below  $20 \times 10^9/L$ . The sample size limited the 95% confidence interval from this single report to 0% to 1.75% risk of any complications. The other two large observational studies detailed the risk of bleeding outcomes in adult patients, where no bleeding complications were observed despite 295 (24%) of 1,240 lumbar punctures performed in both studies with a platelet count of less than  $50 \times 10^9/L$  (21,23). For those patients transfused platelets to achieve a higher platelet count before procedures, one of these studies reported a transfusion reaction rate of 0.95%, suggesting the potential for harm from transfusion exceeds the bleeding risk from the procedure (21).

### **Musculoskeletal procedures**

The bulk of the medical evidence for the bleeding risk from musculoskeletal procedures has been derived from overall bleeding complication rates in consecutive procedures at single-centers or data on anticoagulated patients undergoing procedures without drug cessation. The evidence estimating the risk of bleeding from musculoskeletal invasive procedures is not extensive but universally finds bleeding rates to be under 1%. A case series of 2,027 adult patients undergoing computed tomography (CT)-guided biopsies of the musculoskeletal system reported 4 (0.2%) bleeding complications, all of which required no intervention (3 psoas muscle hematomas, one retroperitoneal hematoma) (24). A series of 430 patients undergoing core biopsy of the spine at a single-center reported 4 (0.9%) bleeding events, none of which required an intervention (25). Similarly, a case series of 386 prospectively monitored patients undergoing CT guided spine biopsies did not detect any hemorrhagic complications (26). A single-center report evaluated the risk

**Table 1** Common procedures divided into low and high-risk procedures as recommended by the Society for Interventional Radiology guidelines (1)

| Procedure type | Examples  |
|----------------|---|
| Low-risk       | <p>Catheter exchanges (gastrostomy, biliary, nephrostomy, abscess, including gastrostomy/gastrojejunostomy conversions)</p> <p>Diagnostic arteriography and arterial interventions: peripheral, sheath &lt;6 French, embolotherapy</p> <p>Diagnostic venography and select venous interventions: pelvis and extremities</p> <p>Dialysis access interventions</p> <p>Facet joint injections and medial branch nerve blocks (thoracic and lumbar spine)</p> <p>IVC filter placement and removal</p> <p>Lumbar puncture</p> <p>Non-tunneled chest tube placement for pleural effusion</p> <p>Non-tunneled venous access and removal (including PICC placement)</p> <p>Paracentesis and thoracentesis</p> <p>Peripheral nerve blocks, joint, and musculoskeletal injections</p> <p>Sacroiliac joint injection and sacral lateral branch blocks</p> <p>Superficial abscess drainage or biopsy (palpable lesion, lymph node, soft tissue, breast, thyroid, superficial bone, extremities and bone marrow)</p> <p>Transjugular liver biopsy</p> <p>Trigger point injections including piriformis</p> <p>Tunneled drainage catheter placement</p> <p>Tunneled venous catheter placement/removal (including ports)</p> |
| High-risk      | <p>Ablations: solid organs, bone, soft tissue, lung</p> <p>Arterial interventions: &gt;7 French sheath, aortic, pelvic, mesenteric, CNS</p> <p>Biliary interventions (including cholecystostomy tube placement)</p> <p>Catheter directed thrombolysis (DVT, PE, portal vein)</p> <p>Deep abscess drainage (lung parenchyma, abdominal, pelvic, retroperitoneal)</p> <p>Deep nonorgan biopsies (spine, soft tissue in intraabdominal, retroperitoneal, pelvic compartments)</p> <p>Gastrostomy/gastrojejunostomy placement</p> <p>IVC filter removal complex</p> <p>Portal vein interventions</p> <p>Solid organ biopsies</p> <p>Spine procedures with risk of spinal or epidural hematoma (kyphoplasty, vertebroplasty, epidural injections, facet blocks cervical spine)</p> <p>Transjugular intrahepatic portosystemic shunt</p> <p>Urinary tract interventions (including nephrostomy tube placement, ureteral dilation, stone removal)</p> <p>Venous interventions: intrathoracic and CNS interventions</p>   |

IVC, inferior vena cava; PICC, peripherally inserted central catheter; CNS, central nervous system; DVT, deep vein thrombosis; PE, pulmonary embolism.

of bleeding after bone biopsy in two cohorts of patients, one during a time period where routine INR and platelet count were required ( $n=323$ ) and a subsequent time period where pre-procedure testing was eliminated ( $n=332$ ); there were no bleeding complications in either time period and testing identified only two patients with abnormal laboratory tests (27). A case series of 127 children undergoing musculoskeletal biopsies observed no serious bleeding complications (2 children had minor bleeding without need for intervention) (28).

Bleeding complication rates after vertebral augmentation procedures (vertebroplasty and kyphoplasty) were evaluated in a large study with data obtained from a national inpatient registry detailing outcomes after 63,459 inpatient procedures in over 1,000 institutions (225,259 vertebroplasty and 81,790 kyphoplasty procedures). Anemia occurred in 1.76% of the vertebroplasty procedures and 1.27% of the kyphoplasty patients (29). Due to the lack of chart review to determine if the anemia was due to hemorrhage from the procedure, the risk of bleeding may have been overestimated by this report.

There is also a small body of literature suggesting anticoagulated patients are also at a low-risk of hemorrhage. A single-center case series of 640 arthrocentesis procedures in patients on anticoagulation observed 1 (0.2%) non-life-threatening bleeding complication in a patient with an INR of 2.3 (30). A single-center report of 6,935 nerve block procedures in patients on either antiplatelet agents or anticoagulants did not observe a single hemorrhagic complication (31).

The SIR guidelines place most of these musculoskeletal procedures into the low-risk category where an INR  $<2.0$  to 3.0 and platelet count in excess of  $20 \times 10^9/L$  is sufficient (although no testing is required), except for kyphoplasty, vertebroplasty, epidural injections and cervical spine facet blocks where an INR  $<1.5$  to 1.8 and platelet count  $>50 \times 10^9/L$  are recommended (1).

### Paracentesis and thoracentesis

Many retrospective and observational studies have evaluated bleeding risk and patient outcomes after image-guided, diagnostic and therapeutic paracentesis and thoracentesis, and support the restrictive transfusion approach in the SIR guidelines (1). Rowley *et al.* reviewed 3,116 ultrasound-guided paracenteses in 678 patients performed within the radiology department without prophylactic transfusion (6). The platelet count was  $<50 \times 10^9/L$  in 368 (12%) of procedures and INR  $>2.0$  in 437 (14%).

Bleeding events occurred in 6 of 3,116 procedures (0.19%) without a single bleeding patient having a platelet count  $<50 \times 10^9/L$ . Neither platelet count nor INR were found to be risk factors for post-paracentesis hemorrhage. The authors also demonstrated significant cost savings, totaling 816,000 USD, from the prevention of unnecessary transfusion with this restrictive strategy compared to the historical practices (plasma to correct the INR to  $\leq 2.0$  and platelet transfusions for a count of  $<50 \times 10^9/L$ ). Pache *et al.* demonstrated a similar risk of hemorrhage in 4,729 procedures at their institution with 9 (0.19%) bleeding events (32). Paracentesis was performed exclusively in patients with severe liver disease either without image guidance by residents or gastroenterologists, or ultrasound-guided by interventional radiology. While complete laboratory and transfusion data on the entire cohort was not available, bleeding was not found to be associated with platelet count, INR or operator experience. Grabau *et al.* prospectively assessed the impact of platelet count and INR in 1,100 large volume non-image-guided paracenteses performed at a single institution (33). In this study, 54% of patients had a platelet count  $<50 \times 10^9/L$ , 74% had an INR  $>1.5$ , and 26% having an INR  $>2.1$  without significant bleeding occurring in a single patient.

The bleeding risk in patients undergoing thoracentesis has been evaluated and found to be low, even in the presence of severe thrombocytopenia and abnormal tests of coagulation. The two largest studies detail a combined 2,085 thoracenteses with only 4 (0.2%) bleeding complications reported (34,35). Of these 2,085 cases, 1,940 had a recorded pre-procedural platelet count with 306 (16%)  $<50 \times 10^9/L$  and 1,799 had pre-procedural INR values with 1,063 (59%) having an INR  $>1.5$ . In the most recent of these two studies, Hibbert *et al.* (34) assessed bleeding outcomes after ultrasound-guided thoracentesis for patients in two groups: those not transfused and those transfused based on pre-procedural platelet count and INR (either platelets or plasma at treating physician's discretion). Of the 1,009 procedures evaluated, the overall bleeding rate was 0.40%. Notably, 706 (70%) were performed without transfusion with a bleeding rate of 0.0% (95% CI: 0.00–0.68%) and 303 (30%) were performed with pre-procedural transfusion with a bleeding rate of 1.32% (95% CI: 0.51–3.36%). Patel *et al.* (35) detailed the outcomes of 1,076 ultrasound-guided thoracentesis with no bleeding complications identified. The platelet count was  $<50 \times 10^9/L$  in 6% of cases and  $<25 \times 10^9/L$  in 1% cases, while the INR values in this study were  $>1.5$  in 35% of cases. No



bleeding events occurred in any group.

Another study assessed bleeding risk specific to thoracentesis performed in adult oncology patients with severe thrombocytopenia, which the authors defined as a platelet count  $<30 \times 10^9/L$  (7). The analysis comprised 436 procedures with a cumulative bleeding rate of 0.69% (3 bleeding events). Of the 310 procedures performed under ultrasound guidance, 32 patients (10.3%) had severe thrombocytopenia and no bleeding events occurred. In the 126 procedures performed without ultrasound guidance, 9 (7.14%) patients had severe thrombocytopenia and it was within this group that all detected bleeding events occurred (3 events, 33% of those with severe thrombocytopenia, without ultrasound guidance) suggesting reduced risk with image guidance.

### Angiographic procedures—6 French or less

Large retrospective studies demonstrate the safety of angiographic procedures in patients on anticoagulants or having abnormal tests of coagulation. A retrospective study of 779 consecutive patients undergoing a coronary angiographic procedure had an overall rate of bleeding complication of 3.7%, with no difference in complication rate between patients with INR  $<1.6$ , compared to patients with an INR  $>1.6$  or those on oral anticoagulants (36). In a retrospective study of 1,000 consecutive patients undergoing interventional radiology femoral sheath access, abnormal coagulation parameters were not associated with increased bleeding complications (37). Similarly, coagulopathy in the context of chronic liver disease has not been associated with increased bleeding complications. A retrospective study of 240 patients with chronic liver disease undergoing heart catheterization demonstrated no correlation between INR and post-procedure hemoglobin levels (38).

There is evidence that pre-procedural transfusion of plasma to correct a coagulopathy does not change the overall bleeding complication rate. In a retrospective study of 2,271 patients undergoing angiographic procedures through radial access, 176 were identified to have an INR  $>1.5$ , and pre-procedural plasma transfusion did not reduce bleeding complications (39).

The evidence regarding the risk of bleeding in the presence of thrombocytopenia is mixed. In the previously mentioned study of 1,000 interventional radiology procedures with femoral artery access procedures (37), a platelet count  $<100 \times 10^9/L$  was associated with increased bleeding complications with an odds ratio (OR) of 9.2. A smaller retrospective study of 99 patients demonstrated

that a platelet count  $<150 \times 10^9/L$  was associated with an increased risk of pseudoaneurysm (OR =5.0) (40). This evidence is counterbalanced by large studies demonstrating no association. In a retrospective review of 1,353 visceral angiograms, a platelet count  $<50 \times 10^9/L$  was not associated with increased bleeding risk (41). A study of 98 oncology patients with thrombocytopenia (platelet count  $<100 \times 10^9/L$ ) reported 4 minor bleeds; however, platelet count  $<30 \times 10^9/L$  was not associated with an increased bleeding complication rate compared to higher levels (42). In a large retrospective review of 3,412 patients undergoing coronary angiograms, the bleeding complication rate was lower for patients with platelet count  $<100 \times 10^9/L$  (1.2%) when compared to the patients with platelet count  $>100 \times 10^9/L$  (4.3%) (43). The overall evidence for thrombocytopenia is therefore mixed, with no robust reproducible evidence correlating thrombocytopenia with an increase in bleeding complications during routine angiograms.

There is evidence that restricting sheath size reduces bleeding complications. In the previously mentioned analysis of 1,000 interventional angiograms, sheath size  $>5$  French resulted in increased bleeding complication rates (OR =3.7) (37).

### Tunneled and non-tunneled central/peripheral venous access

There is one landmark study assessing the safety of tunneled dialysis line insertion in patients with coagulopathy (44). This single institution retrospective study reviewed 3,188 tunneled dialysis line insertions performed in an academic interventional radiology department using sonographic guidance, identifying 428 tunneled line insertions in patients with a platelet count  $<50 \times 10^9/L$ , and 361 patients with an INR  $>1.5$ . None of these line insertions had pre-procedural transfusions of plasma or platelets. There were 3 (0.09%) bleeding complications in the whole cohort and none in patients with abnormal laboratory tests. Infection-free catheter survival and overall catheter survival were examined to assess for possible subclinical bleeding and risk of increased infection within a presumed tunnel subclinical hematoma. There was no overall catheter survival difference between the patients with and without abnormal laboratory test results. This high-quality study followed the SIR Technology Assessment Committee reporting standards (45).

In a novel assessment of bleeding risks for tunneled dialysis line insertion, one study compared the bleeding

complication rate of a group of patients on antithrombotic medication (warfarin, clopidogrel or ASA; n=458), patients who had a fistula declotting failure followed by urgent tunneled line insertion and were therefore therapeutically heparinized from the declotting procedure (n=941), and a control cohort of 6,555 tunneled line insertions (46). The incidence of bleeding in the medication group was 0.36%, in the heparinized group was 0.44%, and in the normal cohort was 0.46%.

The larger studies for temporary dialysis catheters are blurred by generalizing the procedure with smaller diameter central line insertions. A study of 1,737 consecutive central venous catheters using sonographic guidance, including both temporary dialysis lines and smaller temporary central venous lines, defined high bleeding risk patients as having an INR >1.8 and/or platelet count <50×10<sup>9</sup>/L; bleeding complications were not higher in the patients with abnormal laboratory tests (47). A separate prospective audit of 658 mixed central venous cannulations in patients with chronic liver disease with an INR >1.5 and/or platelet count <150×10<sup>9</sup>/L demonstrated an increased risk of minor focal site hematoma when the INR was >5.0 or the platelet count was <50×10<sup>9</sup>/L (48). This study included a mixture of triple-lumen central lines, pulmonary arterial flow catheters, and temporary non-tunneled dialysis lines, varying between 7 and 12 French in diameter, without specifying the distribution between the types of lines. In this older study, line insertion was not performed with sonographic guidance and the overall bleeding complication rates of 5% to 10% were higher than more recent studies.

Studies examining non-tunneled dialysis line insertions in coagulopathic patients are smaller. A prospective study examined the complication rate of 133 non-tunneled dialysis line insertions using sonographic guidance in patients with abnormal laboratory test results [platelet count ≤50×10<sup>9</sup>/L, an INR ≥1.5, or an activated partial thromboplastin time (aPTT) level ≥50 seconds, alone or in combination] (49). There were 8 (6%) minor bleeding complications, with no association between laboratory test results and bleeding complication rate. An earlier prospective study examined the bleeding complication rate for non-tunneled dialysis line insertions using sonographic guidance where 61 line insertions were performed in patients with abnormal laboratory test results (using identical criteria) (50). There was a 4.9% minor bleeding complication rate in patients with abnormal test results, with no bleeding complications in the normal group.

Looking specifically at peripherally inserted central

catheter (PICC), a retrospective analysis examined 378 PICC insertions in patients with abnormal laboratory test results (defined as INR >2.0 and/or platelet count <50×10<sup>9</sup>/L, and/or an aPTT >66 seconds or patients receiving antiplatelet therapy) (51). No early or late bleeding complications were seen. Similarly, a prospective analysis of 143 PICC insertions in oncologic patients with a platelet count <50×10<sup>9</sup>/L identified 50 insertions performed in patients with a platelet count <20×10<sup>9</sup>/L (52). In this subcategory of profound thrombocytopenia, there was a single (1 in 50) minor complication of oozing at the entry site and no major bleeding complications.

### Transjugular liver biopsy

TJLBs are inherently safe, with the approach to the liver maintained within the venous system, technically limiting bleeding from the liver into the hepatic veins. A retrospective study of 1,321 TJLB identified 124 patients with platelet count <50×10<sup>9</sup>/L, and 52 with INR >2.0 (53). There was an overall 0.7% major complication rate, with no association with platelet count or INR. A separate retrospective review of 1,600 TJLB included 183 patients who were bone marrow transplant (BMT) recipients (54). The bleeding complication rate was 2.9% in the BMT group, and 0.6% in the control group, but the difference was not statistically significant.

### Superficial biopsies

#### *Thyroid biopsies*

The existing literature, largely retrospective and observational in nature, supports the SIR guideline that thyroid biopsy can be done without the need for pre-procedure laboratory testing. The largest study by Ha *et al.* reported on 6,687 ultrasound-guided core needle biopsies (CNB) of thyroid lesions performed at a single institution. Coagulation screening testing was not routinely performed. However, the medical history was thoroughly reviewed for assessment of bleeding risk. In patients on anticoagulation or antiplatelet therapy, all medications were stopped in advance of the procedure with the guidance of the relevant subspecialists involved in the medication's administration. The bleeding complication rate was very low with two major complications (0.03%) requiring compression and admission for observation and 42 (0.63%) minor complications requiring local compression (55). Cappelli *et al.* reviewed 7,449 ultrasound-guided fine needle aspirations (FNA) of thyroid nodules and similarly found that the bleeding complication rate was very low (0.07%)

with one serious bleeding complication and four minor hematomas. Again, laboratory values were not assessed pre-procedure, but anticoagulants and antiplatelet agents were routinely stopped (56). Abu-Yousef *et al.* retrospectively assessed the safety of ultrasound-guided FNA in 593 patients with neck lesions at their institution with the specific aim to review bleeding complications in those on antiplatelet and/or anticoagulation therapy. Coagulation parameters were not evaluated for any patient prior to the FNA biopsies. A total of 144 (24.3%) were taking various antiplatelet or anticoagulant medications at the time of their procedure. Six (1.0%) patients developed post-procedure hematomas, with no statistically significant difference in the incidence of hematoma between groups ( $P=0.603$ ) (57).

#### **Bone marrow biopsy**

Investigations into the bleeding complications of bone marrow biopsy are largely retrospective. However, given the applicability of the procedure to disorders of the hematologic system these investigations contain greater detail regarding platelet count and coagulation studies compared to those of other superficial biopsy sites.

The largest review details adverse events both retrospectively and prospectively reported by hematologists across the United Kingdom from multiple institutions (58). The combined cohort comprised 54,890 aspirates and/or biopsies. There were 14 bleeding complications identified for an overall bleeding rate of 0.03%. Of the 14 patients with bleeding complications, only 3 had thrombocytopenia {with platelet count between  $[25-68] \times 10^9/L$ } while 13 of the 14, including all 3 who were thrombocytopenic, were felt to have platelet dysfunction due to an underlying hematologic disorder or medication (myeloproliferative disorder, disseminated intravascular coagulation, aspirin, or warfarin). The most common association with bleeding was an underlying myeloproliferative disorder.

Two retrospective studies evaluated the safety of image-guided bone marrow aspirate and biopsy with a focus on thrombocytopenic patients. Liu *et al.* presented complication rates from a single-center in 981 thrombocytopenic patients undergoing CT-guided posterior iliac bone marrow aspirate and biopsy (59). The patients were subdivided into 3 groups based on platelet count:  $<20 \times 10^9/L$  (3.4%),  $[20-50] \times 10^9/L$  (19.1%),  $\geq 50 \times 10^9/L$  (77.6%). There were no bleeding complications recorded in any of the groups. Stensby *et al.* retrospectively evaluated 111 bone marrow aspirates and biopsies performed under fluoroscopic guidance with battery-powered drill assisted coaxial needle in severely thrombocytopenic patients. Patients were divided into

three groups based on platelet count:  $<20 \times 10^9/L$  (16%),  $[20-50] \times 10^9/L$  (16%), and  $\geq 50 \times 10^9/L$  (68%). Bleeding complications were evaluated clinically and radiographically by CT scan within 7 days following the procedure. There were no bleeding events in any of the study patients nor was there a statistically significant difference in post-biopsy CT imaging for subclinical bleeding (60).

#### **Lymph node biopsy**

One prospective study at a single-center evaluated the complication rates of ultrasound-guided FNA (75.7%) and core needle (24.3%) lymph node biopsies in 536 procedures. The anatomical distribution varied widely with intraabdominal (55.3%), cervical (22.4%), inguinal (12.9%), axillary (7.8%), and other (1.7%) included with no complications encountered over the entirety of the study. Coagulation parameters and platelet count were not routinely measured, however, in those with values available the inclusion criteria necessitated a platelet count  $\geq 70 \times 10^9/L$ , prothrombin time (PT)  $\geq 70\%$ , and PTT  $<50$  seconds. Coagulation parameters were documented in 207 (38.6%) procedures and of these only 20 (9.7%) did not meet the pre-established criteria for adequate coagulation status (but the procedures were performed without transfusion due to urgency of the procedure). In 10 (1.9%) procedures, the platelet count was  $<70 \times 10^9/L$  with the lowest count being  $11 \times 10^9/L$ , while the coagulation test results were out of range in a combined 17 (3.17%) procedures with no signal toward increased bleeding risk (61). Another small ( $n=74$ ) retrospective review assessed the complication rate in CT-guided retroperitoneal lymph node biopsies. Pre-procedure requirements were platelet count  $>50 \times 10^9/L$ , PT  $<15$  seconds and activated PTT  $<39$  seconds. Five (6.75%) patients developed small retroperitoneal hematomas on CT scan immediately following the biopsies, but these were asymptomatic and did not require intervention or change in care (62).

Unfortunately, due to an overall paucity of data in this area, it is challenging to make a definitive recommendation on specific coagulation parameters that should be performed for lymph node biopsies. Based on the accessibility of the site for compression and/or alternative intervention in the case of hemorrhage, those sites that are superficial (neck, axilla, inguinal) can be safely biopsied without pre-procedure testing or transfusion, regardless of coagulation parameters or platelet count. In contrast, retroperitoneal, abdominal, or pelvic biopsies may require greater precaution due to proximity to vascular structures, possibly increasing the likelihood of serious complication and incompressibility



in the circumstance of a bleeding event.

### Low-risk procedures: conclusions and guidance

Most of the evidence for low-risk procedures involves a retrospective study design, with little prospective or randomized trial data. This collective body of evidence emphasizes the very low rates of bleeding with these common procedures, even in the presence of marked thrombocytopenia and abnormal tests of coagulation. These studies support the assertion that these procedures can be performed safely without pre-procedural laboratory testing. Although higher quality evidence is always welcomed, clinicians “holding out” for a prospective, randomized, double-blind trial are likely to be disappointed given the recent Cochrane review for lumbar punctures estimates a trial would need to include at least 47,030 patients to detect a reduced risk of bleeding from 2 in 1,000 to 1 per 1,000 (8). The current evidence base strongly supports a restrictive use of pre-procedure transfusions for patients with thrombocytopenia and/or abnormal tests of coagulation.

There have been significant improvements in techniques for interventional radiology procedures over the past 25 years. The use of image guidance, low profile techniques (micropuncture needles, coaxial biopsy systems, vascular closure devices) has increased and is now widespread in interventional radiology practice. When evaluating the risk of a procedure and balancing the role for correction of anticoagulation and thrombocytopenia, consideration should be given to overall training and expertise of the proceduralist, quality of image guidance, body habitus and equipment utilized. The overall medical health of the patients is also a factor, where individual risks of transfusion should be carefully weighed against the risk of bleeding. These variables are generally not accounted for in the overall evidence. Lastly, interventional radiologists should not lose sight of the risk of transfusion reactions in their discussions with patients and clinicians regarding peri-procedure transfusion decisions.

### High-risk procedures

High-risk procedures, as classified by the SIR guidelines, are detailed in *Table 1* (1). According to this guideline, it is recommended to perform pre-procedure laboratory testing (INR and platelet count) before these more invasive procedures due to their higher bleeding risk. The threshold levels for considering pre-procedural transfusions are an INR of greater than 1.5 to 1.8 and a platelet count less than

$50 \times 10^9/L$ . The evidence base for these recommendations and the bleeding risk to patients for the more common procedures will be evaluated. A partial thromboplastin time (PTT) is not indicated as a screening test before interventional procedures, unless there is a clinical history suggestive of an undiagnosed bleeding disorder or there is a concern the patient is on certain anticoagulant agents (e.g., heparin or dabigatran).

### Percutaneous liver biopsy

Percutaneous liver biopsy is a useful procedure for evaluating diffuse liver disease and focal hepatic lesions. While it has a higher bleeding risk compared to TJLB, it is generally considered safe. A retrospective analysis of 6,613 image-guided liver biopsies showed that percutaneous liver biopsy is associated with an overall low-risk of adverse events (0.7%) (63). Specific adverse events include hematoma requiring transfusion or intervention (0.5%), infection (0.1%), hemothorax (0.06%), and death (0.05%).

The literature provides evidence-based platelet count thresholds to guide transfusions. In a retrospective review by Boyum *et al.*, a higher frequency of hemorrhage was reported in patients with a platelet count  $<50 \times 10^9/L$  compared to a higher platelet count (2.2% *vs.* 0.5% respectively,  $P=0.01$ ) (63). This is supported by data in patients with hepatitis C related fibrosis or cirrhosis that were enrolled in the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) Trial (64). In this study, 2,740 liver biopsies were performed, and the most common adverse event was bleeding, occurring in 16 (0.6%) of cases. There was a clear relationship between the platelet count and risk of bleeding, with a 5.3% risk of bleeding for platelet count  $<60 \times 10^9/L$ . Lastly, a retrospective review of 177 percutaneous liver biopsies also showed no difference in bleeding rate in patients with platelet count  $>100 \times 10^9/L$  compared to platelet count  $[50-99] \times 10^9/L$  (65). Together, this data supports the SIR guidelines to transfuse platelets if  $<50 \times 10^9/L$  for percutaneous liver biopsy.

The collective evidence supporting the SIR guidelines to correct INR within the range of 1.5 to 1.8 is less clear. In a large retrospective analysis of image-guided percutaneous liver biopsies, there was no difference in the mean INR between patients with and without hemorrhage {1.1 [standard deviation (SD) 0.2] *vs.* 1.0 (SD 0.1), respectively} (63). All patients who had a hematoma had an INR of 1.5 or less, and there were no hematomas in the 43 patients who underwent a biopsy with an INR greater than 1.5. Similarly, in the HALT-C trial, the bleeding rate

was higher in patients with INR >1.3, however, none of the patients with an INR >1.5 bled (64).

Recent evidence suggests that thresholds less stringent than the SIR guidelines may be acceptable. A retrospective study reviewing 1,846 percutaneous liver biopsies compared two thresholds: a less stringent recommendation for acceptable pre-transfusion laboratory cut-offs of INR  $\leq 2.0$  and platelet count  $\geq 25$  compared with the institution's historical conservative approach (INR  $\leq 1.5$ , platelets  $\geq 50 \times 10^9/L$ ) (66). Less stringent guidelines were not associated with increased bleeding complications despite a significant decrease in pre-procedural plasma (0.8% *vs.* 3.9%,  $P < 0.001$ ) and platelet transfusions (0.3% *vs.* 1.2%,  $P = 0.021$ ) compared to the currently recommended by the SIR guidelines. Interestingly, for unclear reasons, bleeding complications were significantly decreased in the less stringent group compared to the SIR group (1.6% *vs.* 3.4%,  $P = 0.019$ ). While individual bleeding rates increased as the INR increased and platelet count decreased, pre-procedural plasma ( $P = 0.64$ ) and platelet transfusions ( $P = 0.5$ ) did not have a significant impact on bleeding rates. This evidence suggests that less stringent coagulation guidelines (INR  $\leq 2.0$ , platelets  $\geq 25 \times 10^9/L$ ) may be acceptable, however, large observational studies are required before concluding these targets result in similar bleeding rates.

### Renal biopsy

Renal biopsy is an essential tool for the diagnosis and prognosis of most nephropathies and renal masses with a low incidence of serious complications. Bleeding is a substantial risk in patients undergoing renal biopsy due to the vascular nature of the kidney. In patients with renal disease, uremic platelet dysfunction may also play a role.

A large retrospective review of 1,387 consecutive patients who underwent renal biopsy at a single-center demonstrated that minor bleeding was common (24% of patients experienced hematuria or other minor bleeding events), but severe bleeding requiring transfusion was rare [12 patients (0.87%); 8 for hematuria-related blood loss and 4 for hematomas] (67). These complication rates are consistent with other published reports (68-71).

Renal mass biopsy is also a safe procedure with a low complication rate. In a meta-analysis detailing 5,228 patients undergoing a renal biopsy, the median overall complication rate was 8.1%, with only three Clavien grade  $\geq 2$  reported complications (72). The incidence of minor Clavien grade 1 hematomas was 4.3% and the incidence of Clavien grade 2 hematomas (requiring blood transfusion or

intervention) was 0.7% of cases.

The available evidence is conflicting with respect to platelet transfusion thresholds in patients undergoing kidney biopsy, but the majority support the SIR guidelines (platelet transfusion for platelet count  $< 50 \times 10^9$ ). Stratta *et al.* identified factors that increased risk for major and minor bleeding complications such as autoimmune disease (OR =2.06), end stage kidney disease or acute tubular necrosis (OR =2.96), prolonged bleeding time test (OR =1.87), and blood pressure  $> 140/90$  mmHg (OR =1.15) (67). While platelet count was not associated with bleeding in this study, a large retrospective review of 2,204 ultrasound-guided percutaneous native renal biopsies did identify platelet count as a risk factor for increased bleeding, including a statistically significant decreased risk of bleeding with a platelet count  $> 100 \times 10^9/L$  ( $P = 0.001$ ) (73). Another large study confirmed that platelet count is an independent risk factor for severe bleeding complications, with each  $10 \times 10^9/L$  increase in platelet count associated with an 11% decrease in severe bleeding risk (OR =0.89,  $P = 0.02$ ) (74).

There is no robust data to support the SIR guidelines of INR target in patients undergoing renal biopsy. A prospective cohort study of 471 patients who underwent ultrasound-guided kidney native biopsy found that the risk of post-biopsy bleeding was higher in patients with a higher PTT (OR =1.26,  $P = 0.032$ ), however, the INR was not a predictor of bleeding (70). Overall, the majority of studies confirmed these findings that the INR was not a predictor of post-biopsy bleeding (68,70,73,74).

### Percutaneous deep abdominal lesion biopsy

Biopsy of deep abdominal lesions is extremely important in the diagnosis, staging and follow-up of patients with suspected or known malignancy. For this review, the focus is on CNB (not lower risk FNA), along with peritoneal and retroperitoneal biopsies.

The bleeding risk of a percutaneous biopsy of peritoneal, mesenteric, and omental lesions is low. However, the data is limited to a small number of single-center retrospective studies. The largest published series detailed 186 biopsies of the omentum and peritoneum, with only a single bleeding complication (0.5%) in a patient who developed a mesenteric hematoma requiring no intervention (75). A second series of 153 patients who underwent percutaneous biopsy of peritoneal or omental lesions encountered minor bleeding from the biopsy site in two patients requiring no intervention (1%), and no major bleeding complications (76). Lastly, Hewitt *et al.* reported only a

single bleeding complication with a rectus sheath hematoma in their review of 149 women undergoing percutaneous biopsies for peritoneal carcinomatosis (77).

The studies investigating retroperitoneal biopsies are single-center retrospective studies. A Brazilian study reviewed 225 procedures, with 43 (19%) retroperitoneal biopsies. Bleeding complications were seen in 12 patients. There was only one major bleeding complication in the retroperitoneal cohort, which was managed conservatively (78). The largest dedicated series by Dvorak *et al.* reviewed 202 retroperitoneal biopsies over 10 years (79). They found an overall bleeding complication rate of 3% (6 minor bleeds managed conservatively). There was no increased bleeding complication with a different needle gauge (16 *vs.* 18 gauge) and the number of biopsies.

Despite their classification as high-risk procedures, the bleeding complication rate is low for biopsy of deep abdominal lesions in the peritoneal and retroperitoneal space. Therefore, there is little evidence based on the review of the available studies to support the SIR guidelines recommending transfusion for a platelet count less than  $50 \times 10^9/L$  or INR  $>1.5$  to 1.8 in this patient population undergoing deep abdominal biopsies.

#### **Gastrostomy/gastrojejunostomy tube insertion**

Despite the frequency of placement of gastrostomy and gastrojejunostomy tubes, there is little to no data on the safety of this procedure with low platelet count or abnormal tests of coagulation. No large studies have been published comparing bleeding rates between patients with and without abnormal pre-procedural laboratory tests. The SIR guidelines recommend a platelet count  $>50 \times 10^9/L$  and an INR  $<1.5$  to 1.8 (1). A case series of 574 adults at a single-center documented the risk of upper gastrointestinal bleeding at 1.4% (8 of 574 patients) (80). Similarly, a case series of 467 children undergoing percutaneous or laparoscopic gastrostomy observed only 3 (0.6%) cases of bleeding (81). Given the very low rate of bleeding, multicenter observational studies will likely be necessary to provide clarity on the role of coagulation testing and the use of platelet and plasma components before this common procedure.

#### **Deep abscess drainage**

Percutaneous fluid drainage has marked benefits compared to open surgical drainage for non-resolving abscesses, where open drainage is now only considered when percutaneous drainage fails or is technically impossible. Commonly, CT

guidance is used when performing abscess drainage as it clearly delineates both the abscess and the surrounding tissue. There is no evidence-based guidance on transfusion thresholds in this setting; likely given the lack of literature, the variability of risk depending on abscess location and patient co-morbidities, and variability in practice.

One single-center case series of 154 percutaneous drainages for pelvic abscesses utilizing a CT-guided transluteal approach, which seeks to avoid vital structures in the area, has been published (82). Three episodes of bleeding occurred, however, all occurred with a transpiriformis approach. In two of the patients, hemorrhage occurred through a pseudoaneurysm that required embolization. The third patient developed a large pelvic hematoma, but there was spontaneous resolution with conservative management.

#### **Urinary tract interventions**

Urinary tract interventions such as PCN and percutaneous nephrolithotomy (PCNL) are well established to ensure patency of the urinary tract and prevent post-obstructive renal failure. While these procedures are commonly performed, concerns exist regarding the risk for major hemorrhage due to the highly vascular nature of the renal parenchyma (renal blood flow at 1 liter/minute). Standards released by the Society of Cardiovascular and Interventional Radiologists (SCVIR) and the American College of Radiologists suggest quality improvement thresholds of major hemorrhage (defined as requiring transfusion) rates at  $<4\%$  and  $<15\%$  for PCN and PCNL respectively (83). No literature exists to support an optimal prophylactic transfusion threshold for these procedures.

The literature describing complication rates are limited to single-center case series, fortunately finding reassuringly low rates of bleeding. A 10-year retrospective study of 1,113 PCNs found perirenal hematomas in 8 patients (0.7%); transient, self-limited macroscopic hematuria in 159 patients (14.3%) (84). Similarly, a 10-year study of 765 PCNs demonstrated a major hemorrhage rate of 1.5% (defined as requiring transfusion) (85). A study of 569 PCNs using fluoroscopic, ultrasound, and CT guidance found a bleeding rate of 0.5% (one required embolization and two blood transfusion) (86). A single-center series of 454 consecutive PCNs found a major hemorrhage rate of 2.8% (87). The authors suggest an association between platelet count  $<100 \times 10^9/L$  and requirement for blood transfusion but did not control for any confounders. Lastly, a study of 318 PCNs performed under fluoroscopic and

ultrasound guidance found a hemorrhage rate of 0.6% (n=2, neither patient had abnormal laboratory tests of coagulation and bleeding resolved spontaneously) (88).

The literature for PCNL is of lower methodological quality but suggests a possibly higher rate of bleeding than seen for PCN. A single-center case series of 131 patients had a major bleeding rate of 18% (89). Similarly, another single case series of 96 patients found a major bleeding rate of 23%; pre-operative hemoglobin and estimated blood loss were associated with peri-operative blood transfusion (90).

For symptomatic bladder outlet obstruction and neurogenic bladder dysfunction, indwelling suprapubic drains are inserted to aid bladder emptying and prevent bladder outlet obstruction. The available reports are of low methodological quality, though reassuringly major bleeding rates appear to be low. A single-center study found a minor bleeding rate per case (minor defined by interventions not being required) of 3.5% (19 of 549 procedures) and 1.8% (8 of 439 procedures) for primary suprapubic bladder tube insertions and tube changes, respectively, of which the majority were performed under fluoroscopic or ultrasound guidance (91). In a single study of 60 patients of suprapubic catheters placed under fluoroscopic guidance, one patient had superficial track bleeding (92).

### Lung biopsy

Percutaneous transthoracic lung biopsies are performed to diagnose pulmonary masses, typically performed with ultrasound or CT guidance. While they are generally considered safe procedures, pneumothoraces, air embolism, and bleeding (usually presenting as hemoptysis) are uncommon complications. Interventional radiologists generally consider a lung biopsy a high bleeding risk procedure. Hemoptysis and air embolism can rapidly deteriorate and are commonly challenging to manage. However, the literature does not provide an evidence-based threshold to guide transfusions.

A survey performed in the United Kingdom with data from 157 centers encompassing 5,444 biopsies, of which 39 centers collected data on 1,860 biopsies prospectively, reported an overall rate of hemoptysis of 4.8% (n=261) (93). The study also reported that there were only 8 (0.1%) cases of major hemoptysis requiring transfusion.

A single-center retrospective study of 15,181 percutaneous core biopsies included 1,174 lung biopsies (94). The study attempted to find an association between aspirin use and bleeding, where only two episodes of major hemorrhage occurred in patients post-lung biopsy with no aspirin

use. Interestingly, using logistic regression, the authors suggest that lower platelet count and increased INR were associated with major bleeding. However, the median platelet count and INR in patients with major bleeding was  $189 \times 10^9/L$  and 1.2 respectively. The same group also subsequently attempted to determine the incidence of bleeding complications for percutaneous CNB in hypertensive (>160/90 mmHg) *vs.* normotensive patients. Of the 4,756 biopsies performed in that study, 782 were lung biopsies (95). The cohort largely had normal platelet and coagulation testing results, though some patients did have INRs up to 3.0. Overall, only one bleeding complication occurred after lung biopsy, observed in a normotensive patient. Differences in bleeding rates across biopsies between hypertensive and normotensive patients were not statistically significant.

Another single-center retrospective study of 660 CT-guided percutaneous biopsies with follow up CT scans to detect occurrences of post-biopsy complications found an overall bleeding rate of 30% (n=201) (96). However, the majority of these complications (86%, n=173) were only visualized by follow-up CT scan and not clinically significant. This study found a 4% (n=26) rate of moderate bleeding (<30 mL hemoptysis) and one patient with a hemodynamically stable hemothorax.

### Epidural and regional anesthesia procedures

Bleeding complications can occur with any regional anesthetic procedure. Bleeding into the spinal canal is of specific concern as a non-expandable space that is difficult to access if there is a bleeding event. Spinal cord compression may result in neurologic ischemia and permanent complications such as paraplegia. The incidence of clinically significant spinal hematoma is less than 1 in 200,000 procedures based on a large, prospective, multicenter database developed to assess serious complications (97). It is unclear whether lab abnormalities in platelet count or coagulation test results predict risk; or if that risk can be mitigated with transfusion.

Professional organizations recommend prophylactic platelet transfusions before neuraxial anesthesia for a platelet count ranging from  $30 \times 10^9/L$  to  $100 \times 10^9/L$ , acknowledging that thresholds may need to be individualized based on balancing risk and benefit (98). In a 2020 systematic review and meta-analysis, 7,509 neuraxial procedures in heterogeneous thrombocytopenic patients were assessed, where the risk of spinal epidural hematomas was highest in lumbar punctures with a platelet count  $<50 \times 10^9/L$  (99).



However, a Cochrane review concluded that no evidence from either randomized controlled trials or non-randomized studies could properly inform a platelet transfusion threshold for neuraxial procedures; and further suggested that a randomized trial of platelet transfusions in this setting would require over 47,000 patients to be properly powered to detect a difference in major procedure-related bleeding (8).

A multicenter retrospective observational study of 573 patients receiving neuraxial anesthesia with a platelet count  $<100 \times 10^9/L$  found no cases of epidural hematoma, even with a platelet count  $<50 \times 10^9/L$ . The authors also performed a systematic review which found 14 relevant studies encompassing 951 patients that also found no cases of epidural hematoma (100). A subsequent single-center retrospective study in 471 peripartum patients receiving neuraxial blocks with a platelet count  $<100 \times 10^9/L$  found no cases of epidural hematoma. The authors of the aforementioned study attempted to estimate the upper limits of the 95% confidence interval for risk of spinal epidural hematomas based on the pooled results of their study, the multicenter retrospective study above, as well as their systematic review. They estimated that for platelet counts  $[70-100] \times 10^9/L$ ,  $[50-69] \times 10^9/L$ , and  $<50 \times 10^9/L$ , the upper limits of the 95% confidence interval were 0.19%, 2.6%, and 9% respectively (101).

Finally, though numbers are small, reassuringly patients on antiplatelet agents and/or nonsteroidal anti-inflammatory drugs (NSAIDs) do not appear to be at greater risk of bleeding complications. One prospective study assessing the risk of spinal hematoma in 1,000 episodes of spinal or epidural anesthesia pre-operatively found no episodes. While the lowest platelet count was  $94 \times 10^9/L$  and only minimal elevations of coagulation test results were seen, 39% of patients were on antiplatelet agents pre-operatively including 32 patients on multiple antiplatelets. Multivariate analysis did not find any association of laboratory abnormalities nor antiplatelet medications with minor hemorrhagic complications (102). Another study assessing 402 episodes of celiac plexus blockade with 58 receiving antiplatelets and/or NSAIDs found no bleeding complications requiring emergency and/or neurological intervention (103).

### Liver radiofrequency ablation

RFA is a widely used and accepted minimally invasive treatment for liver neoplasms as an alternative to invasive surgical resection. The incidence of hemorrhagic

complications has been generally found to be less than 1%, based on multiple single-center case series studies. A recent meta-analysis of seven randomized controlled trials comparing RFA and microwave ablation, two imaging-guided therapies used in hepatocellular carcinoma (HCC), found low rates of bleeding (0.98%; 9/921 patients) (104).

A single-center case series of 4,133 treatments with percutaneous RFA found 63 total bleeding episodes, with hemoperitoneum being the most common (0.7%;  $n=29$ ), followed by hemothorax (0.3%;  $n=14$ ) and hemobilia (0.5%;  $n=20$ ) (105). Patients required a platelet count of  $50 \times 10^9/L$  and prothrombin activity  $\geq 50\%$  for inclusion. Approximately a third of patients with hemoperitoneum and hemothorax ( $n=10$  and  $n=5$ , respectively) required blood transfusion, where only one case of hemobilia required transfusion. Though increased platelet count was associated with decreased risk of bleeding (OR =0.88 per  $10 \times 10^9/L$  increase in platelet count), the study did not suggest a threshold platelet count for RFA. Tumor size and location were found to have a stronger association with bleeding complications.

Another large multicenter report of 2,542 percutaneous RFA and 72 surgical RFA treatments found 11 episodes of intraperitoneal hemorrhage, 5 episodes of hemothorax, 4 episodes of subcapsular hematoma, and 3 episodes of gastrointestinal bleeding (overall bleeding complication rate of 0.9%) (106). A literature review encompassing 82 studies of RFA published between 1990 and 2001, found that the overall bleeding rate across 2,898 patients treated with percutaneous RFA was 1.6% ( $n=46$ ) (61). The most common bleeding complications were intraperitoneal bleeding and subcapsular hematoma ( $n=22$  and  $n=18$ , respectively).

Smaller studies demonstrate low bleeding rates in heterogeneous populations. A prospective single-center study of percutaneous RFA in 202 patients with a platelet count  $>100 \times 10^9/L$  had one episode of subcapsular hematoma (107). A multicenter prospective case series of 226 percutaneous RFA treatments had a bleeding complication rate of 1.3% (108). A 5-year case series of 124 intraoperative and 226 percutaneous RFA treatments, in patients with a platelet count  $>75 \times 10^9/L$  and INRs  $<1.5$ , found a bleeding rate of 0.9% without the need for transfusion (109).

### High-risk procedures: conclusions and guidance

In general, the current evidence base supports continued adherence to the 2019 SIR guidelines. Additional large, multicenter studies are needed to further clarify the risk-



benefit ratio of pre-procedure transfusions for INR >1.5 to 1.8 and a platelet count of  $<50 \times 10^9/L$ . First, there is little evidence to support that patients with INR over 1.5 bleed more than patients with less deranged levels. Second, the range of 1.5 to 1.8 places an unnecessary cognitive burden on clinicians whose patients may fall within this range. Third, plasma is ineffective in reducing the INR (let alone the bleeding risk) when the INR is 1.5 to 1.9 (110) and has appropriately led the British Committee for Standards in Haematology to recommend against plasma for these patients (13). Hence, the upper range of 1.8 is more logical and attainable to be incorporated into local hospital protocols. In addition, many of the designated high-risk procedures have very low bleeding complication rates (below 1%) and therefore additional studies are needed to determine if some can be reclassified as low-risk procedures.

## Discussion

This narrative review on the use of blood components prior to invasive procedures finds common themes arising from these large retrospective reports detailing the risk of bleeding from different procedure types. Routine pre-procedure coagulation testing does not identify a group of patients at high-risk for complications, supporting the recommendation that for low-risk procedures we can forego this step and expedite procedures without testing. Across all procedure types, even in high-risk solid organ biopsies, the risk of major hemorrhagic complications requiring transfusion of red blood cells or interventions to stop bleeding is reassuringly rare. The transfusions of platelets and plasma are associated with measurable harm and there is no evidence from propensity-matched cohort studies that transfused patients have better outcomes and may have worse outcomes (15,17). The substantial volume of observational data supports the SIR guidelines for a restrictive approach to the use of transfusions prior to procedures (1).

Practice audits suggest that there is substantial room for improvement in our use of plasma for patients undergoing procedures. A very large audit of 4,365 patients transfused plasma at 309 hospitals found 1,063 (24%) were transfused for pre-procedure prophylaxis, with 40% of patients receiving a dose of less than 10 mL/kg (subtherapeutic dose) for a median INR of 1.9 (111). Similarly, pre-procedure platelet transfusions in adults are a common indication for transfusion with one large multisite study finding 416 (25%) of 1,693 orders infused before a procedure (112).

Both qualitative and quantitative studies are required to better understand the drivers for the continued use of pre-procedure transfusions despite minimal evidence to support this practice and assist with the design and implementation of quality improvement studies to bring practice in line with guidelines.

One of the important concepts that must be communicated to physicians caring for patients pre-procedure is that classic individual patient randomized trials are not possible due to the large number of patients required and the unethical exposure of patients to the harms of unnecessary transfusions in the liberal transfusion arm (8,113). It would be feasible to design and conduct pre- to post-implementation of a restrictive transfusion practice and measure bleeding and other complication rates in a large multicenter cluster trial enrolling consecutive patients as part of a quality improvement initiative. The other research option is to compare liberal and restrictive transfusion hospitals to obtain similar data to support the lack of harm from restrictive transfusion practices. Many physicians may be reluctant to forego transfusions until such studies are performed and provide evidence to support a shift from local liberal transfusion strategies. Some hospitals are working to drive down inappropriate plasma use. A single-center implemented an electronic alert for plasma orders for INR levels below 1.7 and found an overall decrease in plasma use by 17% and a reduction in use in patients with borderline INR levels (114). Similarly, another center focused their quality improvement initiative in an intensive care unit with an education and feedback initiative and reduced inappropriate use from 60% to 46% of plasma transfusions (115).

It is important to note some of the limitations of this review. First, we excluded patients undergoing procedures in the operating room. Second, we could not detail the results of every small to medium sized retrospective study on bleeding rates after procedures and have focused this review on the largest and most comprehensive reports. In addition, we did not provide a review of every single procedure performed by interventional radiologists or bedside clinicians. Lastly, we did not include a discussion regarding the management of patients on anticoagulants but did include some of these reports as evidence to support a restrictive transfusion strategy (i.e., studies detailing consecutive procedures performed on patients on full dose anticoagulants without significant bleeding risk).

We have identified some potential gaps in the evidence base that would allay physician concerns regarding

unacceptable bleeding risk leading to continued use of pre-procedure transfusions. Larger observational studies are needed for high-risk procedures to understand if adherence to a platelet count of  $50 \times 10^9/L$  or higher and INR less than 1.5 to 1.8 is warranted. Active surveillance studies to detail the transfusion complications associated with these pre-procedure transfusions are needed to provide clarity on the risk-benefit balance since most of the reports detailed above only looked for the potential benefit of transfusions (reduced bleeding risk) but not harm (transfusion reactions). Audits of clinical practice would be of assistance for understanding the gap between the SIR guidelines and current practice (1). Lastly, research on the optimal laboratory testing strategy for patients undergoing procedures, particularly for patients with cirrhosis, is needed. Two randomized trials of thromboelastography (TEG) guided pre-procedure assessment, as compared to conventional laboratory testing (platelet count and INR), have been performed (116,117). The first trial randomized 60 patients with cirrhosis going for low and high-risk procedures to either a TEG guided transfusion protocol *vs.* standard laboratory testing (116). The TEG-guided patients were less likely to be transfused (100% *vs.* 17%) and had no increased risk of bleeding complications (one patient in the standard of care arm experienced bleeding). In the second trial, 58 patients with cirrhosis undergoing high-risk liver related procedures were randomized to TEG *vs.* standard of care lab testing (117). Similar to the first study, the TEG-guided patients had lower transfusion rates (100% *vs.* 31%) without an increase in the bleeding risk (no bleeding complications in either arm). Certainly, larger studies need to be performed to validate if whole-blood viscoelastic blood testing is superior to conventional laboratory testing; but these studies raise the concern that current thresholds for transfusion may be higher than medically justified.

In conclusion, the liberal use of blood products for the correction of abnormal laboratory values prior to invasive procedures has been an unquestioned medical practice for generations of physicians. The numerous large retrospective studies detailed in this review strongly support the restrictive use of blood products, with adherence to the 2019 SIR guidelines (1). Many studies also suggest that these guidelines may be too liberal and thus exposing patients unnecessarily to the risk of blood products and that this approach is costly to healthcare systems. Because it is impractical to perform large, randomized trials to answer these questions (rare event rate and risk of exposing liberally transfused arm patients to blood products), additional

clarity is likely to come in the form of large, multicenter observational studies.

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