Title

Management of coagulopathy among patients with cirrhosis undergoing upper endoscopy and paracentesis: Persistent gaps and areas of consensus in a multispecialty Delphi

Journal

Hepatology, 80(2)

ISSN

0270-9139

Authors

Tapper, Elliot B

Warner, Matthew A

Shah, Rajesh P

et al.

Publication Date

2024-08-01

DOI

10.1097/hep.0000000000000856

Peer reviewed

Published in final edited form as:

Hepatology. 2024 August 01; 80(2): 488–499. doi:10.1097/HEP.0000000000000856.

Management of coagulopathy among patients with cirrhosis undergoing upper endoscopy and paracentesis: persistent gaps and areas of consensus in a multispecialty Delphi

Elliot B. Tapper, MD[1], **Matthew A. Warner, MD**[2], **Rajesh P. Shah, MD**[3], **Juliet Emamaullee, MD**[4], **Nancy M. Dunbar, MD**[5], **Michelle Sholzberg, MDCM MSc**[6], **Jacqueline N. Poston, MD**[7,8], **Robin J. Soto, NP**[9], **Ammar Sarwar, MD**[10], **Anjana Pillai, MD**[11], **Karina Reyner, MD**[12], **Shivang Mehta, MD**[13], **Marwan Ghabril, MD**[14], **Timothy R. Morgan, MD**[15], **Stephen Caldwell, MD**[16]

[1]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan, USA

[2]Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, Minnesota, USA

[3]Section of Radiology – Veterans Affairs Palo Alto Health Care System, Department of Radiology, Stanford University, Stanford, California, USA

[4]Department of Surgery, Keck Medicine of USC/Children's Hospital-Los Angeles, Los Angeles, California, USA

[5]Department of Pathology and Laboratory Medicine and Department of Medicine, Geisel School of Medicine at Dartmouth, Hanover, New Hampshire, USA

[6]Departments of Medicine and Laboratory Medicine and Pathobiology, St. Michael's Hospital, Li Ka Shing Knowledge Institute, University of Toronto, Toronto, Ontario, Canada

[7]Division of Hematology/Oncology, Department of Medicine, Larner College of Medicine at the University of Vermont, Burlington, Vermont, USA.

[8]Division of Clinical Pathology, Department of Pathology, Larner College of Medicine at the University of Vermont, Burlington, Vermont, USA

[9]Division of Gastroenterology and Hepatology, UC San Diego Health, San Diego, California, USA

[10]Department of Radiology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

[11]Division of Gastroenterology, Hepatology and Nutrition, University of Chicago Medicine, Chicago, Illinois, USA

[12]Department of Emergency Medicine, Baylor Scott and White, Dallas, Texas, USA

[13]Division of Transplant Hepatology, Baylor Scott and White, Fort Worth, Texas, USA

Correspondence: Elliot Tapper, MD, 1500 E Medical Center Dr, Ann Arbor, MI 48109, USA. etapper@umich.edu.

AUTHOR CONTRIBUTIONS

Concept, writing, and guarantor: Elliot B. Tapper. *Design:* Practice Measures Committee of AASLD (Elliot B. Tapper, Marwan Ghabril, Timothy R. Morgan, Shivang Mehta). *Delphi and revision:* remaining authors.

[14]Division of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, IN, USA

[15]VA Long Beach Healthcare System – Section of Gastroenterology. Long Beach, California, USA

[16]Division of Gastroenterology, University of Virginia, Charlottesville, Virginia, USA

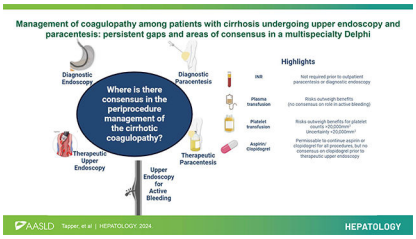
Abstract

Background and Aims: Patients with cirrhosis have abnormal coagulation indices such as a high international normalized ratio (INR) and low platelet count, but these do not correlate well with peri-procedure bleeding risk. We sought to develop consensus among the multiple stakeholders in cirrhosis care to inform process measures that can help improve the quality of the peri-procedure management of coagulopathy in cirrhosis.

Approach and Results: We identified candidate process measures for peri-procedure coagulopathy management in multiple contexts relating to the performance of paracentesis and upper endoscopy. An 11-member panel with content expertise was convened. It included nominees from professional societies for interventional radiology, transfusion medicine, and anesthesia as well as representatives from hematology, emergency medicine, transplant surgery, and community practice. Each measure was evaluated for agreement using a modified Delphi approach (3 rounds of rating) to define the final set of measures. Out of 286 possible measures, 33 measures made the final set. INR testing was not required for diagnostic or therapeutic paracentesis as well as diagnostic endoscopy. Plasma transfusion should be avoided for all paracenteses and diagnostic endoscopy. No consensus was achieved for these items in therapeutic intent or emergent endoscopy. The risks of prophylactic platelet transfusions exceed their benefits for outpatient diagnostic paracentesis and when platelet counts > 20,000/mm^3. It is uncertain whether risks outweigh benefits below 20,000/mm^3 in other contexts. No consensus was achieved on whether it was permissible to continue or stop systemic anticoagulation. Continuous aspirin was permissible for each procedure. Clopidogrel was permissible for diagnostic and therapeutic paracentesis and diagnostic endoscopy.

Conclusions: We found many areas of consensus that may serve as a foundation for a common set of practice metrics for the peri-procedure management of coagulopathy in cirrhosis.

Graphical Abstract: Central Illustration of Consensus Measures



Keywords

liver disease; plasma; platelets; paracentesis; endoscopy

INTRODUCTION

Regulation of hemostasis in patients with cirrhosis is complex.[1] There is a “rebalancing” of *in vivo* hemostatic function despite abnormal laboratory values such as the international normalized ratio (INR) and platelet counts.[2,3] As such, neither INR nor platelet count accurately predicts bleeding risk in patients with cirrhosis.[4,5] Reliance on the results of these tests may lead to overutilization of prophylactic blood components and products in patients with cirrhosis undergoing procedures.[6,7] Concerns regarding the risk of volume overload, worsening portal hypertension,[8] possible worsened hemostatic function,[9] and transfusion reactions have led to efforts to reduce unnecessary transfusions by multiple professional societies. The American Association for the Study of Liver Diseases (AASLD),[10] American Gastroenterology Association (AGA),[,11] European Association for the Study of Liver Disease,[] Society for Interventional Radiology (SIR),[] and International Society on Thrombosis and Haemostasis (ISTH)[] have all released guidance recommending against evaluation or correction of INR or platelet count prior to low-risk procedures such as paracentesis or upper endoscopy (with or without band ligation for varices) (Table 1). There persists, however, a major gap in clinical practice because patients with cirrhosis continue to be transfused with blood components and products prior to invasive procedures in order to “correct” their abnormal test results: 1 in 3 hospitalized patients with cirrhosis receives a plasma transfusion,[] 70% of which are for pre-procedure prophylaxis.[]

To fill this knowledge-to-action gap, the AASLD Practice Metrics Committee (PMC) organized a multispecialty panel of experts with official representation from SIR, Association for the Advancement of Blood & Biotherapies (AABB), and American Society of Anesthesiologists (ASA) along with representatives from hematology, community practice, emergency medicine, and transplant surgery. We aimed to convene multiple stakeholders across disciplines and practice settings to address these gaps and develop consensus statements that could be operationalized as process measures. Process measures are needed to track and reduce unnecessary, ineffective, and potentially harmful prophylactic measures.

METHODS

Identification of the candidate measures set

We followed similar methodology to the prior approach of the AASLD PMC in developing quality measures in cirrhosis.[17,18] The PMC members formed a self-nominated 5-person working group from US academic centers and without conflicts of interest (as examined by the AASLD governing board). The working group convened through monthly conference calls between July 2020 and September 2021. The working group identified candidate measures based on a review of published clinical practice guidelines.[] Following an iterative process, the measures were focused on common procedures performed on these patients, especially paracentesis and upper endoscopy, in a variety of settings. We focused on the relatively low-risk procedures from Table 1 because they were the most common, involved the most stakeholders, and would allow for simplification of the survey. All items were phrased as declarative statements for which the Delphi panel experts would rate using a 5-point Likert scale from Strongly Disagree to Strongly Agree.

Scenarios

1. Diagnostic endoscopy: **The primary intention** of this procedure is diagnostic, meaning that we could be screening for varices, other gastrointestinal conditions, or a cause of abdominal symptoms. This procedure may involve mucosal biopsies. The patient may or may not have had a prior endoscopy.
2. Endoscopy with intent to treat varices: The patient is not actively bleeding. **The primary intention** of this procedure is to apply bands to esophageal varices to prevent variceal bleeding.
3. Bleeding endoscopy: In this scenario, the goal is to manage acute gastrointestinal hemorrhage in a patient with cirrhosis presenting with melena, hematemesis, and/or anemia. **The primary intention** of this procedure is to determine the source of suspected bleeding and address it. The most likely pretest explanation is bleeding esophageal varices.
4. Diagnostic paracentesis: **The primary intention** of this procedure is to determine the cause or nature of the ascites. The procedure is considered clinically important, namely, to diagnose spontaneous bacterial peritonitis (a life-threatening condition) or the cause of the ascites. The procedure can be performed without an incision through a small-bore needle.
5. Therapeutic paracentesis: **The primary intention** of this procedure is to provide immediate relief from symptomatic ascites and generally requires a very small incision but a larger caliber cannula.

Preliminary item set

The first survey presented to the Delphi panel of experts consisted of 286 items (**Supporting Information**). Each scenario was addressed by items that examined the role of the INR and platelet count prior to the procedure for in- and outpatient settings and for patients with compensated and decompensated cirrhosis. We used the term “decompensated” in place of the Child-Pugh-Turcotte classification to indicate a higher severity of underlying illness. To simplify the survey, we used the inpatient context to specify acute illness without specifying frequent conditions such as infection and renal injury. Transfusion decision-making was queried in a binary manner and further examined by providing items for a range of thresholds for INR and platelet count. Assessments were solicited regarding use of thrombopoietin receptor agonists, viscoelastic testing (e.g., thromboelastography, rotational thromboelastometry), timing of antiplatelet agent (aspirin, clopidogrel) use, and timing of systemic oral anticoagulant (coumadin, direct oral anticoagulants [DOACs], enoxaparin) use. For the cases of paracentesis, we also asked if the considerations would apply to patients requiring thoracentesis.

Delphi panel selection

The goal was to select a panel that was strengthened by the participant expertise, nomination by professional societies, and size ≥10 participants (which has been shown to produce validity equivalent to larger panels).[] Leadership of SIR, ASA, AHA, and AABB each appointed one expert to join the panel. Additional representatives were invited

by AASLD who represented interventional hepatology, community hepatology practice, advanced practice providers focused on liver care, transplant surgery, transplant hepatology, hematology, transfusion medicine, and emergency medicine. Any financial conflicts of interest were declared by participants and submitted to and evaluated by AASLD staff to ensure that >50% of the panel lacked any financial conflicts. A total of 11 experts participated.

Delphi activities

The candidate measures underwent a 3-round modified Delphi method to identify the final set of measures based on the consensus of the expert panel.[] In the first round, each expert rated their agreement with each candidate measure individually. Consensus was defined as ≥75% agreement without extreme variation (<2 dissenting votes required for consensus). In the second round, measures were reevaluated for rephrasing and again rated through an equally weighted vote. All experts had the opportunity to modify the measures focusing on editing of suboptimally worded measures for accuracy by consensus, deletion of measures that were deemed problematic or irrelevant by consensus, and identification of additional measures not identified and included in the list of measures that they reviewed. In a third round, measures that were identified for re-vote and rewording by the experts were rated through an equally weighted vote. Experts were also asked to enumerate priorities for research from a review of the measures without consensus. Because the coronavirus pandemic and time zone differences reduced expert availability, a face-to-face meeting was deferred, and each round took place over multiple iterative surveys with each member having the opportunity to rewrite measures for re-voting. The process occurred from October 2021 to May 2022.

RESULTS

All consensus statements are summarized in Table 2, along with discussion in the context of each of the 5 procedure scenarios relating to upper endoscopy and paracentesis. Items not reaching consensus are summarized in Table 3. The main messages are underscored in a summary in Table 4. Finally, the items proposed by the experts for further research are summarized in Table 5.

Diagnostic endoscopy

For upper endoscopies with diagnostic intent, the panelists achieved consensus on 7 measures. For all patients, panelists formed consensus that INR values were not required prior to endoscopy and that risks of prophylactic plasma transfusions outweighed the benefits for all patients with cirrhosis. Similarly, process measures were formed by consensus to forgo pre-procedure platelet counts and platelet transfusions for patients with compensated cirrhosis. For those with decompensated cirrhosis, a process measure to avoid prophylactic platelet transfusions was formed because the risks were felt to outweigh benefits, especially for patients with preprocedural platelet counts >20,000/mm^3. At platelet counts above >20,000/mm^3, there was agreement regarding the lack of benefit of transfusion, but below 20,000/mm^3, there was not a recommendation for transfusion but uncertainty whether the risks outweighed the benefits. Continuation of aspirin and

clopidogrel is permissible, but no consensus formed regarding continuation of anticoagulant use. No consensus was reached regarding process measures on the role of thrombopoietin agonists and viscoelastic testing.

Upper endoscopy with intent to treat varices

For upper endoscopies with the intent to treat varices, consensus formed for 5 measures. For all patients, process measures to avoid prophylactic plasma transfusions were developed because the risks were felt to outweigh benefits. A process measure to avoid prophylactic platelet transfusions was formed because the risks were felt to outweigh benefits for all patients with preprocedural platelet counts >20,000/mm^3. At platelet counts above >20,000/mm^3, there was agreement regarding the lack of benefit of transfusion, but below 20,000/mm^3, there was not a recommendation for transfusion but uncertainty whether risks outweighed benefits. Continuation of aspirin is permissible. No consensus was achieved regarding process measures for preprocedural coagulation testing (INR, platelet counts, or viscoelastic tests), clopidogrel use, or anticoagulant use. The role of INR or platelet count testing despite consensus regarding the disutility of transfusions was related to the potential role played by these tests as markers of disease severity and their value in assessing the trajectory of the patient's disease course.

Endoscopy for gastrointestinal bleeding

Two measures met consensus for the management of coagulopathy in the patients with active gastrointestinal hemorrhage. These included that the INR should not be used in isolation to guide plasma transfusion and that platelet transfusions were felt to increase risks without benefits for all patients with platelet counts >20,000/mm^3.

Diagnostic paracentesis

Ten measures met consensus agreement. These included process measures for forgoing preprocedural INR testing in all settings and that the risks of prophylactic plasma transfusion outweigh benefits. For outpatients, process measures were agreed upon for forgoing platelet count testing prior to diagnostic paracentesis and avoiding platelet transfusions because the risks of platelet transfusion outweigh potential benefits. For inpatients, no consensus was reached regarding a measure for preprocedural platelet count assessment. A measure to avoid prophylactic platelet transfusions was agreed upon for patients with platelet counts >20,000/mm^3 because they were felt to increase risks without benefits. Although there was no consensus on the risk/benefit ratio for patients with lower platelet counts, there was uncertainty and concern that other extrahepatic processes could be at play. There was consensus regarding the permissibility of performing the procedure for patients taking aspirin or clopidogrel (but no consensus regarding anticoagulant use such as DOACs and warfarin). Although there was consensus that viscoelastic testing should not play a role prior to the procedure in outpatients, there was no consensus regarding its role among inpatients. Finally, the experts did not reach consensus that similar statements could be applied to diagnostic thoracenteses.

Therapeutic paracentesis

The panel formed consensus on 9 measures regarding the performance of therapeutic paracentesis. First, a process measure to forgo preprocedural INR testing was agreed upon for outpatients but not inpatients. As discussed previously, the lack of consensus regarding testing related not to the role in indicating the need for transfusion but to the role played by these tests as markers of disease severity (e.g., Model for End-Stage Liver Disease [MELD] score). Second, process measures supporting forgoing plasma transfusion for all patients were agreed upon given that the risks of prophylactic plasma transfusion were felt to outweigh the benefits. Third, there was no role for preprocedural viscoelastic testing for outpatients, but a similar consensus was not reached for inpatients. Fourth, no consensus was reached regarding pre-procedure platelet testing process measures, but measures supporting avoiding prophylactic platelet transfusions were agreed upon for patients with platelet counts >20,000/mm^3 because they were felt to increase risks without benefits. Finally, it was felt to be permissible to perform therapeutic paracentesis for patients taking both aspirin and clopidogrel, but no consensus was reached regarding systemic anticoagulation.

Research frontiers

After reviewing the items without consensus, the panel compiled a list of 7 proposed research priorities. First, they advocated for research regarding better diagnostic tests to assess hemostasis and bleeding risk with endoscopy and paracenteses. This included better defining the role of viscoelastic testing in blood product stewardship and its impact on clinical outcomes, preferably through randomized trials and investigation of more practical test interpretation. Second, data to inform deliberate transfusion strategies for active variceal hemorrhage were identified as an important management gap. This may include evaluation of ratio-based or point-of-care viscoelastic testing-guided blood component transfusion strategies and the incorporation of transfusion alternatives such as factor and fibrinogen concentrates into massive hemorrhage scenarios. Third, platelet transfusion thresholds for patients with renal dysfunction are unclear given the qualitative defects in platelet function caused by uremia. Fourth, the role of thrombopoietin receptor agonists was felt to be unclear until data demonstrating improved clinical outcomes became available. Fifth, prospective data demonstrating the outcomes associated with uninterrupted DOAC or enoxaparin use for patients undergoing procedures like paracentesis and band ligation are uncertain, and more data are needed. Sixth, more data on the peri-procedure risk of bleeding and risk-mitigation strategies for thoracentesis are needed. Finally, large prospective data are needed to inform the personalized risk of periprocedural bleeding risk.

DISCUSSION

Procedures such as paracentesis to manage ascites and endoscopy to manage esophageal varices are important and frequent reasons for health care encounters for patients with cirrhosis. The goal of guideline statements from AASLD, AGA, SIR, and ISTH is to provide evidence-based recommendations regarding what is known about the risks and benefits of blood product use prior to common procedures and summarize the data regarding the ability of INR or platelet count testing for predicting periprocedural hemorrhage. The disutility of pre-procedure transfusions and testing can be inferred from these guidelines but

contrasts with clinical practice. Transfusions are frequently used, and pre-procedure testing is often required.[15,16] This contrast poses a challenge for translating the guidelines to process measures for quality assurance. Understanding the context-dependent considerations that influence clinical decision-making from stakeholders involved in the peri-procedure management of patients with cirrhosis is essential in forming consensus. We convened a multi-society panel to provide consensus on context-specific process measures that help operationalize guideline statements.

The value of multispecialty consensus

Our process measure set helps advance the goals of AASLD/AGA/ISTH/SIR guidelines in 3 ways. First, we convened multiple stakeholders in periprocedural care whose specialties lack similar guidelines. Second, our process measures help provide specificity to guideline statements by enumerating multiple clinical contexts—compensated/decompensated; outpatient/inpatient; and diagnostic/therapeutic intent. Whereas guidelines do not recommend *routine* use of coagulation testing or transfusions, our process measures specify clinical scenarios for direct interpretation by providers. Third, we address what is likely a common, if implicit, concern from providers who choose not to follow guidelines because of perceptions of medical liability relating to bleeding risk. This multispecialty consensus reinforces the growing body of knowledge regarding the rebalanced hemostasis of cirrhosis.[] If quality metrics favoring transfusion restriction are established, they could be used to reduce fears that omitting tests and transfusions is a legal liability. By framing transfusions as posing more risk than benefit in multiple contexts, we draw attention to the data that blood product transfusions carry potential harms such as transfusion-associated circulatory overload,[] worsened hemostatic function,[9] transfusion reactions, and exacerbated portal hypertension.[9] These complications may carry liability, necessitating careful documentation of thoughtful consideration.

Coagulation testing

Society guidance (Table 1) specifies that INR and platelet count testing should not be routinely performed prior to low-risk procedures. In line with these recommendations, there are no situations in which the panel felt that INR and platelet count determination were *required* prior to a procedure. However, in contexts in which consensus could not be achieved regarding testing of INR (upper endoscopy with intent to treat varices or active bleeding) or platelet count (patients with decompensated cirrhosis or varices requiring therapy), reasons given were that these tests provided data regarding severity and trajectory of disease. Because they are widely used for this purpose (e.g., MELD score), process measures to forgo testing may not be feasible. The INR or platelet count was not advocated to be considered as a measure of bleeding risk in isolation, but the panel members felt they could supplement other factors such as blood volume loss, value trajectory (as used to diagnose disorders of disseminated coagulation), and the presence of mucosal bleeding.

The complex interaction between subspecialty tradition, context-specific factors, and platelet function may explain why consensus could not be achieved for process measures relating to platelet testing outside of diagnostic paracentesis and endoscopy (in patients with compensated cirrhosis). This may also explain why therapeutic paracentesis, which

involves a small incision, is viewed differently from diagnostic paracentesis. Additionally, the panel suggested additional research to determine the impact of renal dysfunction on platelet function at multiple thresholds in patients with cirrhosis. Label indications for thrombopoietin agonists, such as platelets <50,000/mm^3, are not associated with bleeding risk from the procedures studied, and this may be why there was no consensus on the use of these agents. Viscoelastic testing is a tool often proposed to help reduce prophylactic transfusions. It is felt to offer more information about coagulation function than INR and platelet counts alone (or in combination). Viscoelastic testing can safely reduce plasma utilization in the management of gastrointestinal hemorrhage.[] In the context of liver transplantation in which coagulation function is dynamic, viscoelastic testing is recommended by the American Society for Transplantation to assess factors such as fibrinolysis and reduce unnecessary transfusions.[] Our panel felt that viscoelastic testing does not play a role for diagnostic paracentesis or outpatient therapeutic paracentesis but did not arrive at consensus for process measures relating to viscoelastic testing in other contexts.

Transfusions

Consistent with guideline recommendations, there was no context in which process measures supporting prophylactic plasma transfusions were endorsed. Furthermore, process measures indicating that plasma transfusions should be avoided were endorsed for all paracentesis procedures and diagnostic endoscopies. No consensus was achieved for endoscopies intending to ligate varices or those for hemorrhage, which reflects the variance in contemporary practice. Many centers may be able to reduce or eliminate prophylactic plasma transfusions, but the lack of consensus for a process measure in this instance may reflect the need for continuing efforts to achieve consensus through local stakeholder engagement, agreements, and policies. Process measures were endorsed to avoid prophylactic platelet transfusions for all patients with platelet counts >20,000/mm^3 and without consideration of platelet counts prior to outpatient diagnostic paracentesis and diagnostic endoscopy in patients with compensated cirrhosis. The consensus was not that platelets should be transfused below 20,000/mm^3 but rather that there was uncertainty regarding the risk-benefit balance at this point. These process measures do not supplant society guidance but inform quality metric measurement by establishing which patients could be excluded from the denominator for metric adherence.

Antiplatelets and anticoagulants

Consensus was reached to establish process measures for continuing aspirin for all procedures and clopidogrel for all paracenteses and diagnostic endoscopy. No consensus was reached on whether systemic anticoagulants should be held or discontinued because this was identified as an important research frontier.

Setting the research agenda

Despite being a common feature of everyday clinical care, the optimal management of patients with cirrhosis and periprocedural bleeding risk receives limited research focus, resulting in confusion and practice variance. By leveraging a multidisciplinary panel of active and experienced clinicians, we aimed to provide a framework of meaningful research questions and strategies for researchers. Tools to provide personalized periprocedural risk

assessment that incorporate hemostatic factors, renal function, and viscoelastic testing should be prioritized, particularly in studies that examine clinical endpoints. Finally, experts highlighted the need for prospective and preferably randomized data regarding the impact of uninterrupted systemic anticoagulants and the potential role of thrombopoietin receptor agonists. Beyond these ideas, it is clear from the proceedings that additional efforts are needed to bridge gaps in the management of low-risk procedures before addressing those for high-risk procedures (Table 2).

Development of process measures

This multispecialty analysis will be helpful in crafting and selecting process measures for the peri-procedure management of patients with cirrhosis in 3 main ways. First, process measures for team-based care require broad endorsement. Whereas cirrhosis guidelines can be converted into process measures with a narrower stakeholder group,[] measures based on liver cancer guidelines required a larger group (involving radiologists and palliative care clinicians, for example),[18] and periprocedural bleeding risk management required an even broader coalition of providers. Second, whereas general cirrhosis care–focused measures required prioritization based on importance and gap, the unmet need in periprocedural bleeding risk management was not prioritization but agreement. Efforts to impose practice metrics would have been premature without first developing areas of consensus with the multiple stakeholders. By determining the contextual limitations on agreement, we can use the proceedings of this consensus to delineate the areas where process measures will be effective and to define the population denominators from which data should be collected (e.g., inpatient vs. outpatient procedures). This work aids that of groups crafting process measures, such as the Cirrhosis Quality Collaborative, by defining the inclusions and exclusions for any metric. Third, it is clear from these proceedings that process measures amenable to broad support include those limiting use of prophylactic plasma and prophylactic platelet transfusions (particularly for people with >20,000 mm^3 platelet counts) and requiring pre-procedure lab testing in multiple contexts.

CONCLUSION

Many professional societies have provided guidance on the periprocedural management of coagulopathy in cirrhosis, but the use of prophylactic measures remains variable at this time. To address the persistent gaps between principle and practice, we assembled a multi-society panel of experts. The panel agreed upon multiple areas where process measures that operationalize the guideline recommendations in several common clinical contexts can be considered. Where gaps remain, research proposals required to advance the field have been proposed.

Funding information

Funding for this Delphi panel was provided by the American Association for the Study of Liver Diseases. Elliot B. Tapper receives funding from the National Institutes of Health through NIDDK (1K23DK117055, U01DK130113). Matthew A. Warner receives funding from the National Institutes of Health through NHLBI (K23HL153310). Juliet Emamaullee received funding from the National Cancer Institute and the Children's Heart Foundation.

CONFLICT OF INTEREST STATEMENT

All conflicts were examined and resolved by the AASLD prior to Delphi participation. Elliot B. Tapper has served as a consultant to Novartis, Axcella, and Allergan; has served on advisory boards for Mallinckrodt, Bausch Health, Kaleido, and Novo Nordisk; and has received unrestricted research grants from Gilead and Valeant. Timothy R. Morgan received funding for clinical trials from AbbVie, Merck, Gilead, and Genfit. Marwan Ghabril has served as a consultant for PTC Therapeutics, CymaBay, BioCryst, and Zydus Therapeutics. He has received grants paid to his institution from Bausch/Salix. Matthew A. Warner serves (unpaid, volunteer) on the Patient Blood Management committee of the American Society of Anesthesiologists (ASA) and on the board of directors for the Society for the Advancement of Patient Blood Management (SABM). Michelle Sholzberg has received honoraria for advisory board work for Octapharma, Takeda, Novo Nordisk, Bayer, Roche, and Pfizer, and she has received unrestricted research funding from Takeda, Amgen, and Pfizer. Anjana Pillai serves on the data safety monitoring board for Exelixis, Eisai, AstraZeneca, Genentech/Roche, and Replimune.Nancy M. Dunbar is on the medical advisory board for Verax Biomedical. Rajesh P. Shah has served as a consultant to Artio Medical, Genentech/Roche, Intuitive Surgical, and HistoSonics and receives funding for clinical trials from Lucence Health and Canon. Jacqueline N. Poston is a consultant for TeraImmune. Stephen Caldwell has received grants paid to his institution from Cour, Exact, Galectin, Ipsen, Mallinckrodt, Target, Zydus, Genfit, Gilead, Madrigal, Inventiva, AstraZeneca, Ultragenyx, and royalties from Avanos. The remaining authors have no conflicts to report.

Abbreviations:

AASLD	American Association for the Study of Liver Diseases
AGA	American Gastroenterology Association
DOAC	direct oral anticoagulant
INR	international normalized ratio
ISTH	International Society on Thrombosis and Haemostasis
SIR	Society for Interventional Radiology

References

1. Caldwell SH, Hoffman M, Lisman T, et al. Coagulation disorders and hemostasis in liver disease: pathophysiology and critical assessment of current management. Hepatology 2006;44(4):1039 [PubMed: 17006940]
2. Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. Blood 2010;116(6):87885.
3. Blasi A, Beltran J, Pereira A, et al. An assessment of thromboelastometry to monitor blood coagulation and guide transfusion support in liver transplantation. Transfusion 2012;52(9):198998.
4. Northup PG, Caldwell SH. Coagulation in liver disease: a guide for the clinician. Clin Gastroenterol Hepatol. 2013;11(9):106474.
5. O'Leary JG, Greenberg CS, Patton HM, Caldwell AGA Clinical Practice update: coagulation in cirrhosis. Gastroenterology 2019;157(1):3443.e1.
6. Intagliata NM, Henry ZH, Shah N, Lisman T, Caldwell SH, Northup Prophylactic anticoagulation for venous thromboembolism in hospitalized cirrhosis patients is not associated with high rates of gastrointestinal bleeding. Liver Int. 2014;34(1):2632.
7. Northup PG, McMahon MM, Ruhl AP, et al. Coagulopathy does not fully protect hospitalized cirrhosis patients from peripheral venous thromboembolism. Am J Gastroenterol. 2006;101(7):15248; quiz 1680.
8. Zimmon DS, Kessler RE. The portal pressure-blood volume relationship in cirrhosis. Gut 1974;15(2):99101.
9. Rassi AB, d'Amico EA, Tripodi A, et al. Fresh frozen plasma transfusion in patients with cirrhosis and coagulopathy: Effect on conventional coagulation tests and thrombomodulin-modified thrombin generation. J Hepatol. 2020;72(1):8594.

10. Northup PG, Garcia-Pagan JC, Garcia-Tsao G, et al. Vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2021;73(1):366413.
11. O'Shea RS, Davitkov P, Ko CW, et al. AGA Clinical Practice Guideline on the management of coagulation disorders in patients with cirrhosis. Gastroenterology 2021;161(5):1615e1. [PubMed: 34579936]
12. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis. J Hepatol. 2022;76(5):1151 [PubMed: 35300861]
13. Roberts LN, Lisman T, Stanworth S, et al. Periprocedural management of abnormal coagulation parameters and thrombocytopenia in patients with cirrhosis: guidance from the SSC of the ISTH. J Thromb Haemost. 2022;20(1):3947.
14. Patel IJ, Rahim S, Davidson JC, et al. Society of Interventional Radiology consensus guidelines for the periprocedural management of thrombotic and bleeding risk in patients undergoing percutaneous image-guided interventions-part II: recommendations: endorsed by the Canadian Association for Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe. J Vasc Interv Radiol. 2019;30(8):1168.e1. [PubMed: 31229333]
15. Desborough MJ, Hockley B, Sekhar M, et al. Patterns of blood component use in cirrhosis: a nationwide study. 2016;36(4):522
16. Lu Y, Sun G, Liu X, et al. Plasma transfusion in patients with cirrhosis in China: a retrospective multicenter cohort study. 2017;31(2):107
17. Kanwal F, Tapper EB, Ho C, et al. Development of quality measures in cirrhosis by the Practice Metrics Committee of the American Association for the Study of Liver Diseases. Hepatology 2019;69(4):1787 [PubMed: 30586188]
18. Asrani SK, Ghabril MS, Kuo A, et al. Quality measures in HCC care by the Practice Metrics Committee of the American Association for the Study of Liver Diseases. Hepatology;75(5):1289–99.
19. Lynn MR. Determination and quantification of content validity. Res. 1986;35(6):382–5.
20. Fitch K, Bernstein SJ, Aguilar MD, et al. The RAND/UCLA appropriateness method user's manual RAND
21. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. 2011;365(2):147
22. Piccin A, Spizzo G, Popovski MA, et al. Transfusion-associated circulatory overload in gastroenterology. Blood Transfus. 2021;19(3):197204.
23. Shenoy A, Louissaint J, Shannon C, Tapper EB, Lok Viscoelastic testing prior to non-surgical procedures reduces blood product use without increasing bleeding risk in cirrhosis. Dig Dis Sci. 2022;67(11):5290–9. [PubMed: 35122595]
24. Pillai AA, Kriss M, Al-Adra DP, et al. Coagulopathy and hemostasis management in patients undergoing liver transplantation: defining a dynamic spectrum across phases of care. Liver Transpl. 2022;28(10):1651–63. [PubMed: 35253365]

- This document is endorsed by the American Society of Transplantation, AST
- This document is endorsed by the Society of Interventional Radiology, SIR
- The American Society of Anesthesiologist, ASA, affirms the value of this document.

TABLE 1

Summary of guideline recommendations.

	Factor	American Association for the Study of Liver Diseases[10]	American Gastroenterology Association[,11]	Society for Interventional Radiology[]	International Society on Thrombosis and Haemostasis[]
Low risk (Paracentesis, endoscopy, band ligation)	INR	Do not use to gauge risk, do not correct	Test not routinely recommended; do not correct	Test not routinely recommended	Do not evaluate
	Platelet count	Do not routinely correct	Test not routinely recommended; do not correct	Test not routinely recommended	Do not correct
High risk * (e.g. Liver biopsy)	INR	Do not use to gauge risk, do not correct	Do not routinely correct	Correct INR to <2.5 **	Do not evaluate
	Platelet count	Do not routinely correct	Correct platelet to<50,000/mm^3	Correct platelet to <50,000/mm^3 **	Do not correct

Abbreviation: INR = international normalized ratio.

* High risk procedures are specialty specific. For example, polypectomy is referred to in gastroenterology guidance but not radiology.

** These recommendations apply to high risk procedures performed by interventional radiologists such as liver biopsy

TABLE 2

Consensus statements.

Diagnostic endoscopy	Agreement
It is permissible to perform a diagnostic endoscopy without checking the INR prior to the procedure in patients with compensated cirrhosis.	91%
It is permissible to perform a diagnostic endoscopy without checking the INR prior to the procedure in patients with decompensated cirrhosis.	82%
For patients with decompensated cirrhosis who are undergoing diagnostic endoscopy, the risks of plasma transfusion outweigh the benefits.	91%
It is permissible to perform a diagnostic endoscopy without checking the platelet count prior to the procedure in patients with compensated cirrhosis.	100%
The platelet count threshold below which the benefits of prophylactic platelet transfusion may outweigh the risks for patients with decompensated cirrhosis is <20,000/mm^3.	91%
It is permissible to perform a diagnostic endoscopy for a patient with cirrhosis who is taking aspirin.	91%
It is permissible to perform a diagnostic endoscopy for a patient with cirrhosis who is taking clopidogrel.	91%
Upper endoscopy with intent to treat varices (without active bleeding)	
For patients with compensated cirrhosis who are undergoing therapeutic endoscopy, the risks of plasma transfusion outweigh the benefits.	91%
For patients with decompensated cirrhosis who are undergoing therapeutic endoscopy, the risks of plasma transfusion outweigh the benefits.	91%
The platelet count threshold below which the benefits of prophylactic platelet transfusion may outweigh the risks for patients with compensated cirrhosis undergoing therapeutic endoscopy is <20,000/mm^3.	100%
The platelet count threshold below which the benefits of prophylactic platelet transfusion may outweigh the risks for patients with decompensated cirrhosis undergoing therapeutic endoscopy is <20,000/mm^3.	100%
It is permissible to perform a therapeutic endoscopy for a patient with cirrhosis who is taking aspirin.	82%
Endoscopy for gastrointestinal bleeding	
The INR should not be used in isolation to guide plasma transfusion in patients who are experiencing a gastrointestinal bleed.	100%
The platelet count threshold below which the benefits of platelet transfusion may outweigh the risks for patients with cirrhosis who are bleeding undergoing endoscopy is <20,000/mm^3.	82%
Diagnostic paracentesis	
It is permissible to perform a diagnostic paracentesis without checking the INR prior to diagnostic paracentesis in outpatients.	91%
It is permissible to perform a diagnostic paracentesis without checking the INR prior to diagnostic paracentesis in inpatients.	82%
The risks of plasma transfusion outweigh the benefits in outpatients undergoing diagnostic paracentesis.	91%
The risks of plasma transfusion outweigh the benefits in inpatients undergoing diagnostic paracentesis.	82%
It is permissible to perform a diagnostic paracentesis without checking the platelet count prior to diagnostic paracentesis in outpatients.	82%
The risks of platelet transfusion outweigh the benefits in outpatients undergoing diagnostic paracentesis.	91%
The platelet count threshold below which the benefits of prophylactic platelet transfusion may outweigh the risks for inpatients undergoing diagnostic paracentesis is <20,000/mm^3.	100%
There is no role for viscoelastic testing (e.g., thromboelastography, rotational thromboelastometry) prior to diagnostic paracentesis in outpatients.	91%
It is permissible to perform a diagnostic paracentesis for a patient with cirrhosis who is taking aspirin.	82%
It is permissible to perform a diagnostic paracentesis for a patient with cirrhosis who is taking clopidogrel.	82%
Therapeutic paracentesis	
It is permissible to perform a therapeutic paracentesis without checking the INR prior to the procedure in outpatients.	91%
It is permissible to perform a therapeutic paracentesis without checking the INR prior to the procedure in inpatients.	91%

Diagnostic endoscopy	Agreement
The risks of prophylactic plasma transfusion may outweigh the benefits for outpatients with cirrhosis who are undergoing therapeutic paracentesis.	82%
The risks of prophylactic plasma transfusion may outweigh the benefits for inpatients with cirrhosis who are undergoing therapeutic paracentesis.	91%
There is no role for viscoelastic testing prior to the therapeutic paracentesis in outpatients.	91%
It is permissible to perform a therapeutic paracentesis for a patient with cirrhosis who is taking aspirin.	91%
It is permissible to perform a therapeutic paracentesis for a patient with cirrhosis who is taking clopidogrel.	82%
The platelet count threshold below which the benefits of prophylactic platelet transfusion may outweigh the risks for outpatients undergoing therapeutic paracentesis is 20,000/mm^3.	100%
The platelet count threshold below which the benefits of prophylactic platelet transfusion may outweigh the risks for inpatients undergoing therapeutic paracentesis is 20,000/mm^3.	91%

Abbreviation: INR = international normalized ratio.

TABLE 3

Items without consensus.

Diagnostic endoscopy	Agreement
It is permissible to perform a diagnostic endoscopy in a patient who has recently (≤24 h) taken direct-acting anticoagulants.	45%
The platelet count does not need to be checked prior to the procedure in patients with decompensated cirrhosis.	45%
There is a platelet count threshold below which we should provide thrombopoietin receptor agonists in patients with compensated cirrhosis before the procedure.	9% for 50,000/mm^3 27% for 10,000–30,000/mm^3
There is a platelet count threshold below which we should provide thrombopoietin receptor agonists in patients with decompensated cirrhosis before the procedure.	0% for 40,000–50,000/mm^3 36% for 20,000–30,000/mm^3 54% for 10,000/mm^3
There is no role for viscoelastic testing prior to the procedure in patients with compensated cirrhosis.	45%
There is a role for viscoelastic testing prior to the procedure in patients with decompensated cirrhosis.	54%
It is permissible to perform diagnostic endoscopy if the patient has taken enoxaparin within the past 24 h.	63%
It is permissible to perform a diagnostic endoscopy in a patient who has taken direct-acting anticoagulants within the past 24 h.	54%
It is not permissible to perform a diagnostic endoscopy in a patient who has taken coumadin within the past 24 h.	54%
Upper endoscopy with intent to treat varices	
The INR does not need to be checked prior to the procedure in patients with compensated cirrhosis.	63%
The INR does need to be checked prior to the procedure in patients with decompensated cirrhosis.	54%
There is no role for FFP prior to the procedure in patients with compensated cirrhosis.	72%
There is no role for FFP prior to the procedure in patients with decompensated cirrhosis.	45%
The platelet count does not need to be checked prior to the procedure in patients with compensated cirrhosis.	54%
The platelet count does need to be checked prior to the procedure in patients with decompensated cirrhosis.	72%
It is permissible to perform a therapeutic endoscopy in a patient who has recently (≤48 h) taken clopidogrel.	60%
It is permissible to perform the procedure if the patient has taken enoxaparin within the past 24 h.	45%
It is not permissible to perform a therapeutic endoscopy in a patient who has taken direct-acting anticoagulants within the past 24 h.	72%
There is no role for viscoelastic testing prior to the procedure in patients with compensated cirrhosis.	54%
There is a role for viscoelastic testing prior to the procedure in patients with decompensated cirrhosis.	45%
Endoscopy for gastrointestinal bleeding	
The INR should be checked prior to the procedure.	64%
There is a role for FFP prior to the procedure.	73%
The platelet count should be checked prior to the procedure.	73%
There is a role for viscoelastic testing prior to the procedure.	55%
Diagnostic paracentesis	
It is permissible to perform a therapeutic paracentesis without checking the platelet count prior to the procedure in inpatients.	36%
There is a platelet count threshold below which we should provide thrombopoietin receptor agonists in outpatients or inpatients before the procedure.	9% for 20,000–50,000/mm^3 18% for 10,000/mm^3
It is permissible to perform a diagnostic paracentesis for a patient with cirrhosis who has taken DOAC within ≤24 h.	45%

Diagnostic endoscopy	**Agreement**
It is permissible to perform a diagnostic paracentesis for a patient with cirrhosis who has taken coumadin within ≤24 h.	36%
It is permissible to perform a diagnostic paracentesis for a patient with cirrhosis who has taken enoxaparin within ≤24 h.	45%
The considerations regarding antiplatelet and anticoagulant therapies are the same for those undergoing thoracentesis.	73%
Therapeutic paracentesis	
The platelet count does not need to be checked prior to the procedure in outpatients.	73%
The platelet count should be checked prior to the procedure in inpatients.	55%
There is a platelet count threshold below which we should provide thrombopoietin receptor agonists in outpatients before the procedure.	0% for 50,000/mm^3 9% for 10,000–40,000/mm^3
There is a platelet count threshold below which we should provide thrombopoietin receptor agonists in inpatients before the procedure.	9% for 10,000–50,000/mm^3
There is no role for viscoelastic testing prior to the procedure in inpatients.	55%
It is permissible to perform a diagnostic paracentesis for a patient with cirrhosis who has taken DOAC within ≤24 h.	36%
It is permissible to perform a diagnostic paracentesis for a patient with cirrhosis who has taken coumadin within ≤24 h.	36%
It is permissible to perform a diagnostic paracentesis for a patient with cirrhosis who has taken enoxaparin within ≤24 h.	36%
The considerations regarding antiplatelet and anticoagulant therapies are the same for those undergoing thoracentesis.	64%

Abbreviations: DOAC = direct oral anticoagulant; FFP = fresh frozen plasma; INR = international normalized ratio.

TABLE 4

Summary table.

		A role for laboratory testing prior to procedure?			A role for prophylactic transfusion?		Permissible to continue medications?			
		INR	Platelet count	Viscoelastic testing	Plasma	Platelets	Aspirin	Clopidogrel	Anticoagulants (within 24 h)	
Diagnostic paracentesis	Outpatient	No	No	No	No	No	Yes	Yes	All	
	Inpatient	No		No	No	Uncertainty when <20,000 mm^3				
Therapeutic paracentesis	Outpatient	No		No	No	Uncertainty when <20,000 mm^3	Yes	Yes	All	
	Inpatient	No			No	Uncertainty when <20,000 mm^3				
Diagnostic endoscopy	Compensated	No	No		No	No	Yes	Yes		
	Decompensated	No			No	Uncertainty when <20,000 mm^3				
Upper endoscopy with therapeutic intent	Compensated					Uncertainty when <20,000 mm^3	Yes		DOAC warfarin	Enoxaparin
	Decompensated					Uncertainty when <20,000 mm^3				
Endoscopy for hemorrhage						Uncertainty when <20,000 mm^3	N/A	N/A	N/A	

Note: Consensus is denoted with green color (>75% agreement), yellow indicates that there was 50%–75% agreement, and red indicates that there was <50% agreement on whether to endorse the process measures. All raw data are abstracted from Tables 2 and 3.

TABLE 5

Research priorities.

Defining the role of viscoelastic testing on blood product stewardship and its impact on clinical outcomes
Defining the optimal use of blood products in the management of active variceal hemorrhage
Impact of renal dysfunction on platelet function at multiple thresholds in patients with cirrhosis
Development of patient-specific bleeding risk prediction models and incorporation into clinical practice
Defining the role of thrombopoietin receptor agonists in trials with clinical endpoints
Defining the risks and benefits of uninterrupted systemic periprocedural anticoagulant use
Developing further data on bleeding risk during thoracentesis