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TABLE 1. Definitions of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) to Identify Colonoscopy Adverse Events

ICD-9-CM	Definition	Comments
56983	Perforation of intestine	Nonspecific code. This could be large or small bowel perforation due to many etiologies (colitis, enteritis, etc.)
9982	Accidental puncture or laceration during a procedure, not elsewhere classified	Nonspecific code. This could result from any surgical operation or procedure (eg, hysterectomy, gastrectomy, cystectomy, etc.)
99811	Hemorrhage complicating a procedure	Nonspecific code. This could represent bleeding from any procedure or surgery (eg, pacemaker placement, vascular grafts, colorectal surgery, etc.)
86500, 86501, 86502, 86503, 86504, 86509	Splenic injury	Nonspecific code. This could have been present on admission. Its relation to colonoscopy cannot be ascertained

Therefore, we believe that the validity of the results of the study is severely undermined by the high risk of misclassification bias. Several studies in the field of gastroenterology have tried to link nonspecific diagnosis codes to specific procedures (post-endoscopic retrograde cholangiopancreatography pancreatitis,^{10,11} post-endoscopic retrograde cholangiopancreatography sepsis¹²) using NIS data, with similar methodological flaws as described above. Unfortunately, these research practices appear common. In a study of 120 recent publications utilizing the NIS, Khera et al¹³ found that 54.4% of studies used nonspecific secondary diagnosis codes to infer in-hospital events.

Although we do not recommend that the NIS be used to study procedural complications, there are steps that the authors could perform to clarify the results. Adverse events coded in the principle diagnosis (DX1) should be identified and excluded because these are present on admission and should not count as adverse events. Records with adverse events should be screened for surgeries that could result in adverse events with the same codes and flagged as possible misclassification. In records with adverse events, the timing of colonoscopy in relation to the timing of discharge should be clarified. If the patient was discharged <2 days after the colonoscopy, then these adverse events (especially perforation and splenic injury) are very unlikely related to the colonoscopy. Records with “hemorrhage complicating a procedure,” codes for a diagnostic colonoscopy without biopsy or polypectomy should be identified and excluded because it is unlikely that bleeding occurred as an adverse event of these purely diagnostic colonoscopies. Performing these additional steps in the analysis does not validate the results, but it would at least provide some reassurance and context to the reader.

In summary, the NIS is not an appropriate database to study post-procedural adverse events due to the lack of specificity in the ICD-9 codes. ICD-10

codes, implemented in 2015, appear to be more specific (eg, ICD-10: K91.71—accidental puncture and laceration of a digestive system organ or structure during a digestive system procedure), and may provide a better opportunity to study adverse events. The study by Olaiya and Adler¹ represents a great effort to study adverse events from a colonoscopy, but we strongly question the validity of the results given the methodological concerns mentioned above.

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Interpreting Hemostatic Profiles Assessed With Viscoelastic Tests in Patients With Cirrhosis

To the Editor:

With great interest, I have read the recent paper by Hum et al¹ in *J Clin Gastroenterol*, in which hemostatic status of hospitalized patients with cirrhosis was

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assessed using thromboelastography (TEG). In line with a previous study on outpatients with cirrhosis,² this study found TEG parameters to be well-preserved, but with a decrease in clot formation with increasing severity of the liver disease. The observation that TEG tracings in patients with cirrhosis are remarkably similar to the tracings of healthy individuals is in line with the concept of rebalanced hemostasis in patients with cirrhosis.³ Although I fully concur with the conclusion that TEG better reflects hemostatic capacity in patients with cirrhosis compared with the international normalized ratio (INR), there are important caveats in interpreting TEG test results in patients with cirrhosis.

First, although TEG better reflects the balance between procoagulant and anticoagulant factors than the INR it still underestimates the coagulation capacity of patients with cirrhosis. The INR is only sensitive for levels of procoagulant factors VII, X, V, II, and fibrinogen, and quantitative or qualitative decreases in 1 or more of these factors will cause an INR prolongation.⁴ In patients with cirrhosis, however, there are simultaneous changes in both procoagulant and anticoagulant factors, and the INR fails to capture the compensation of decreases in procoagulants by decreases in anticoagulants. TEG is sensitive to levels of some, but not all, anticoagulant factors. Notably, TEG is insensitive to the important anticoagulant protein C system, which requires the endothelial cell transmembrane protein thrombomodulin (TM) to become activated. The lack of endothelial cells or a protein C activator in the TEG reagent results in a lack of protein C activation during clot formation in the TEG device. Because protein C levels are decreased in patients with cirrhosis,⁵ and as the protein C deficiency of cirrhosis is an important driver of hypercoagulability in cirrhosis,⁶ the TEG per definition underestimates the coagulation capacity of a cirrhotic blood sample. This concept has been extensively investigated using thrombin generation tests, which have been executed in the presence and absence of a soluble form of TM to allow for protein C activation.⁷⁻¹² TM-modified thrombin generation in patients with cirrhosis is consistently more hypercoagulable than thrombin generation in the absence of TM when compared with healthy volunteers.

Second, in patients with advanced cirrhosis, TEG is particularly hypo-coagulable in terms of the maximum amplitude, which to a large extent reflects thrombocytopenia. However,

the thrombocytopenia of cirrhosis has been suggested to be compensated, at least in part, by highly elevated levels of the platelet adhesive protein von Willebrand factor (VWF).¹³ VWF is crucial in attracting platelets to the site of vascular injury as evidenced by the bleeding tendency of individuals with an isolated VWF deficiency. VWF is only active as platelet adhesive protein under conditions of flow, which are virtually absent in a TEG assay. Therefore, TEG is insensitive to changes in plasma levels of VWF and fails to capture compensation of cirrhotic thrombocytopenia by elevated VWF levels. Again, for this reason, the TEG actually underestimates true hemostatic potential.

Third, part of the delay in clot formation in cirrhotic blood likely relates to defects in fibrin polymerization, which has been shown to relate to changes in glycosylation of the fibrinogen molecule.¹⁴ However, despite the delay in clot formation, the quality of the clot that is eventually formed is more thrombogenic as compared with clots formed from healthy blood as was demonstrated using fibrin permeation assays.^{15,16} This aspect of clot quality again is not captured by TEG, and may also lead to an underestimation of true clot quality.

Fourth, the initiation of clot formation in this study was by the addition of kaolin, which activates the intrinsic pathway of coagulation. However, intrinsic coagulation activation is not relevant in physiological hemostasis,¹⁷ although it does play a role in pathologic thrombosis.¹⁸ This again makes it difficult to interpret TEG test results.

Thus, although TEG much better reflects the hemostatic capacity of a cirrhotic blood sample than an INR, there are important limitations of the TEG that need to be acknowledged. TEG almost certainly underestimates the hemostatic capacity of a cirrhotic blood sample as it does not take the protein C deficiency and high levels of VWF into account. In fact, it is increasingly acknowledged that patients with cirrhosis may actually be hypercoagulable as evidenced by their increased risk of venous thrombotic events¹⁹ and enhanced thrombin generation by TM-modified thrombin generation tests. Therefore, although TEG indeed may lead to a reduction of unnecessary transfusions, it may be that patients with mildly abnormal TEGs still do not benefit from blood product

transfusions, as their hemostatic status is actually normal.²⁰

It is important to stress that the bleeding risk of many common procedures in patients with cirrhosis is low,²¹ and that prophylactic blood product transfusion with the aim to avoid bleeding (even in those patients with abnormal baseline TEGs) is likely, not helpful as hemostatic status is normal and bleeding risk is low.²² In addition, a substantial proportion of spontaneous or procedure-related bleeds that due occur are unrelated to defective hemostasis but are rather caused by portal hypertension or mechanical causes such as puncture or laceration of vessels during invasive procedures. As it is uncertain whether abnormal TEG test results predict procedural bleeding risk, the most important use of TEG or other viscoelastic tests may be in guiding transfusion in patients that are actively bleeding and in whom hemostatic failure likely contributes to the bleed.

In aggregate, the study by Hum and colleagues reinforces the notion that routine diagnostic tests of hemostasis such as the INR should not be used to assess the hemostatic capacity of patients with cirrhosis.⁴ However, notwithstanding the advantages of whole blood viscoelastic tests,²³ the caveats of those tests in patients with complex alterations in their hemostatic system should be taken into account when using TEG in routine clinical practice and in clinical studies on hemostatic management of these patients.

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