

## CASE REPORT

# Rivaroxaban-calibrated chromogenic anti-Xa assay in cirrhosis: Use to rule out disseminated intravascular coagulation

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## Abstract

Peritoneovenous shunts (PVSs) are used to relieve ascites in cirrhosis. Disseminated intravascular coagulation (DIC) is a complication of PVSs requiring immediate PVS removal. We report a patient who developed new elevations of prothrombin time (PT) and activated partial thromboplastin time (aPTT) 6 hours after PVS placement, concerning for new-onset DIC. We address the key clinical question of distinguishing DIC from rivaroxaban effect on labs. The patient took rivaroxaban 3 hours after PVS placement, suggesting rivaroxaban effect. Rivaroxaban-calibrated anti-Xa level was in the expected treatment range. Over 12 hours, coagulation labs and rivaroxaban levels declined, with no evidence of DIC. The sudden PT/aPTT increase was attributed to rivaroxaban, however, the distinction between DIC and rivaroxaban effect was possible only with the rapid availability of rivaroxaban levels. While there are no US Food and Drug Administration-approved tests for rivaroxaban levels in the United States, this case demonstrates they can have significant clinical impact, encouraging more widespread adaptation of these assays.

## KEYWORDS

blood coagulation, disseminated intravascular coagulation, liver cirrhosis, peritoneovenous shunt, rivaroxaban, rivaroxaban-calibrated chromogenic anti-Xa assay

## Essentials

- Disseminated intravascular coagulation (DIC) can occur after peritoneal shunt placement.
- Simultaneous rivaroxaban treatment may mask recognition of DIC.
- We discerned DIC from rivaroxaban-effect using rivaroxaban-calibrated anti-Xa test.
- Findings support clinical impact of this testing, encouraging more widespread use.

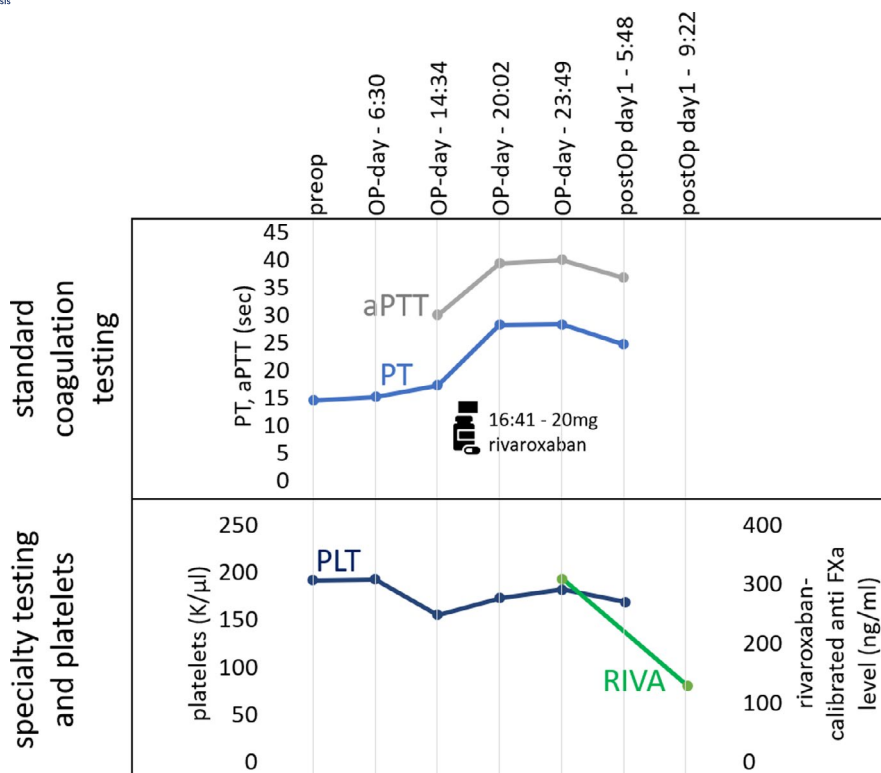
## 1 | CASE

A 47-year-old patient was admitted for postprocedural pain control and monitoring after paracentesis (removal of 11 L ascites) and placement of a peritoneovenous shunt (PVS) for more definite management of

refractory ascites due to cardiac cirrhosis from severe congenital heart disease. Over the previous year, the patient had required repeated paracentesis, which had increased in frequency and volume. Preoperative labs showed a prothrombin time (PT) of 15.1 seconds, white blood cell count of 5.29 K/ $\mu$ L, hemoglobin of 16.2 g/dL, and platelets of 193 K/

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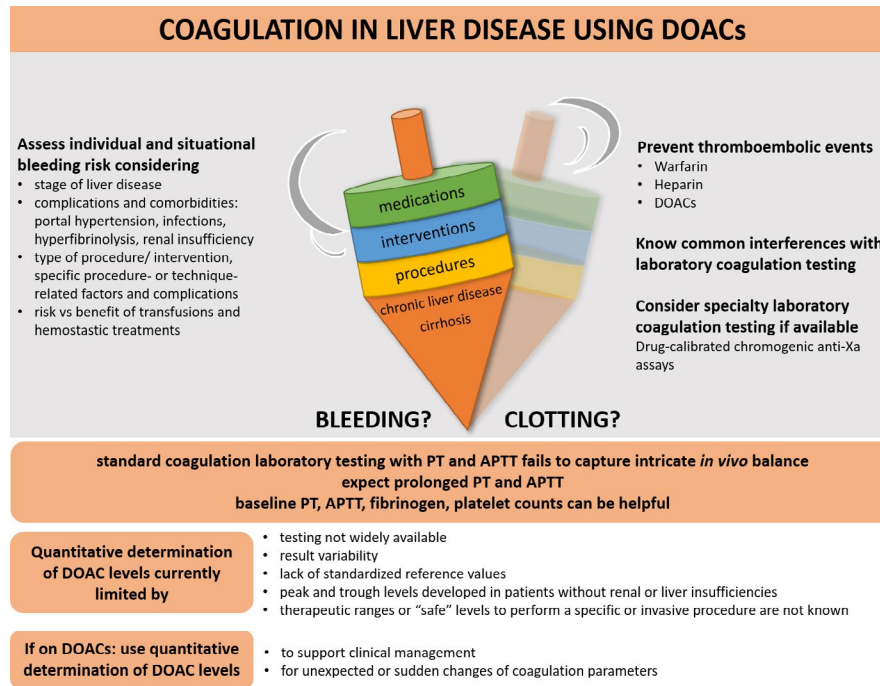
**FIGURE 1** Coagulation parameters before, during, and after shunt placement. Latest reference ranges (Brigham and Women's Hospital Central Laboratory, Boston, MA): prothrombin time (PT), 11.5–14.5 s; activated partial thromboplastin time (aPTT), 23.8–36.6 s; anti-factor Xa rivaroxaban: lower limit of detection, 23 ng/mL; platelets (PLT), 150–450 K/ $\mu$ L. Note: Rivaroxaban levels (5th–95th percentiles) from clinical trials and simulation experiments for prevention of atherothrombotic events in patients with acute coronary syndrome (2.5 mg twice daily): trough, 6–34 ng/mL; peak, 28–66 ng/mL; prevention of venous thromboembolism (VTE) after hip and knee replacement (10 mg once daily): trough, 1–38 ng/mL; peak, 91–196 ng/mL; VTE treatment in patients with reduced kidney function (15 mg once daily): trough, 18–136 ng/mL; peak, 178–313; treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), and prevention of recurrence (20 mg once daily): trough, 19–60 ng/mL; peak, 175–360; prevention of stroke in patients with nonvalvular atrial fibrillation (NVAf; 20 mg once daily): trough, 12–137 ng/mL; peak, 184–343<sup>3,4,15</sup>

$\mu$ L, all of which were comparable to prior laboratory values. Bilirubin was normal, and baseline D-dimer was elevated. The patient's procedural bleeding risk was estimated to be very low, and preprocedural blood products or hemostatic agents were not administered. A Denver shunt was placed by Interventional Radiology without complications. On postoperative labs 6 hours later, a marked elevation of PT and activated partial thromboplastin time (aPTT) from 17.2 to 28.2 seconds and 30.0 to 39.4 seconds were noted (Figure 1). This raised the concern for DIC, a known complication of shunt placement<sup>1,2</sup>; importantly, if DIC is noted, a shunt is immediately removed. However, fibrinogen levels were stable (6 hours after surgery, 248 mg/dL from 293 mg/dL; reference range, 200–450 mg/dL), and platelet counts and smear morphology remained largely unchanged. A review of medications by hematology service revealed that the patient had taken their regular daily dose of once-daily 20 mg of the direct oral anticoagulant (DOAC) rivaroxaban 3 hours after PVS placement and 3 hours before the alterations in coagulation parameters were noted. As our laboratory in a large US tertiary care center had recently established in-house rivaroxaban/apixaban level testing using a rivaroxaban/apixaban-calibrated chromogenic assay, rivaroxaban-calibrated anti-Xa levels were obtained. This showed a level of 309 ng/mL, consistent with peaks reported for

treatment of deep vein thrombosis, pulmonary embolism, and prevention of recurrence, and for prevention of stroke in patients with nonvalvular atrial fibrillation (NVAf) receiving 20 mg once daily.<sup>3,4</sup> The next morning, coagulation labs and rivaroxaban levels were repeated. This showed a decrease for PT to 24.7 seconds, for aPTT to 36.8 seconds, and for rivaroxaban levels to 129 ng/mL, consistent with reported near trough/trough concentrations.<sup>3,4</sup> Together, it was concluded that the likelihood of DIC was very low, and the sudden increase in PT/aPTT was attributed to rivaroxaban effect on standard coagulation testing. However, this rationale could be fully supported only by the rapid and around-the-clock availability of rivaroxaban levels. As a result, the decision was made to leave the Denver shunt in place, and the patient was discharged shortly after without any additional events.

## 2 | DISCUSSION

Patients with cirrhosis show various altered hematologic and coagulation parameters, including abnormal clotting factor synthesis, reduced platelet numbers, and impaired platelet and endothelial functions.<sup>5</sup> However, the overall hemostatic function is largely maintained due to



**FIGURE 2** Graphical abstract summary. APTT, activated partial thromboplastin time; DOAC, direct oral anticoagulant; PT, prothrombin time.

a net balance of deficiencies in both pro- and anticoagulant factors and several compensating mechanisms, such as increased von Willebrand factor (VWF) and factor VIII synthesis, and decreased ADAMTS-13 and plasminogen levels—a concept commonly referred to as “rebalanced hemostasis.”<sup>5</sup> However, this window of functional hemostasis is narrow and easily disturbed, and coexisting morbidities such as portal hypertension, infections, hyperfibrinolysis, or renal failure increase the bleeding propensity<sup>6</sup>; especially gastrointestinal bleeding from portal hypertension or vessel injury can be a frequently occurring and serious complication. Patients with cirrhosis also undergo recurrent interventions such as therapeutic paracentesis, thoracentesis, or routine upper endoscopy for variceal ligation, as well as biopsies or device placements, adding the risk of procedural bleeding or postprocedural hematologic complications.<sup>5,6</sup> To predict procedural bleeding risk, practice recommendations have been developed, for example, by the American Association for the Study of Liver Diseases.<sup>6</sup> In this document, it is recommended to consider procedure- or technique-related factors, severity of liver disease, coexisting morbidities (especially acute and chronic kidney disease), and medications when estimating procedure-related bleeding risks.<sup>6</sup> In general, a procedure is considered high risk if major bleeding is expected in >1.5% of procedures, or if minor bleeding is likely to result in permanent organ damage or death. Postprocedural hematologic complications are largely related to specific procedures, for example, coagulopathy or DIC after PVS placement.<sup>1,2</sup>

Routine coagulation laboratory testing with PT and aPTT has been shown to inaccurately capture the intricate hemostatic *in vivo* balance, and patients with liver disease often exhibit prolonged PT and aPTT while generating normal or even increased amounts of thrombin.<sup>5-7</sup> In addition, thrombocytopenia and hypofibrinogenemia can be present. However, most compensatory mechanisms

cannot be detected using routine diagnostic testing. The prediction of bleeding risk using PT, aPTT, platelet count, and fibrinogen level is therefore challenging and potentially can be misleading. Recent guidance for gastroenterologists suggests that procedures such as paracentesis, thoracentesis, upper endoscopy, and diagnostic colonoscopy do not routinely require coagulation testing.<sup>5,7</sup> However, preprocedural measurements of PT, aPTT, platelet count, and fibrinogen levels can provide a baseline and facilitate the workup of sudden changes, as presented in the patient case above. If available, whole blood viscoelastic testing such as thromboelastography and rotational thromboelastometry can provide a real-time global measurement of clotting abilities,<sup>8</sup> but these methods still underestimate the contributions of VWF and protein C to the hemostatic balance.<sup>5</sup>

While trying to minimize bleeding risk, treatment with low-molecular-weight heparin or vitamin K antagonists is generally recommended for patients with cirrhosis,<sup>7,9</sup> as this reduces the risk of thromboembolic events (eg, splanchnic and portal vein thrombosis or NVAf) and improves overall outcome.<sup>10,11</sup> DOACs such as apixaban and rivaroxaban are increasingly used as alternative safe and effective treatment options in stable patients, but their role in more advanced liver disease is unclear.<sup>5,7,9</sup> The use of DOACs introduces another level of complexity to coagulation testing in patients with cirrhosis. DOACs may affect standard coagulation testing, and even patients without cirrhosis may show pronounced alterations of PT, aPTT, and anti-Xa activity in the context of DOAC treatment.<sup>12-14</sup> Drug-calibrated chromogenic anti-Xa assays provide a quantitative determination of rivaroxaban/apixaban levels, but testing is not widely available due to concerns regarding result variability and lack of standardized reference values.<sup>12,13</sup> Moreover, peak and trough levels have been reported in patients without renal or liver

insufficiencies.<sup>15</sup> For patients with liver disease, therapeutic ranges or “safe” levels to perform a specific or invasive procedure and the exact relationship between rivaroxaban/apixaban levels and other coagulation parameters are currently not known. However, these levels may be of value to explain unexpected or sudden changes of coagulation parameters, and to narrow the differential diagnosis of conditions such as DIC, especially in patients without or only mild hyperbilirubinemia, where interference with chromogenic assay-based testing is usually not expected. These findings are summarized in the graphical abstract that is included as Figure 2.

### 3 | RECOMMENDATION

Coagulation assessment in patients with liver disease and cirrhosis is very complex and often requires multidisciplinary management and access to specialty hematology testing. To adequately evaluate bleeding and thrombotic risk, knowledge of the pathophysiology of hemostasis and its effect on hematology and coagulation laboratory assays, as well as limitations of anticoagulants laboratory monitoring, is essential. PT and aPTT are insufficient parameters to gauge hemostasis. At a minimum, fibrinogen and platelets should also be determined to provide a patient-specific baseline that can aid in the interpretation of sudden or unexpected changes. Hematology centers should pursue in-house implementation of rivaroxaban/apixaban-calibrated anti-Xa testing, as their availability can have a significant clinical impact. The rivaroxaban/apixaban-calibrated anti-Xa test can be easily performed with a rapid turnaround time in any clinical laboratory with automated coagulation analyzers. The lack of regulatory approval (in the United States) should not be an impediment for implementation. In the case presented here, obtaining rivaroxaban levels helped solve a clinical conundrum by ruling out new-onset DIC.

#### AUTHOR CONTRIBUTIONS

FL and EMB wrote the manuscript, created the figures, and finalized the manuscript. FL, OP, JMC, and EMB developed and implemented DOAC testing in-house. MSS performed patient care and stent placement. JMC and EMB provided hematology consult for the patient case. All authors edited the manuscript and approved the final version for submission.

#### RELATIONSHIP DISCLOSURE

The authors declare no conflicts of interest.

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