The Complex Role of Anticoagulation in Cirrhosis: An Updated Review of Where We Are and Where We Are Going

Tawfik Khoury, Abu Rmeileh Ayman, Jonah Cohen, Saleh Daher, Chen Shmuel, Meir Mizrahi

Key Words
Cirrhosis · Anticoagulation · Venous thromboembolism

Abstract
Venous thromboembolism (VTE) in cirrhotic patients is an increasingly encountered problem in the daily clinical practice; there is still a debate on the ideal measures to be followed for prophylaxis and treatment of VTE among this population. Although traditionally, liver cirrhosis has been considered a disease with hypocoagulability state and increasing bleeding tendency due to severe homeostatic disruption in liver disease, until recently there is increasing awareness and evidence that cirrhotic patients are not completely protected from thrombotic events although they

Key Points
- Increasing evidence supports the hypercoagulability of CLD, and patients with cirrhosis are not naturally anticoagulated as has been historically believed.
- Cirrhotic patients with PVT can be successfully treated with anticoagulation without excess bleeding risks and a study shows improved survival and decreased hepatic decompensation in the setting of treating such thrombosis.
- To date, there are no well-established assays for correctly evaluating the hemostatic phenotype in cirrhotic patients; however, recently several novel techniques are in experimental phases and may better estimate bleeding tendency.
- Several anticoagulation drugs are available for clinical use including several new oral anticoagulants. Each drug has its own advantages and disadvantages. Still no consensus is available regarding the preferred anticoagulant agents used in cirrhosis.
- Overall, sufficient evidence exists, promoting the use of anticoagulation in cirrhotic patients for both VTE prophylaxis and treatment in carefully selected patients after consideration of pharmacologic or endoscopic variceal bleeding prophylaxis.
have an elevated international normalized ratio and autoanticoagulation. Furthermore, hypercoagulability is now an increasingly recognized aspect of chronic liver disease (CLD), and the bleeding risk of VTE prophylaxis and treatment remains unclear. In this review, we provide an updated discussion on the mechanisms involved in hemostasis in CLD as well as on the benefits and complications of anticoagulant therapy in cirrhotic patients. Overall, sufficient evidence exists, promoting the use of anticoagulation in cirrhotic patients for both VTE prophylaxis and treatment in carefully selected patients after consideration of pharmacologic or endoscopic variceal bleeding prophylaxis.

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Introduction

Venous thromboembolism (VTE) in patients with liver cirrhosis is an increasingly recognized clinical condition for which there remains controversy over the ideal approach to prophylaxis and treatment. Although cirrhosis has classically been considered a hypocoagulable disease state with enhanced risk of bleeding due to homeostatic disruption of hepatic clotting factors, recently there has been burgeoning evidence that cirrhotic patients are not absolutely protected from thrombotic events despite their elevated international normalized ratio (INR) and autoanticoagulation. Moreover, hypercoagulability with resultant VTE is now an increasingly recognized aspect of chronic liver disease (CLD). Although this fact is widely known and understood, there still remains difficulty in identifying markers of hypercoagulability in cirrhotic patients and the risk of bleeding with VTE prophylaxis, and treatment is still unclear. In this review, we provide an updated discussion on the mechanisms involved in hemostasis in CLD as well as on the benefits and complications of anticoagulant therapy in cirrhotic patients. Overall, sufficient evidence exists, promoting the use of anticoagulation in cirrhotic patients for both VTE prophylaxis and treatment in carefully selected patients after consideration of pharmacologic or endoscopic variceal bleeding prophylaxis.

Mechanisms of Dysregulated Hemostasis in Cirrhosis

Hemostasis is a delicately balanced physiologic process that is significantly altered in cirrhosis. The cumulative effect of coagulation dysregulation in CLD is complex, leading to both hemorrhagic and thrombotic complications. One of the laboratory changes that occurs in cirrhotic patients is an elevation in the INR due to a reduction in the synthesis of pro-coagulant factors II, V, VII, X, XI, XII, XIII and fibrinogen, which contributes to the increased bleeding risk in these patients. Cirrhosis, however, is also a disease state associated with hypercoagulability due to decreased synthesis of anticoagulant factors, such as anti-thrombin, proteins C and S, as well as decreased production of fibrinolytics such as plasminogen [1–4]. Additionally, favoring the pro-coagulant balance is the increased generation of thrombin as well as endothelial-derived pro-coagulant factors, such as factor VIII, von Willebrand factor and hyperhomocysteinemia secondary to vitamin B12 and folate deficiencies [2, 5–8] (fig. 1). It has been reported that patients with cirrhosis can have elevated levels of anti-phospholipid antibodies, which also predispose to thrombotic events [9, 10]. Finally, the well-known traditional risk factors for VTE are often present in cirrhotic patients including frequent and lengthy hospitalization, immobility, elevated estrogen levels, advanced age and the potential risk for cancer development. For these aforementioned reasons, to globally predict the hemostatic balance between bleeding and thrombotic tendencies across the population of cirrhotic patients is a major challenge, and it is even difficult to make such predictions at the individual patient level.

Risk of VTE in CLD

VTE including either deep vein thrombosis (DVT) or pulmonary embolism (PE) is a common cause of worldwide mortality and morbidity. In the general population, the incidence rate of VTE is 1–2 per 1,000 person-years. Among selected groups such as the elderly, cancer patients, or patients with multiple medical comorbidities, such as chronic heart or lung disease, the incidence rate can be as high as 1 per 100 person-years [11–14]. The main complications of VTE include the post-thrombotic syndrome, chronic pulmonary hypertension, and even sudden death. Approaches for preventing VTE include reduction of risk factors and anticoagulant treatment. VTE is a multi-factorial disease with several prominent risk factors including fractures, surgery, cancer, estrogen intake, thrombophilia and pregnancy [15, 16]. Current guidelines provide a Class 1A recommendation for the administration of thromboprophylaxis in many of these patients; however, such guidelines do not currently include patients with cirrhosis [17]. Many health care professionals incorrectly perceive patients with liver disease...
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to be auto-anticoagulated and thus protected from VTE secondary to an elevated INR and thrombocytopenia. Notably, the coagulopathy of liver disease involves a complex interplay between procoagulant and anticoagulant factors, which are not accurately assessed by standard biochemical indices [4, 18, 19]. Although patients with more advanced liver disease synthesize fewer clotting factors, they also synthesize fewer clotting inhibitors such as protein C, protein S, and anti-thrombin III, and thus more thrombotic events may occur as liver function worsens [20]. Recent population studies have provided evidence, which challenge the theory that patients with cirrhosis are purely hypocoaguable [2]. As mentioned previously, CLD leads to an imbalance in the coagulation system and many recent studies have shown that the liver disease-induced coagulopathy may be associated with thrombosis [21–23]. Several previous studies had reported a varying incidence of VTE rate among cirrhotic patients ranging from 0.5 to 6.3% [22–29]. All the aforementioned studies conclude that patients with cirrhosis are not at decreased risk for developing VTE episodes compared to non-cirrhotic controls without other significant co-morbidities, such as congestive heart failure, chronic kidney disease or solid organ cancers. Furthermore, the presence of lower serum albumin level was a strong predictor of increased risk of VTE episodes in cirrhotic patients; thus, serum albumin deficiency may indicate low levels of endogenous anticoagulants. Moreover, an elevated partial thromboplastin time (PTT) and INR do not appear to protect against the development of hospital-acquired VTE (table 1). The varying incidence and prevalence in these different studies can be partially explained by differences in study design, inclusion or exclusion criteria and data collection. Another large cross-sectional study addressing the risk of VTE in hospitalized patients with cirrhosis in the United States including almost 650,000 hospital admissions with cirrhosis (408,000 with compensated cirrhosis comprised cirrhotic patients without neither ascites or varices or patients with varices without bleeding, and almost 242,000 with decompensated cirrhosis defined by the presence of ascites with or without varices and patients with variceal bleeding with or without ascites) and 575,000 admissions without liver disease found that the risk of having an in-hospital VTE was 21% higher in patients with compensated cirrhosis and 39% higher in patients with decompensated cirrhosis, compared to hospitalized patients without liver disease up to the age of 45 and thereafter, the prevalence of VTE in non-liver disease patients was similar to the cirrhotic patients and this gap decreased with increasing age. Furthermore, VTE-related mortality was higher in the decompensated and compensated cirrhosis compared to the control group without liver disease (11.1 and 7.6 vs. 2.3%, respectively) [30]. In addition to the aforementioned factors mediating pro-thrombotic events in cirrhosis, several additional factors contribute hypercoagulability in cirrhosis. Of them, systemic thrombophilic factors such as factor V Leiden and prothrombin 20210 gene mutations were found in cirrhotic patients with symptomatic PVT compared with controls [31, 32], and low levels of anticardiolipin antibodies were found in approximately 20% of patients with CLD [9]. Finally, both stasis and eventual reversal of blood flow in the portal circulation of cirrhotic patients coupled with the frequent

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**Fig. 1.** Factors predisposing for both bleeding and thrombosis in cirrhotic patients.
occurrence of intra-abdominal inflammatory processes, such as spontaneous bacterial peritonitis and gastrointestinal infections, can promote endothelial activation and further reduce flow in the portal vein resulting in a prothrombotic state and increased risk of thrombosis [33, 34].

While it is well established that thromboprophylaxis decreases the risk of VTE in hospitalized medical patients, a meta-analysis in 2007 (that included a total of 12,391 patients from 9 studies), which assessed the rate of VTE reduction among hospitalized medically ill patients with prophylactic anticoagulation, found that there was a significant reduction in the rate of DVT in patients treated with low molecular weight heparin (LMWH) or unfractionated heparin (UH) compared to placebo. However, the rate of DVT reduction between LMWH and UH was similar. Interestingly, there was no significant effect on the rate of PE among placebo, LMWH or UA groups. Furthermore, treatment with LMWH or UH was associated with a significant increase in minor bleeding events compared to placebo (p = 0.003). However, this effect was similar between the LMWH and UH groups. There was no difference in major bleeding among all groups [35]. However, patients with cirrhosis are usually excluded from these trials and thus, there is controversy over whether thromboprophylaxis would expose cirrhotic patients to an increased risk of bleeding with subsequently greater risk of morbidity and mortality. Thus, it is less certain if this benefit extends to patients with cirrhosis. Recent expert opinion has advocated that hospitalized cirrhotic patients should be considered for venous thromboprophylaxis [36]. Recent data have examined the risk of anticoagulation therapy in patients with portal vein thrombosis (PVT) and cirrhosis. Overall, anticoagulation for PVT has been shown to be relatively safe and effective [37–39] (table 2), although large studies examining the safety and efficacy in hospitalized patients are scarce and there remains little direct evidence to support or reject the safety of thromboprophylaxis in hospitalized cirrhotic patients. Thus, further randomized controlled trials are still needed.

**VTE Prophylaxis and Therapy in Cirrhosis**

As previously discussed, the use of anticoagulation for VTE prophylaxis in cirrhosis remains controversial and it is not yet universal practice to provide hospitalized cirrhotic patients with such prophylaxis due to the concerns

### Table 1. Incidence of VTE in cirrhotic patients in published studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of study</th>
<th>Number of patients</th>
<th>% of anticoagulation</th>
<th>VTE, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gulley et al. [21]</td>
<td>Case-control</td>
<td>963 (cirrhosis) vs. 12,405 (control)</td>
<td>0</td>
<td>1.8 vs. 0.9% (p = 0.007)</td>
</tr>
<tr>
<td>Dabbagh et al. [22]</td>
<td>Retrospective</td>
<td>190</td>
<td>25</td>
<td>6.3</td>
</tr>
<tr>
<td>Northup et al. [23]</td>
<td>Retrospective case-control</td>
<td>113</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>García-Fuster et al. [24]</td>
<td>Retrospective</td>
<td>17</td>
<td>0</td>
<td>0.8</td>
</tr>
<tr>
<td>Anthony Lizarraga et al. [25]</td>
<td>Retrospective case-control</td>
<td>108</td>
<td>0</td>
<td>0.73</td>
</tr>
<tr>
<td>Wu and Nguyen [26]</td>
<td>Retrospective</td>
<td>0</td>
<td>8.1 and 8.2 per 1,000 patients for compensated and decompensated cirrhosis, respectively</td>
<td></td>
</tr>
<tr>
<td>Saleh et al. [27]</td>
<td>Retrospective</td>
<td>4,927,000 (chronic ALD) and 4,565,000 (chronic NALD)</td>
<td>0</td>
<td>1.05</td>
</tr>
<tr>
<td>Aldwood et al. [28]</td>
<td>Retrospective</td>
<td>226</td>
<td>24</td>
<td>2.7</td>
</tr>
<tr>
<td>Ali et al. [29]</td>
<td>Retrospective</td>
<td>449,798</td>
<td>0</td>
<td>1.8</td>
</tr>
</tbody>
</table>

ALD = Alcoholic liver disease; NALD = nonalcoholic liver disease.
of bleeding risk. One recent study found that 76% of inpatient cirrhotic patients received neither pharmacological nor mechanical DVT prophylaxis [28]. Another group found that only 9% of hospitalized patients with CLD were treated with pharmacological VTE prophylaxis, while only 16% received mechanical VTE prophylaxis [23]. At present, there are no large prospective randomized controlled trials regarding the safety of VTE prophylaxis in cirrhosis.

Regarding the evaluation of the balance between risks of bleeding with VTE development in cirrhosis, a retrospective study done in 229 patients examined the risk of VTE episodes or bleeding associated with postoperative LMWH prophylaxis in cirrhotic patients after hepatic resection for hepatocellular carcinoma. The study reported that 68.5% of patients received VTE prophylaxis with LMWH, while 31.5% did not. Only 0.63% in the VTE prophylaxis group developed VTE postoperatively compared with 1.38% of patients not receiving prophylaxis; however, this difference did not reach statistical significance. One patient in the non-prophylaxis group died due to liver failure secondary to PVT. The percent of hemorrhage prevalence in the postoperative stage was also not statistically different between the 2 groups. Furthermore, the authors showed that the presence of esophageal varices was the only statistically significant independent risk factor for increased risk of bleeding; however, other risk factors, including model of end-stage liver disease (MELD) score, platelet count and age were not associated with increased risk for either VTE or bleeding risk [40].

Another study on 84 patients with cirrhosis who were treated with LMWH for either prophylaxis or for therapeu-
acute or extensive PVT/mesenteric vein thrombosis may develop severe gastrointestinal bleeding, ascites and/or intestinal ischemia, which can be progressive or even fatal [44–46]. Currently, guidelines from the American College of Chest Physicians (ACCP) in 2012 on antithrombotic treatment and prevention of thrombosis recommend the use of anticoagulation therapy in cirrhotic patients with symptomatic splanchnic thrombosis except in the case of incidental asymptomatic splanchnic thrombosis [47]. Retrospective studies have shown that anticoagulation therapy is associated with improved rates of re-canalization in acute PVT [45]. Another study involving cirrhotic patients with chronic PVT that were treated with therapeutic enoxaparin have shown no significant bleeding complications after complete variceal band ligation in spite of the fact that the initial presentation of the PVT was variceal bleeding for almost half of these patients [38]. Moreover, it was shown that patients with splanchnic venous thrombosis awaiting liver transplantation did not have more bleeding episodes while on therapeutic anticoagulation and in fact, it showed an improved survival rate than those not anticoagulated for PVT [37]. An additional group reported no excess bleeding in cirrhotic patients with PVT while on anticoagulation [48]. A recent study by Villa et al. [39] provides compelling data regarding the potential safety and efficacy of prophylactic anticoagulation in reducing the rate of acute PVT in cirrhotic non-hospitalized patients. This study examined the use of enoxaparin in preventing PVT in patients with advanced stages of cirrhosis given Child–Pugh scores of B and C. The primary end was portal vein or mesenteric vein thrombosis, and secondary end points included overall survival and clinical hepatic decompensation. These authors also examined the rate of hemorrhage and thrombocytopenia as safety end points related to anticoagulation. Overall, the study period was 24 weeks, in which enoxaparin 4,000 IU or placebo were administered daily for participants for 12 months, followed by another 12-month observation period. No hemorrhagic events were reported at the end of the observation period (24 months), although one patient developed thrombocytopenia secondary to the enoxaparin. In the first year, no one in the enoxaparin treated group developed PVT compared with the placebo group (0 vs. 16.7%). During the follow-up year, this effect was lost, with 3 PVTs occurring in the enoxaparin group (2–6 months after discontinuation of the drug) and 4 in the placebo group. Notably, the rate of clinical hepatic decompensation was lower in the enoxaparin group compared to the control group (11.7 vs. 59.4%, p < 0.0001). The survival was higher in the enoxaparin group and no excess bleeding or side effects were reported in the enoxaparin group. Furthermore, this study showed that enoxaparin therapy might exert its beneficial effect via an anti-inflammatory mechanism as well as through improved intestinal microcirculation, which decreases bacterial gut translocation. However, limitations of this study included its limited sample size and absence of assays assessing the degree of anticoagulation, which currently precludes the incorporation of this approach into management protocols in cirrhotic patients.

The effect of improved intestinal microcirculation mediated by anticoagulation has been demonstrated in previous work by another group showing that portal hypertension is associated with stasis of flow in the intestinal microcirculation, which may lead to an increased risk of bacterial translocation from the gut and spontaneous bacterial peritonitis [50]. These findings are consistent with other human and animal studies, suggesting that a hypercoagulable state in cirrhosis favors progression of liver fibrosis and conversely, that anticoagulant therapy can slow this process [2]. Finally, it is possible that systemic anticoagulation may reduce the formation of intrahepatic micro-thrombi formation, which has been implicated as a possible contributing factor to progressive portal hypertension and parenchymal fibrosis [51, 52]. Another study reported that anticoagulation with enoxaparin in patients with cirrhosis caused no serious side effects, including bleeding during 6–17 months of treatment [38]. Importantly, once variceal bleeding occurs, in the context of PVT and cirrhosis, it is difficult to control and the one-year survival rate decreases to 61–86% [53]. Thus, prophylactic management of gastroesophageal varices is paramount prior to initiating anticoagulation therapy.

**Conventional Anticoagulation Used in Cirrhosis**

**Heparin Agents**

Several classes of heparin are currently available for prophylactic or therapeutic purposes including UH, LMWH and fondaparinux. UH is conventionally monitored via activated PTT (aPTT) assay, while LMWH can be monitored via the anti-Xa assay in the general population excluding patients with liver failure. The clearance of LMWH predominantly depends on kidney function and thus dose adjustment is required in renal failure patients. Unfractionated subcutaneous heparin is a useful and safe treatment for the prevention of VTE in hospitalized non-cirrhotic patients. While evidence in the literature is lim-
Vitamin K Antagonists

Vitamin K antagonists (VKA) are a widely used treatment for thromboembolic diseases in the general population. VKA block the vitamin K-synthesized procoagulant factors (II, VII, IX, X). Furthermore, VKA decreases the production of anticoagulant proteins S and C. Thus, the net effect of VKA is hypocoagulability. INR measurement is required to assess the degree of anticoagulation of VKA. However, in cirrhotic patients, the INR is already elevated making it difficult to decide on a target INR in a warfarin-treated patient. It is important to note that the already elevated INR in cirrhotic patients does not reflect the true hemostatic phenotype as despite an elevated INR, evidence indicates that such patients are still prone to thrombosis [32, 56]. Furthermore, it is difficult to interpret the causes of INR elevation in cirrhotic patients treated with VKA and several studies have addressed the variability in between laboratories in the measurement of INR in cirrhotic patients, which can affect the chance for liver transplantation due to incorrect INR and MELD score underestimation [57–59]. In cirrhosis, the use of VKA has been associated with adverse thrombotic events as the anticoagulation degree may be suboptimal due to the baseline prolonged INR. Finally, cirrhotic patients treated with VKA are known to also have an increased risk of hemorrhagic complications [25, 60]. Thus, the development of more accurate tests for VKA monitoring in cirrhosis is greatly needed.

Looking Toward the Future

Hemostasis is highly dependent on hepatic synthetic function and the delicate interaction between the procoagulation/anticoagulation pathways as well as the fibrinolytic cascade. A recent review by Saner et al. [61] had addressed the fine balance of hemostatic pathophysiology in advanced liver cirrhosis and reviewed the recent measures for hepatic coagulopathy assessments and treatment in such patients. The standard coagulation profile processed in most clinical laboratories includes prothrombin time (PT), INR and aPTT. As these assays do not fully estimate actual thrombin generation, attempts to correlate a coagulation phenotype with a tendency toward bleeding in cirrhotic patients has had limited success. This difficulty in predicting the coagulation phenotype is attributed to several factors including altered hepatic synthesis and clearance of clotting factors as well as inhibitors of coagulation factors, dysfibrinogenemia, thrombocytopenia and disseminated intravascular coagulation [62]. Many consider the PT assay to be the test of choice for diagnosing either inherited or acquired coagulopathies, in addition to VKA monitoring. However, in patients with CLD, the PT assay fails to assess all the changes in coagulation activity and thus cannot accurately assess bleeding tendency in such patients. Multiple studies have shown that PT does not correlate with severity of gastrointestinal bleeding in cirrhotics, and is a poor predictor of bleeding following liver biopsy as well as other surgical procedures [63–65]. To better estimate bleeding tendency in CLD, other tests have been recently developed. These include thrombin generation time, thromboelastography (TEG) and thromboelastometry, which are similar to TEG and sonorheometry. The thrombin generation assay is modified by adding thrombomodulin to measure thrombin formation and thus, it assess the serum coagulation factors and the coagulation inhibitors in patients with CLD. TEG measures the global homeostatic function, including the initial interaction of platelets with fibrin, platelets aggregation through clot formation and clot dissolution [66]. TEG has been shown to have better predictive capability of postoperative bleeding compared to conventional coagulation testing in cirrhotic patients [67–69]. Further, a recent study showed that TEG was predictive of early variceal bleeding, while standard coagulation tests were not [70]. A recent publication by Bedreli et al. [71] had addressed the role of rotational thromboelastometry (RTE) in decreasing both bleeding and thrombotic adverse effects in 37 patients with advanced cirrhosis, which was managed according to RTE-
Based on the literature, particularly the investigations by Jiang et al. [38], the routine semi-automated waveform-derived parameters of sonorheometry were found to be valuable in assessing the dynamic properties of blood viscosity. These findings were consistent with the capabilities of doppler flowmetric analysis, which was used by Mair et al. [39] to show that sonorheometric parameters could accurately predict changes in blood viscosity. Moreover, the sonorheometric method has been shown to be sensitive to changes in blood viscosity that occur during thrombus formation and lysis, as demonstrated by Mair et al. [39].

In conclusion, the use of sonorheometry as a monitoring tool for anticoagulants in cirrhotic patients represents a promising approach in the management of VTE prevention and therapy. The ability of sonorheometry to accurately assess changes in blood viscosity and provide real-time feedback on anticoagulant effects could potentially improve patient outcomes and optimize anticoagulant management in cirrhotic patients.
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management. Overall, the safety of prophylactic or therapeutic anticoagulation in carefully selected patients with cirrhosis without the presence of high-risk esophageal varices appears to be comparable to general medical patients. Based on the best available evidence, VTE prophylaxis appears overall relatively safe in cirrhosis and should be considered in all hospitalized cirrhotics unless absolutely contraindicated. While the risk of bleeding from therapeutic anticoagulation does exist in advanced liver disease, treatment of VTE with anticoagulant agents should be carefully considered and may provide important clinical benefits, which may outweigh the risks of hemorrhage on a case-by-case basis involving balanced risks assessment. We do, however, propose a treatment algorithm for managing hospitalized cirrhotic patients regarding the use of either prophylactic or therapeutic anticoagulation treatment and we recommend that cirrhotic patients receive primary or secondary prophylaxis for esophageal varices with either endoscopic variceal ligation or use of non-selective beta-blockers prior to initiation of anticoagulation when possible (fig. 2). In summary, sufficient evidence exists, promoting the use of anticoagulation in cirrhotic patients for both VTE prophylaxis and treatment in carefully selected patients after consideration of pharmacologic or endoscopic variceal bleeding prophylaxis and patient-centered discussion about the risks and benefits of anticoagulation.

Disclosure Statement
None.

Financial Support
None.

Author’s Contributions
T.K., A.R.A., S.D., C.S., J.C. and M.M. have all contributed to the conception, design data collection, analysis and drafting of the final manuscript.

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Digestion 2016;93:149–159
DOI: 10.1159/000442877