Liver stiffness and thrombin generation in compensated cirrhosis

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Abstract

Background: Decompensated cirrhosis is associated with coagulation abnormalities that can increase the risk of thrombosis and bleeding. It is unclear precisely when these abnormalities arise and whether they are exacerbated as compensated cirrhosis progresses. Transient elastography using FibroScan generates liver stiffness measurements (LSM) that associate with portal hypertension, clinical outcomes and provides prognostic information at an earlier stage than traditional liver function scores eg, MELD score.

Objective: To characterize thrombin generation in patients with compensated cirrhosis and to determine whether parameters of coagulation change throughout compensated cirrhosis, staged using LSM.

Patients/Methods: Blood samples were collected from well-compensated cirrhotic patients n = 61, All Child Pugh A stage) attending the Mater Misericordiae University Hospital, Ireland. Comprehensive clinical staging of liver disease, including LSM, was performed. Tissue Factor-stimulated thrombin generation was measured by calibrated automated thrombography.

Results: Using LSM to stage well-compensated cirrhotic patients, we demonstrate a significant decrease in the rate of propagation, the rate of attenuation, and total thrombin generation as LSM increase. LSM correlated with endogenous thrombin potential, peak thrombin generation, the rate of propagation, and the rate of attenuation. This association between thrombin generation and LSM was still evident in sub-analyses excluding patients with ongoing alcohol use, active HCV infection, or a history of decompensation. In contrast, there was no significant correlation between thrombin generation, prothrombin times, Child-Pugh scores, or MELD scores.

Conclusion: Liver stiffness measurements identify differences in parameters of thrombin generation within a cohort of compensated cirrhotic patients before changes in clotting times occur.

KEYWORDS
blood coagulation, cirrhosis, liver disease, thrombin
1 | INTRODUCTION

Patients with cirrhosis, particularly decompensated cirrhosis, are prone to both bleeding and thrombotic complications. Clotting times are frequently prolonged in cirrhotic patients, but poorly predict procedure-related bleeding in cirrhosis, because these assays are insensitive to coexisting anticoagulant pathway deficiencies seen in cirrhotic patients, such as reduced levels of protein C and antithrombin. Thrombin generation measured by calibrated automated thrombography (CAT) is considered a more accurate representation of an individual's coagulation phenotype. Tissue factor (TF)-stimulated thrombin generation responses can be reduced, normal, or enhanced in cirrhotic patients relative to healthy controls. In contrast, thrombomodulin modified TF-stimulated thrombin generation responses, a more accurate representation of coagulation status in cirrhosis as it takes into account reduced Protein C levels, range from normal to enhanced responses. These differences in thrombin generation are most apparent in patients with advanced or decompensated cirrhosis.

It is not known precisely when during the course of cirrhosis progression these changes begin to take place. Understanding the progression of thrombin generation in compensated cirrhosis is important for a variety of reasons. First, coagulation enzymes have been reported to promote fibrosis progression. Many mechanisms have been described including thrombin-mediated activation of stellate cells through protease activated receptors; microthrombi and parenchymal extinction. As a result, anticoagulation may in time be used as a direct therapy for liver fibrosis and cirrhosis. Enoxaparin therapy has been shown to delay the occurrence of decompensation and improve survival in patients with advanced cirrhosis. Second, there is a tendency to avoid anticoagulation for other clinical reasons in patients with cirrhosis due to fears of variceal and nonvariceal hemorrhage. These fears may be misplaced, and a better understanding of hemostasis would help to encourage best practice for other conditions such as stroke and venous thromboembolism. Recent meta-analysis data for anticoagulation and portal vein thrombosis is encouraging for safety.

Transient elastography (Fibroscan, Echosens) measures the velocity of a shear wave as it passes through the liver to generate a liver stiffness measurement (LSM). Transient elastography is used to detect and stage fibrosis as well as identify thresholds within cirrhosis that are associated with worsening disease (the development of portal hypertension) and prognosis. Traditional liver function scoring systems are well-validated to determine prognosis in decompensated cirrhosis, or end-stage liver disease rather than compensated cirrhosis. The Mayo End Liver Disease Score (MELD) score has greater predictive and finer stratification ability than the Child Pugh score (e.g., in transplant allocation or mortality after transjugular intrahepatic portosystemic shunt [TIPS]). In comparison, LSM has been shown in meta-analyses to perform well with greater discrimination in predicting decompensation in patients with compensated cirrhosis.

We hypothesized that segregating well compensated cirrhotic patients (defined by Child-Pugh, MELD scores, and clotting times) based on their respective LSMS would allow us to identify patients with early observable differences in parameters of thrombin generation. As such, LSM thresholds were used to separate compensated cirrhotic patients and a cross-sectional analysis of thrombin generation and routine liver function assays were made across LSM groups.

2 | METHODS

2.1 | Patients

Patients were recruited from a single site, prospective cohort study of patients with compensated cirrhosis, over a 2-year period (2013-2015). All patients gave written informed consent. The study was conducted in line with the Declaration of Helsinki and approved by the Mater Hospital Institutional Review Board. Inclusion criteria for the cohort study were: a diagnosis of liver cirrhosis by a consistent clinical history and one of the following: (i) biopsy-proven cirrhosis; (ii) endoscopic or radiological evidence of varices and thrombocytopenia (platelets <150 \times 10^9/L) or radiological evidence of splenomegaly (spleen diameter >11 cm); or (iii) LSM >22.6 kPa for subjects with alcoholic liver disease, LSM >14.6 kPa for subjects with hepatitis C or LSM >17.3 kPa for subjects with all other etiologies of liver disease. Patients who had a previous history of decompensation were compensated for at least 6 months, and decompensation was defined as ascites, encephalopathy, and variceal bleeding. Once patients were enrolled in the cohort study, they were screened for the following exclusion criteria: history of venous thromboembolism, history of portal vein thrombosis, malignancy, the use of anticoagulant or antipla-let agents, active bacterial infection. Same-day phlebotomy and transient elastography using Fibroscan were performed by a single experienced operator. We used LSM cut-offs previously described in the literature in patients with compensated cirrhosis as being...
associated with the development of clinically significant portal hypertension (21 kPa) and decompensation (35 kPa). Reliability criteria were defined as more than 10 valid measurements, with IQR/M of 0.10 or 0.10 < IQR/M 0.30, or IQR/M > 0.30 when LSM < 7.1 kPa Measurements were considered reliable based on a median of 10 readings, using validated criteria. As the study protocol was drawn up prior to the introduction of fasting for Fibroscan, patients were not fasted.

2.2 | Blood collection

Blood was collected into vacutainers containing 0.106 mmol/L sodium citrate as anticoagulant (10% vol/vol). Platelet-poor plasma was prepared by centrifugation of whole blood at 2000 g for 10 minutes. Plasma was aliquoted and stored at −80°C until analysis.

2.3 | Calibrated automated thrombography

Thrombin generation in citrate-anticoagulated platelet-poor plasma was assessed by CAT using a Fluoroskan Ascent Plate Reader (ThermoLab System, Helsinki, Finland) in combination with Thrombinscope software (Thrombinscope BV, Maastricht, the Netherlands). Plasma was incubated with 20 μL “platelet-poor plasma (PPP) reagent” containing 1 pmol/L soluble tissue factor (TF) and 4 μmol/L phospholipid vesicles (60% phosphatidylcholine, 20% phosphatidylserine, 20% phosphatidylethanolamine). Thrombin generation was initiated by automatic dispensation of fluorogenic thrombin substrate (Z-Gly-Gly-Arg-AMC.HCl) and 100 mmol/L CaCl2 into each well (final concentrations, Z-Gly-GlyArg-AMC.HCl, 0.42 mmol/L and CaCl2, 16.67 mmol/L). Thrombin generation was determined using a thrombin calibration standard and characterized by measurement of specific parameters, including lag time to initiation of thrombin generation, peak thrombin generated, time to peak thrombin generation, the area under the thrombin generation curve (endogenous thrombin potential, ETP), rate of propagation (or velocity index, calculated as peak thrombin/time to peak-lagtime), and the rate of attenuation (calculated as peak thrombin/start tail-time to peak). The operator was blinded to patient information until time of data analyses.

2.4 | Statistical analysis

Data were analyzed using GraphPad Prism (Horsham, PA). Data were expressed as the mean ± standard deviation or the median ± the interquartile range. The Kilmogorov-Smirnov test was used to determine if data sets were parametric or nonparametric. Comparisons of variables across the < and > 35 kPa LSM groups were assessed using unpaired t test or Mann Whitney test. Comparisons of variables across the <21, 21-35, and >35 kPa LSM groups were assessed by one-way analysis of variance (ANOVA) followed by Bonferroni test or the Kruskal Wallis test followed by Dunn’s test. Correlations between variables were assessed using the Spearmann Rank Correlation coefficient.

3 | RESULTS

3.1 | Clinical characteristics

Eighty-five patients were enrolled in the study. Due to unreliable transient elastography (TE) readings, 61 patients (72%) were included in the final analysis, which is consistent with previous studies on TE. Patient characteristics, including etiology and method of diagnosis of cirrhosis are shown in Table 1. Most patients were male (75%) with a median age of 55 years (range 36-76). The majority of patients had either alcohol related liver disease (75.5% were abstinent) or Hepatitis C infection (12% with previous sustained virologic response [SVR]). Disease staging was performed by using standard scoring systems to stage cirrhosis (Childs Pugh, MELD score) as well as by staging disease severity based on LSM (32.3% by XL probe, 67.5% by M probe). Of the 13 patients with previous decompensation, 10 had ascites that was fully resolved on ultrasound for the previous 6 months prior to enrolment, two had previous jaundice associated with alcoholic hepatitis, and one had bleeding varices. All patients had a diagnosis of compensated cirrhosis, with a maximum Child Pugh Score of 7.

3.2 | TF-dependent thrombin generation

TF-dependent thrombin generation (1 pmol/L TF, final concentration) was measured in platelet-poor plasma from well-compensated cirrhotic patients. Patients were grouped based on LSMs, using the previously described cut-offs of 21 and 35 kPa, defined based upon risk for liver-related complications. Comparisons were made between patients with LSMs of <21, 21-35, and >35 kPa (Figure 1) and between patients with LSMs of <35 and >35 kPa (Figure 2). A comparison of parameters of thrombin generation between cirrhotic patients and healthy controls are included in Table S1.

When cirrhotic patients were grouped in LSM groupings of <21, 21-35, and >35 kPa, there were no significant differences in the lag time to thrombin generation (<21 kPa; 5.7 ± 1.2 minutes, 21-35 kPa; 6.1 ± 2.1 minutes, and >35 kPa; 6.8 ± 2 minutes) (Figure 1A). There was also no significant difference in the lag time to thrombin generation when patients with LSM values <35 kPa (5.8 ± 1.5 minutes) when compared to >35 kPa (Figure 2A). Endogenous thrombin potential (ETP) values decreased across the <21 kPa (1421 ± 331 nmol/L/min), 21-35 kPa (1377 ± 413 nmol/L/min), and >35 kPa LSM groupings (1121 ± 364 nmol/L/min, Figure 1B) with a significant difference in ETP when patients with LSM values <35 kPa (5.8 ± 1.5 minutes) when compared to >35 kPa (Figure 2A). Patients with LSM >35 kPa had significantly lower peak thrombin generation values (106 ± 53.7 nmol/L) than patients with LSM <21 kPa (190.4 ± 66.9 nmol/L, P < 0.01, Figure 1C) and <35 kPa (181.2 ± 64.8 nmol/L, P < 0.01, Figure 2C). There was a prolongation in the time to peak thrombin generation when cirrhotic patients with an LSM value >35 kPa (13.1 ± 2.6 minutes, P < 0.05) were compared to patients with LSM values <21 kPa (10.4 ± 2.1 minutes, Figure 1D) and patients with LSM values...
As LSM increased, there were significant decreases observed in the rate of propagation (or velocity index). Cirrhotic patients with LSM >35 kPa had lower rates of propagation (19.8 ± 15 nmol/L thrombin/min) relative to cirrhotic patients with LSM <21 kPa (47.5 ± 28.5 nmol/L thrombin/min, \( P < 0.05 \), Figure 1E) and <35 kPa (44.1 ± 26.6 nmol/L thrombin/min, \( P < 0.05 \), Figure 2E). There was also a significant decrease in the rate of attenuation as LSM increased, suggesting simultaneous decreases in both procoagulant and anticoagulant pathways across LSM groupings. The rate of attenuation was significantly lower in patients with LSM values >35 kPa (5.2 ± 3.3 nmol/L thrombin/min, \( P < 0.01 \)) and 21-35 kPa (7.5 ± 2.9 nmol/L thrombin/min, \( P < 0.05 \)) compared to patients with LSM values <21 kPa (11.2 ± 2.6 nmol/L thrombin/min) (Figure 1F). Similarly, the rate of

| TABLE 1  | Patient demographic information (mean and interquartile range) |
|----------|---------------------------------------------------------------|
| All cases | LSM <21 | LSM 21-34 | LSM >35 | \( P \)-value* |
| n         | 61     | 40      | 14     | 7         | –               |
| Sex (% male) | 75   | 70      | 85     | 57        | 0.4             |
| Age (years) | 55 (44.5-76) | 55 (43-62) | 58 (51-65) | 51 (49-54) | 0.4             |
| BMI (kg/cm²) | 28.1 (24.6-31.4) | 27.4 (24.5-29.9) | 29.9 (24.8-34.3) | 30 (20-34.7) | 0.2             |
| Etiology | AIH (n = 2), ALD (n = 22), Cryptogenic (n = 2), HBV (n = 3), HCV (n = 25), HH (n = 2), NAFLD (n = 4) | AIH (n = 2), ALD (n = 11), Cryptogenic (n = 3), HBV (n = 3), HCV (n = 17), HH (n = 2), NAFLD (n = 3) | ALD (n = 6), Cryptogenic (n = 1), HCV (n = 7) | ALD (n = 5), HCV (n = 1), NAFLD (n = 1) | – |
| Previous decompensation (%) | 21.3 | 17.5 | 21 | 42 | 0.3 |
| Smoking status (% current use) | 41 | 32.5 | 50 | 57 | 0.3 |
| Alcohol use (% current use) | 24.5 | 22.5 | 28.5 | 28.5 | 0.8 |
| Diabetes (%) | 29.5 | 35 | 14 | 28.5 | 0.3 |
| Hematocrit (%) | 41.4 (37.5-43.7) | 41.8 (37.3-44.1) | 41.4 (36.7-42) | 41.3 (39-43) | 0.7 |
| Hemoglobin (g/L) | 14.2 (12.6-14.9) | 14.4 (12.6-15) | 13.7 (12.4-14.5) | 14.6 (13-14.9) | 0.5 |
| Lymphocyte count (×10⁹/L) | 1.5 (1.1-2.1) | 1.5 (1.1-2.1) | 1.48 (0.9-1.7) | 1.9 (1.45-2.2) | 0.35 |
| White cell count (×10⁹/L) | 5.6 (4.2-7.3) | 5.6 (4.0-7.2) | 5.4 (4.2-7.2) | 7.2 (4.8-9.3) | 0.46 |
| Platelet count (×10⁹/L) | 133 (102-176) | 143 (108-197) | 111 (75-156) | 124 (88-161) | 0.18 |
| Albumin (g/L) | 39 (37-41.5) | 40 (37.2-41) | 38 (37-42) | 36 (35-44) | 0.79 |
| Bilirubin (μmol/L) | 15 (10.5-22) | 15 (9-20.5) | 15.5 (11.7-25) | 18 (11-27) | 0.6 |
| Creatinine (μmol/L) | 73 (66-88.5) | 71.5 (66-86) | 74.5 (34-66.2) | 45 (34-152) | 0.5 |
| Aspartate aminotransferase (AST, U/L) | 43 (30-55) | 40 (29-52.7) | 45.5 (34-66.2) | 45 (24-152) | 0.5 |
| Alanine aminotransferase (ALT, U/L) | 29 (22-66) | 30 (19.5-65) | 29 (23.5-96) | 29 (24-59) | 0.9 |
| AST:ALT ratio | 1.06 (0.84-1.4) | 1 (0.78-1.35) | 1.1 (0.93-1.58) | 1.42 (1-2.2) | 0.06 |
| Alkaline phosphatase (U/L) | 98 (77-128) | 84 (68-105) | 119 (83.5-150) | 105 (98-174) | 0.01 |
| Haptoglobin (g/L) | 0.94 (0.38-1.23) | 1 (0.42-1.6) | 0.73 (0.2-1.1) | 0.5 (0.42-1.1) | 0.47 |
| Prothrombin time (s) | 11 (11-12) | 11 (11-12) | 12 (11-13.6) | 11 (11-12) | 0.13 |
| International normalized ratio | 1 (1.0-1.1) | 1.0 (1.0-1.1) | 1.1 (1.05-1.2) | 1 (1-1.1) | 0.03 |
| MELD score | 8 (7-9) | 7.5 (7-9) | 8 (7-9.2) | 8 (7-14) | 0.46 |
| Child Pugh Score | 5 (5-5) | 5 (5-5) | 5 (5-6) | 5 (5-6) | 0.76 |
| Liver stiffness measurement (kPa) | 13.4 (10.5-27.2) | 11.6 (8.7-13.3) | 27.5 (24.8-30.7) | 66.4 (43.5-75) | <0.0001 |
| Spleen size (cm) | 12 (11-14) | 11.5 (10.2-12.9) | 12.5 (11.2-15.6) | 14.5 (12.6-14.8) | 0.058 |

AIH, autoimmune hepatitis; ALD, alcoholic liver disease; ALT, alanine aminotransferase; AST, aspartate,aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; HH, hereditary hemochromatosis; LSM, liver stiffness measurements; MELD, Mayo End Liver Disease Score; NAFLD, non-alcoholic fatty liver disease.

*Comparison across LSM groups (One-way ANOVA or Kruskal–Wallis test).
Liver stiffness measurement (kPa)

**FIGURE 1** Thrombin generation in compensated cirrhotic patients separated based on LSM of <21, 21-35, and >35 kPa (mean ± standard deviation). TF-dependent thrombin generation (1 pmol/L TF) was measured in platelet-poor plasma from cirrhotic patients. Patients were separated based on Fibroscan LSM (<21, 21-35, and >35 kPa). (A) Lagtime to thrombin generation. (B) Endogenous thrombin potential (ETP). (C) Peak thrombin generation. (D) Time to peak. (E) Rate of propagation. (F) Rate of attenuation. Data was analysed using one-way ANOVA followed by Bonferroni post test or Kruskal Wallis test followed by Dunn’s test. *P-value less than 0.05. **P-value less than 0.01.

attenuation was significantly lower in patients with LSM values >35 kPa compared to <35 kPa (10.2 ± 4.5 nmol/L thrombin/min, Figure 2F).

Within this cirrhotic patient cohort, LSM correlated significantly with ETP ($r = -0.25, P = 0.048$), peak thrombin generation ($r = -0.35, P = 0.005$), and the rate of propagation ($r = -0.32, P = 0.012$), and the rate of attenuation ($r = -0.42, P = 0.001$). In a sub-analysis of our data with patients with a history of decompensation removed, there was still a significant correlation between LSM and parameters of thrombin generation (peak thrombin generation; $r = -0.321, P = 0.026$, the rate of propagation; $r = -0.3, P = 0.038$, and the rate of attenuation; $r = -0.421, P = 0.003$). LSM significantly correlated with parameters of thrombin generation when patients with ongoing alcohol abuse were excluded from the analysis (peak thrombin generation; $r = -0.454, P = 0.002$, the rate of propagation; $r = -0.425, P = 0.003$, and the rate of attenuation; $r = -0.484, P = 0.001$). LSM also correlated with parameters of thrombin generation when patients with cured HCV infection were excluded from the analysis (peak thrombin generation; $r = -0.381, P = 0.003$, the rate of propagation; $r = -0.349, P = 0.007$, and the rate of attenuation; $r = -0.433, P = 0.001$).

In contrast to the association between LSM and thrombin generation, there was no significant correlation between parameters of thrombin generation and Child-Pugh or MELD scores. For example, there was no significant correlation between peak thrombin generation and Child-Pugh score ($r = -0.099, P = 0.45$) and MELD score ($r = -0.007, P = 0.955$), respectively. Despite observing differences in parameters of thrombin generation, prothrombin times did not differ significantly across the LSM groups (Table 1). Furthermore, there was no significant correlation between LSM and prothrombin time ($r = 0.21, P = 0.1$) in the cirrhotic patient cohort.

4 | DISCUSSION

In this study, we demonstrate that within a cohort of well-compensated cirrhotic patients with similar Child-Pugh scores, MELD scores, and prothrombin times, significant differences in thrombin generation are observed when patients are separated based on LSMs. Patients with higher LSMs exhibited significant reductions in peak thrombin generation, the rate of propagation, and the rate of attenuation. This association between LSMs and thrombin generation was still evident in sub-analyses excluding patients with ongoing alcohol use, active HCV infection, or a history of decompensation.

It is now well-established that conventional laboratory tests including prothrombin time and activated partial thromboplastin time
do not reflect true hemostatic balance in cirrhosis for many reasons; these include insensitivity to differences in anticoagulant pathways. Thrombin generation is considered a more accurate measure of in vivo coagulation. Several studies have characterized thrombin generation in cirrhotic patients and have revealed differences ranging from mildly reduced to enhanced thrombin generation. Tripodi et al reported that a heterogeneous population of cirrhotic patients (n = 44, 14 Child-Pugh A, 16 Child-Pugh B, and 14 Child-Pugh C) exhibited reduced TF-dependent thrombin generation compared to controls. ETP levels inversely correlated with correlated with Child-Pugh and MELD score. Similarly, we demonstrated reduced TF-stimulated thrombin generation in our patient cohort, most notably in patients with higher LSM. Gatt et al. found that patients with advanced cirrhosis (MELD; 12.1 ± 8.8) displayed an increased rate of propagation and a trend towards a reduced rate of attenuation compared to healthy controls. In our cohort, patients with an LSM < 21 kPa also displayed an increased rate of propagation, while patients with a with an LSM > 35 kPa displayed a significantly reduced rate of attenuation.

As cirrhotic patients also display reduced levels of anticoagulant factors, notably Protein C, many investigators have assessed thrombin generation in the presence of thrombomodulin (a cofactor for thrombin in the activation of Protein C to activated Protein C). Tripoldi et al observed no significant difference between cirrhotic patients and controls when thrombin generation was measured in the presence of thrombomodulin. Gatt et al demonstrated an increased ETP in the presence of Protac (an nonphysiological activator of Protein C) suggestive of enhanced thrombin generation and a hypercoagulable state. Similarly, Groeneweld et al reported that patients with higher MELDs generated more thrombin in the presence of thrombomodulin. It is highly likely that reductions in plasma protein C levels are present in our patient cohort and would lead to significant differences in thrombin generation responses when measured in presence of thrombomodulin. Thus, the thrombin generation responses reported within for our cohort do not reflect the true coagulation phenotype of our patients. We aim to characterize thrombomodulin-modified thrombin generation in future studies.

In our study, patients with LSM > 35 kPa were characterized by significant reductions in peak thrombin generation, the rate of propagation and rate of attenuation. Transient elastography is now widely available and easy to use and can add further prognostic information to the MELD and Child Pugh Score with regard to the development of decompensation and death. Our data suggest that transient elastography can be used to identify patients at higher risk.
of displaying coagulation abnormalities. It is likely that most patients with compensated cirrhosis in the future will have regular transient elastography examinations as part of routine clinical care.20

This study has some important limitations. As previously stated, we did not assess thrombomodulin-modified thrombin generation. Moreover, the small cohort size and relatively short period of follow-up, precluded an assessment of clinical hemorrhagic or thrombotic events. We plan to undertake future prospective studies in order to address these limitations. We included patients who had a previous episode of decompensation but remained fully compensated for at least 6 months prior to enrolment. Previous work has shown that previous decompensation had no difference on LSM measurement or liver related outcome at 2 years,21 and in this study we show similar lack of impact.

In conclusion, we demonstrate that patients with well-compensated cirrhosis (stratified by noninvasive testing) display significant differences in thrombin generation. These differences are evident at an early stage in disease progression prior to any detectable differences in standard laboratory tests such as the prothrombin time. Transient elastography is readily available and is likely to become more widely used in the assessment of early cirrhosis progression in the future. It is possible that changes in thrombin generation in combination with change in liver stiffness over the course of compensated cirrhosis could be explored as clinical marker for impending decompensation.

RELATIONSHIP DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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