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Evaluation of the change in liver stiffness after biliary drainage in patients with extrahepatic cholestasis

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Abstract

Increased liver stiffness (LS) due to extrahepatic cholestasis has been reported to reduce after biliary drainage. As far as we know, it has not been evaluated whether the method of drainage makes a difference in the change in liver stiffness until now. The aim of the study was to answer this question. The patients planned for endoscopic biliary drainage (EBD) or percutaneous biliary drainage (PBD) were enrolled for over an 18-months' time period. In those without chronic liver disease or liver tumor, liver stiffness was measured before and 10 days after the intervention, using acoustic radiation force impulse (ARFI) elastography. A total of 30 patients were included in the study excluding the ones not fulfilling the criteria and were divided into two groups: EBD group (n = 15) and PBD group (n = 15). The measurements were above the cut-off value for severe fibrosis (1.55 m/s) in all patients with a mean of 2.50 ± 0.72 m/s before drainage. The pre-drainage values of the PBD group were significantly higher than of the EBD group (2.79 ± 0.58 m/s vs 2.22 ± 0.74 m/s, $p = 0.02$). In all patients except 11, a significant reduction was observed in the stiffness values. The reduction with PBD was more significant than with EBD ($p = 0.04$). Percutaneous biliary drainage provided a more significant reduction in liver stiffness in patients with extrahepatic cholestasis. However, this result appears to be related to the nature of obstruction rather than the method of drainage, making the comparison weaker than expected from the original design.

Keywords: ARFI elastography, biliary drainage, extrahepatic cholestasis, liver stiffness

1. Introduction

Extrahepatic cholestasis (EHC) has been shown to increase liver stiffness (LS) irrespective of fibrosis. Distension of the bile ducts due to obstructed bile flow has been mainly accused of being the reason behind the elevation. It has also been demonstrated that such an increase usually becomes normal thanks to biliary drainage decompressing the obstruction (Millonig et al., 2008; Harata et al., 2011; Trifan et al., 2011; Yashima et al., 2011; Attia et al., 2014; Pfeifer et al., 2014; Kubo et al., 2016; Darweesh et al., 2020). The information and data about the change in LS, evaluated by quantitative US elastography methods including transient elastography (TE) and acoustic radiation force impulse (ARFI) elastography, have mostly been provided by the studies in which endoscopic biliary drainage (EBD) has been used as the primary treatment modality in the setting of EHC. Percutaneous biliary drainage (PBD) is the method that has not been compared with EBD with respect to its effect on LS yet, as far as we know. The aim of this prospective study was to assess whether the method of drainage has an associated impact on LS in patients with EHC, using ARFI elastography.

2. Materials and methods

2.1. Patients

Between March 2018 and October 2019, patients with EHC planned for biliary drainage either by endoscopic or percutaneous method were enrolled in this prospective study. Among them, those without dilated biliary radicles (<2 mm in diameter) or those having a serum total bilirubin level lesser than 2 mg/dl were not included in the study. In addition, patients with chronic liver disease or liver tumors were excluded. Liver stiffness measurement using ARFI elastography was made in all patients immediately before and on the 10th day after biliary drainage which was performed either by endoscopic or percutaneous method. Patients were excluded if biliary drainage was not feasible or biliary drainage was not successful in reducing serum bilirubin level. Additionally, patients who missed the post-drainage measurement, i.e. for whom only the pre-drainage measurement was available, were excluded. Patients who underwent biliary drainage more than one time within the 10 days period were also excluded.

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Fifty-two patients underwent ARFI elastography before drainage. Out of 52 patients, 22 were excluded from the study: 17 patients missed the post-drainage measurement, the attempts to perform EBD were failed in three patients, the biliary drainage with PBD was not successful in reducing the serum bilirubin level in one patient and one patient had to undergo PBD a few days after EBD. As a result, the study population included a total of 30 patients, who were divided into endoscopic biliary drainage (EBD; n=15) and percutaneous biliary drainage (PBD; n=15) groups (Fig. 1). This study was approved by the local Ethical Committee (Approval protocol number: 2018/3). Informed consent was obtained from all patients.

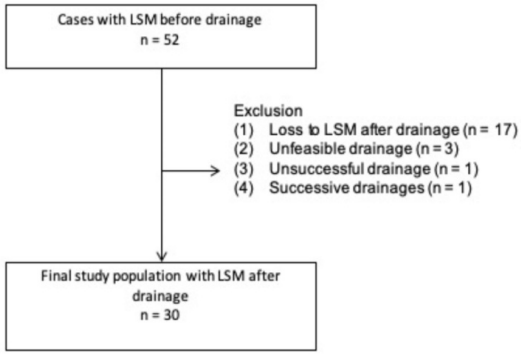

Fig. 1. Flow chart showing the selection of the study population. Twenty-two patients are excluded on the basis of the exclusion criteria, and a total of 30 patients are selected for statistical analysis. *(LSM liver stiffness measurement)*

2.2. Liver stiffness measurement

Liver stiffness was assessed by a single operator (F.U.) in order to avoid operator-related factors, complying with the current EFSUMB guidelines (Sporea, 2017). Using ARFI elastography (Virtual Touch™ Tissue Quantification; Siemens Medical Solutions) integrated in an ACUSON S2000® ultrasound platform (Siemens Medical Solutions, Erlangen, Germany) with a curvilinear array transducer (6C1 HD; Siemens Medical Solutions) at a frequency of 4 MHz, point shear wave speed measurement was performed corresponding with the quantitative value of LS. The measurements using ARFI elastography were performed in a supine position with an intercostal approach to the right liver lobe during relaxed breathing period. The region of interest (6 × 5 mm) was placed in the liver parenchyma with a distance of at least 2 cm from the liver capsule while ensuring not to include visible vessels and biliary radicles.

At least 10 validated measurements were performed in each patient. Results were expressed as the mean value of all measurements, in metres per second (m/s). The results were considered to be reliable when a success rate of measurement of greater than 60% (i.e., the ratio between validated and total measurements) was obtained. Measurements were successful in all patients.

2.3. Biliary drainage

The EBD procedures were performed by two experienced operators (I.G. and A.B.) using a duodenal endoscope (TJF-160VR, Olympus, Tokyo, Japan). The procedures included sphincterotomy, balloon sweeping and stenting, either alone or in combination. Two patients had a sphincterotomy, three patients had plastic stenting, seven patients had a sphincterotomy with balloon sweeping, one patient had a sphincterotomy with plastic stenting, and two patients treated with a combination of all three techniques. The PBD procedures were performed by two experienced operators (F.U. and A.I.S.) under fluoroscopic guidance (Artis Zee, Siemens Medical Solutions, Erlangen, Germany). In all PBD procedures except one, an external/internal biliary drainage catheter (Flexima, Boston Scientific, USA) was placed after crossing the obstruction. Only one patient had a procedure using external drainage due to fixed stenosis.

2.4. Serum cholestasis markers

Serum bilirubin, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT) and alanine aminotransferase (ALT) were recorded before biliary drainage and at 10 days post-biliary drainage. Other well-known markers of cholestasis such as serum bile acids were not obtained as they were not routinely measured in our clinical setting.

2.5. Sample size

In this study, we aimed to compare the effect of endoscopic and percutaneous biliary drainage on LS, using ARFI elastography. Based on previously published data (Pfeifer et al., 2014), this study must have enrolled 15 individuals for each group to have 90% power with 5% type I error to detect a minimum clinically significant difference of 0.89 units, when the average expected value of the LS measurements before drainage was 2.96, with a standard deviation of 0.95, using a paired Student's *t*-test. Assuming dropouts, we set our enrollment goal as 40 patients.

2.6. Statistical analysis

Statistical Package for Social Sciences for Windows, version 21.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. All data were presented as mean ± standard deviation (SD). Repeated-measures analysis of variance (ANOVA) was used for comparison of means regarding the LS measurements and laboratory data. A *p*-value less than 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

The study included a total of 30 patients with EHC. A summary of the basic patient characteristics was presented in Table 1. Most of the patients in the PBD group had cholestasis due to malignant biliary obstruction (11/15), whereas the EBD group mostly included patients with benign causes (13/15). The most common cause for biliary obstruction in the whole study population was choledocholithiasis (40%).

Table 1. Patient characteristics

	EBD group[a] n = 15	PBD group[b] n = 15	*p*
Male/Female	10/5	10/5	1.0[#]
Age, mean (range)	54.9 (24–82)	65.9 (40–89)	0.09*
Causative diseases (benign/malignant)	13/2	4/11	**0.03**[#]
Benign			
Stenosis of biliodigestive anastomosis	1	2	
Choledocholithiasis	10	2	
Periampullary diverticulum	1	None	
Autoimmune pancreatitis	1	None	
Malignant			
Pancreas carcinoma	None	4	
Periampullary tumor	2	4	
Extrahepatic biliary obstruction by metastatic carcinoma	None	3	

[a] Patients treated with endoscopic biliary drainage
[b] Patients treated with percutaneous biliary drainage
[#]*p*-values are calculated with chi-square test, and **p*-value with Mann-Whitney U test. Boldface type indicates statistical significance

3.2. Changes in liver stiffness and serum cholestasis markers

Liver stiffness measurements by ARFI elastography and laboratory data before biliary drainage (Day 0) and on the 10th day after biliary drainage (Day 10) were presented in Table 2.

Table 2. Liver stiffness measurements by ARFI elastography and laboratory data of the patients

	EBD group[a] n = 15		PBD group[b] n = 15		*p*		
					Treat	Time	Int
	Day 0	Day 10	Day 0	Day 10			
LS (m/s)	2.2±0.7	2.0±0.7	2.7±0.5	2.4±0.8	**0.04**	**0.03**	0.55
T-bil (mg/dl)	8.1±7.2	2.3±2.7	12.6±6.7	5.1±5.5	0.07	**<0.001**	0.31
ALP (IU/L)	343±245	175±111	517±378	242±122	0.12	**<0.001**	0.23
GGT (IU/L)	479±439	164±126	607±513	213±196	0.44	**<0.001**	0.53
ALT (IU/L)	257±145	69±47	151±107	54±32	**0.04**	**<0.001**	**0.03**

All data are shown as means ± SD.
LS liver stiffness, *T-bil* total bilirubin, *ALP* alkaline phosphatase, *GGT* gamma-glutamyl transferase, *ALT* alanine aminotransferase
[a] Patients treated with endoscopic biliary drainage
[b] Patients treated with percutaneous biliary drainage
p-values are calculated with repeated measures ANOVA model. Boldface type indicates statistical significance.

The measurements before biliary drainage were above the previously determined cut-off value for severe fibrosis (1.55 m/s) in all patients with a mean of 2.50 ± 0.72 m/s (Friedrich-Rust et al., 2012). Additionally, the mean of the measurements in the PBD group was significantly higher than the EBD group (2.79 ± 0.58 m/s vs 2.22 ± 0.74 m/s, $p = 0.02$, respectively). In all patients except 11, a significant reduction was observed in the measurements secondary to biliary drainage (from 2.52 ± 0.63 m/s to 1.92 ± 0.49 m/s, $p < 0.001$). This reduction in the PBD group was more significant than in the EBD group (Fig. 2).

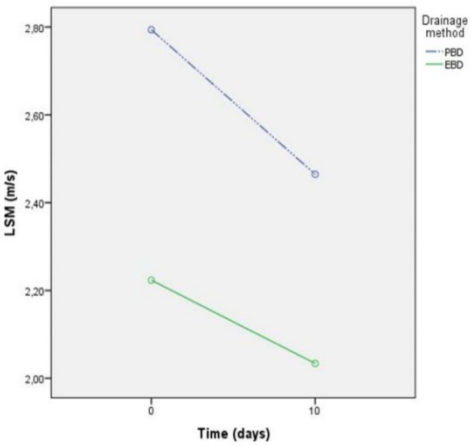

Fig. 2. Graphic showing the change in liver stiffness vs time. The reduction gradient obtained by each drainage method is represented as colored lines. The dashed dark blue line represents PBD and the solid green line EBD. It is obviously seen that the reduction gradient caused by PBD is steeper than by EBD (*LSM* liver stiffness measurement, *PBD* percutaneous biliary drainage, *EBD* endoscopic biliary drainage)

In a subgroup of 11 patients, it was found that LS kept increasing despite successful biliary drainage (from 2.57 ± 0.93 m/s to 2.95 ± 0.97 m/s). Of the 11 patients in this subgroup, six underwent EBD and five underwent PBD. The basic characteristics of this subgroup of patients was presented in Table 3.

In both two groups, it was found that pre-drainage levels of serum bilirubin, ALP, GGT and ALT were all elevated, as expected. Among them, only the levels of ALT in the EBD group were higher than the PBD group before drainage. A remarkable reduction was detected in the levels of all markers after drainage. The reduction in serum total bilirubin levels in the PBD group was considered as more significant than in the EBD group, even though the *p*-value was slightly greater than the significance level (p=0.07). The reduction in ALT levels was significantly higher in the EBD group than in the PBD group, and there was a significant time-treatment (i.e. biliary drainage) interaction, as well. However, the difference between the groups concerning the reduction in ALP as well as GGT levels was not statistically significant (Figs. 3, 4, 5 and 6). Finally, in the subgroup of patients whose LS kept increasing after biliary drainage, post-drainage levels of the serum cholestasis markers were all found to be decreased compared to the baseline levels, which was regarded as the evidence of successful biliary drainage.

Table 3. Characteristics of the patients whose liver stiffness kept increasing after biliary drainage

Patient	Age	Gender	Causative diseases	Drainage method	LS before drainage (m/s)	LS after drainage (m/s)
1	82	M	Choledocholithiasis	EBD	1.99 ± 0.36	2.09 ± 0.39
2	49	M	Choledocholithiasis	EBD	1.59 ± 0.16	1.71 ± 0.48
3	56	M	Choledocholithiasis	EBD	4.01 ± 0.52	4.39 ± 0.34
4	53	M	Choledocholithiasis	EBD	1.57 ± 0.48	2.85 ± 0.45
5	24	M	Autoimmune pancreatitis	EBD	1.58 ± 0.27	1.85 ± 0.37
6	72	M	Periampullary tumor	EBD	1.72 ± 0.13	1.78 ± 0.19
7	79	M	Stenosis of biliodigestive anastomosis	PBD	3.07 ± 0.78	3.28 ± 0.47
8	67	F	Stenosis of biliodigestive anastomosis	PBD	3.19 ± 0.44	3.34 ± 0.82
9	89	M	Pancreas carcinoma	PBD	2.41 ± 0.41	2.53 ± 0.45
10	40	F	Choledocholithiasis	PBD	3.61 ± 0.73	4.25 ± 0.37
11	68	M	Extrahepatic biliary obstruction by metastatic carcinoma	PBD	2.56 ± 0.83	2.80 ± 0.46

All data are shown as means ± SD. *LS* liver stiffness, *EBD* endoscopic biliary drainage, *PBD* percutaneous biliary drainage

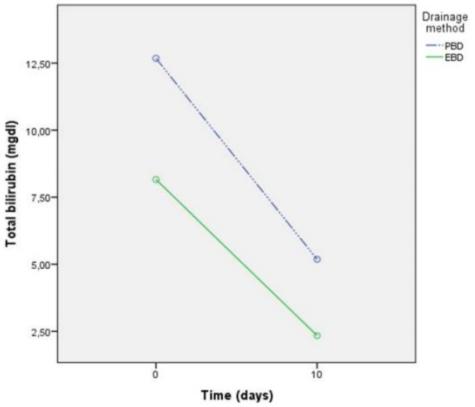

Fig. 3. Graphic showing the change in total bilirubin level vs time. Reduction gradients obtained by each drainage method are represented as colored lines. The dashed dark blue line represents PBD and the solid green line EBD. Although the reduction in serum total bilirubin levels obtained by PBD is considered as more significant than by EBD (please see the results chapter), the reduction gradients are almost similar (*PBD* percutaneous biliary drainage, *EBD* endoscopic biliary drainage)

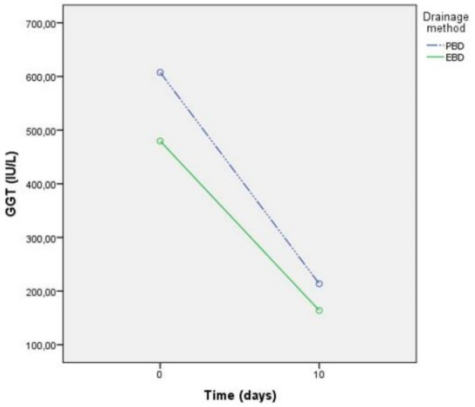

Fig. 5. Graphic showing the change in GGT level vs time. Reduction gradients obtained by each drainage method are represented as colored lines. The dashed dark blue line represents PBD and the solid green line EBD. There is not a significant difference in the reduction gradients caused by PBD and EBD, regarding the change in GGT level (*PBD* percutaneous biliary drainage, *EBD* endoscopic biliary drainage, *GGT* gamma-glutamyl transpeptidase*)*

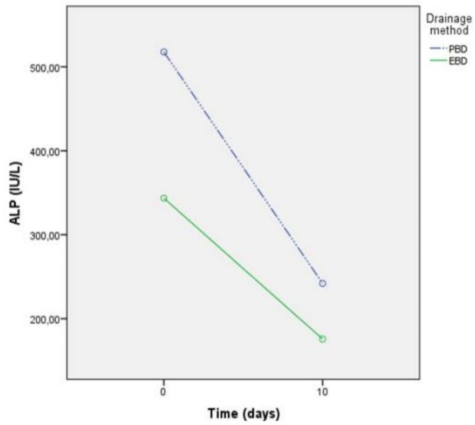

Fig. 4. Graphic showing the change in ALP level vs time. Reduction gradients obtained by each drainage method are represented as colored lines. The dashed dark blue line represents PBD and the solid green line EBD. There is not a significant difference in the reduction gradients caused by PBD and EBD, regarding the change in ALP level (*PBD* percutaneous biliary drainage, *EBD* endoscopic biliary drainage, *ALP* alkaline phosphatase*)*

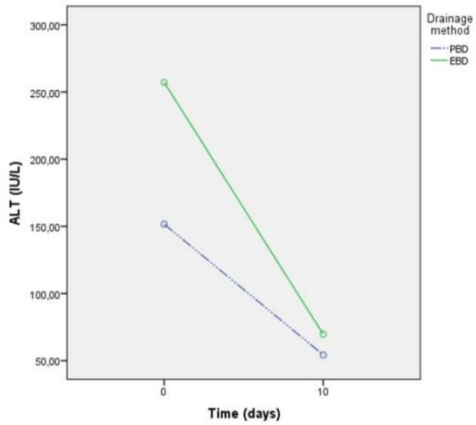

Fig. 6. Graphic showing the change in ALT level vs time. Reduction gradients obtained by each drainage method are represented as colored lines. The dashed dark blue line represents PBD and the solid green line EBD. Regarding the change in ALT level, it is seen that the reduction gradient caused by EBD is steeper than by PBD (*PBD* percutaneous biliary drainage, *EBD* endoscopic biliary drainage, *ALT* alanine aminotransferase*)*

4. Discussion

The main finding of this study is that malignant biliary obstruction causes LS to increase more significantly than benign obstruction. In the patients treated with PBD, the higher LS values as well as the higher serum bilirubin levels at baseline seem to be related to the increased severity of obstruction. In this group, the main reason for EHC was malignant diseases which typically pursue a progressive course, and which finally result in a complete obstruction. However, the patients treated with EBD mostly had EHC due to benign etiologies which are more likely to cause partial obstruction. Therefore, PBD may have yielded a more significant reduction in LS as well as serum bilirubin levels compared to EBD because of the worse cholestatic profile at baseline.

The present study confirmed that successful biliary drainage, either performed by endoscopically or percutaneously, does not necessarily reduce LS to the normal values. While improvement of the cholestatic laboratory profile was observed, the LS measurements did not decrease even after drainage in more than one-third of the patients in our study population. In contrast, an increase emerged when compared to baseline values. This result was slightly different from previously published reports. For instance, in the study reported by Harata et al. (2011), LS did not return to the normal levels in more than half of the patients. Another study revealing a similar result was reported by Attia et al. (2014), in which nearly half of the patients did not reach normal LS values at the end of the follow-up period, although the stiffness was found to be somewhat reduced. In the newly published report (Darweesh et al., 2020), it was noted that a reduction in LS was observed after adequate biliary drainage, even though the resultant values were slightly above the normal limits, measured using both TE and ARFI elastography. Failure to reach normal stiffness values indicates the impact of cofactors on LS. The mechanism behind the elevation of LS due to impaired bile flow was mainly attributed to the increased hepatic hydrostatic pressure (Millonig et al., 2008; Harata et al., 2011; Trifan et al., 2011; Yashima et al., 2011, Attia et al., 2014, Pfeifer et al., 2014; Kubo et al., 2016). Several studies have reported that impaired bile flow also causes cholestatic injury to the liver including hepatocellular necrosis, proliferation of the bile duct epithelial cells and liver fibrosis (Yashima et al., 2011, Kubo et al., 2016). Such changes in the tissue composition secondary to superimposed necroinflammatory damage may cause LS to increase even more (Gujral et al., 2003; Harata et al., 2011; Yashima et al., 2011; Yoon et al., 2012; Attia et al., 2014; Kubo et al., 2016). As a result, a delay may occur in the recovery of LS after an intervention. It seems likely that in the subgroup of patients whose LS kept increasing after drainage, the post-drainage measurements coincided with the secondary inflammatory and fibrotic changes. However, because of its invasiveness, liver biopsy was not performed to rule out probable secondary liver fibrosis formation. Except for this probability, the method of drainage did not appear to be effective on this consequence, because there was almost no difference in the frequency of each method of drainage in this subgroup.

It was previously suggested that LS negatively correlates with ALT levels in patients with EHC. The negative correlation between two variables was attributed to the leakage of bile flow from the bile duct lumen into adjacent potential spaces, with two outcomes (Harata et al., 2011). First, decompression of the bile ducts results in a reduction of hepatic hydrostatic pressure, which eventually causes LS to decrease. Second, ALT levels increase due to hepatocyte injury. Such a tableau is quite different from that observed in acute hepatitis, in which LS positively correlates with ALT levels because the inflammatory liver injury is dominant over increased hepatic hydrostatic pressure (Seo et al., 2010; Harata et al., 2011; Trifan et al., 2011; Bota et al., 2013; Choi et al., 2014). Although we did not analyze the correlation between LS and biochemical parameters, we observed that the patients in the EBD group had lower stiffness values, but had higher ALT levels than that of the patients in the PBD group. Considering the characteristics of the patients entered in the present study, the main difference between two groups was the etiology of biliary obstruction, which may have contributed to this situation. Because benign obstructions usually pursue a rapid course and can trigger acute inflammation, the ALT may have reached higher levels much earlier than LS in the EBD group. In contrast, because malignant obstructions typically pursue a prolonged course and damaged hepatocytes are capable of self-renewal over time, the baseline ALT levels may have been measured relatively less in the PBD group. The significant time-treatment interaction for the changes in ALT levels highlights the course of biliary obstruction, indicating a more rapid amelioration of liver functions in benign disorders.

There are several limitations to our study that need to be considered. First and most importantly, we could not compare the effect of both drainage methods on LS irrespective of the causative disease since the cases did not show a balanced distribution between the treatment groups. If that was possible, we could have clarified whether the method of drainage has an associated impact on the change in LS. This is a single-center study, in which there is an inherent bias in the treatment selection due to the obstructive jaundice patterns. Because of its invasiveness, PBD is not the preferred method of treatment for patients with EHC which EBD has the precedence. Secondly, relatively small sample size of the study may have limited the detection of a significant association between the change in serum bilirubin levels and the method of drainage. Finally, the correlation between LS and biochemical parameters was not analyzed separately. We do believe that a multicenter and larger randomized trial enrolling patient with similar obstruction patterns would be helpful to identify these issues.

In conclusion, our study clearly showed that malignant biliary obstruction increases LS more significantly than benign causes of EHC. Although a more significant reduction in LS was observed in the patients treated percutaneously than in the patients treated endoscopically, this consequence appears to be independent of the method of drainage. Additionally, it was confirmed that successful biliary drainage does not necessarily reduce LS, suggesting superimposed factors such as secondary liver fibrosis impairing the resolution. Finally, as previously defined, the negative correlation between LS and ALT levels was verified.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication that could have influenced its outcome.

Acknowledgments

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