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Elective percutaneous liver biopsy and use of aspirin

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Abstract

Objectives: Percutaneous liver biopsy is an essential diagnostic investigation in hepatology. Among complications, which are rare, bleeding is the most feared. Many patients scheduled for a liver biopsy are taking aspirin. Surprisingly no information is available in the literature on this frequent clinical situation. The American Association for the Study of Liver Diseases (AASLD) position paper on percutaneous liver biopsy does not specifically recommend stopping low dose aspirin prior to an elective percutaneous liver biopsy. The European Association for the Study of the Liver also remains unspecific without giving clear recommendation on stopping or not low dose aspirin before the procedure. The aim of this study is to document current practice concerning the management of patients scheduled for an elective percutaneous biopsy and taking low dose aspirin.

Design: An online questionnaire was designed to gather data on current practice on the perioperative management of percutaneous liver biopsy and use of aspirin.

Settings: The questionnaire was emailed to AASLD members in September 2018.

Participants: Four hundred sixty six responses were collected.

Results: Seventy eight percent postpone elective percutaneous liver biopsy if International Normalised Ratio is $\geq$1.5 or Quick $\leq$50%. Ninety five percent postpone biopsy if platelet count is $\leq$50,000 $\times$ 10^6/L. Seventy five percent stop low dose aspirin, on average, 6 days prior to the percutaneous liver biopsy. This choice of management does not seem to be related to previous complications since 86% report not having experienced any bleeding in patients taking low dose aspirin. Nevertheless, this practice has logistic consequences since 61% of the respondents postponed a liver biopsy due to intake of low dose aspirin.

Conclusions: Despite the lack of clear statement in guidelines and evidence supporting this practice, three quarters of physicians practicing in hepatology stop low dose aspirin before elective percutaneous liver biopsy.

KEYWORDS
aspirin, bleeding, liver biopsy, liver disease

INTRODUCTION

Percutaneous liver biopsy is an essential tool for the diagnostic but also for the assessment and the staging of liver diseases.[1] Despite the minimally invasiveaspect of the technique, liver biopsy may lead to complications. Bleeding is rare but is the most feared complication because it can be serious and require an intervention. The vast majority of percutaneous liver biopsy are scheduled electively allowing to change patients' medication to reduce the risk of bleeding. Oral anticoagulants are stopped and replaced with a more flexible therapy with heparin. Whether one should stop low dose aspirin for a percutaneous liver biopsy is not clear. Low dose aspirin inhibits platelets and is frequently prescribed as primary and secondary prevention for cardiovascular disease. In the United States, in 2012, more than 50 million adults (>16% of the American population in 2012) were taking aspirin.[2] Surprisingly, no data has been published on this frequent clinical situation. The European Association for the Study of the Liver (EASL) recently published clinical practice guidelines, specifically for patients with liver cirrhosis. They recommend managing antiplatelet agents in patient with cirrhosis the same way as in patients without cirrhosis before invasive procedures.[3] The American Association for the Study of Liver Diseases (AASLD) position paper on liver biopsy does not specifically recommend stopping low dose aspirin prior to an elective percutaneous liver biopsy. We were interested to document current practice concerning the management of patients taking low dose aspirin and scheduled for an elective percutaneous biopsy.

Key summary

Summarise the established knowledge

- Many patients scheduled for a liver biopsy are taking aspirin.
- Surprisingly no information is available in the literature on this frequent clinical situation.

New findings

- Despite the lack of clear statement in guidelines and evidence supporting this practice, three quarters of physicians practicing in hepatology stop low dose aspirin before elective percutaneous liver biopsy.

MATERIALS AND METHODS

A survey of nine questions regarding the periprocedural management of antithrombotic agent was developed. To minimize the time required to complete the questionnaire, all questions were to be answered by checking a box or with a simple number. The questions were kept short with less than 20 words and specific. A pilot survey was first sent to a group of eight liver specialists of the university hospital of Bern. The experts, coming from the same center, all gave the same answers. After minor improvements a final version was created and emailed in August 2018 to liver specialists. A reminder email was sent 4 weeks later. The analysis of the responses was done completely anonymously. Results are presented in percentages and mean ± standard deviations. The questions are the following:

1. Does your center have a standard operating procedure (SOP) for percutaneous liver biopsy? (Yes/No)
2. What is the International Normalised Ratio (INR) cut-off (or Quick %) of your center to postpone a percutaneous liver biopsy?
3. What is the platelet count cut-off of your center to postpone a percutaneous liver biopsy?
4. How many percutaneous liver biopsies are yearly performed in your center? (<50; 50–250; >250)
5. Did your center experience severe bleedings complication after percutaneous liver biopsy with patients taking low dose aspirin? (Yes/No)
6. Would low dose aspirin be stopped prior to percutaneous liver biopsy in your center? (Yes/No)
   a. If so, how many days before?
   b. If so, is it because your center has experienced bleeding complication after percutaneous liver biopsy with patients taking low dose aspirin?
7. Has your center experienced cases being postponed due to patients taking low dose aspirin? (Yes/No)

The terms “low dose aspirin” used in our questionnaire refer to the standard treatment for the secondary prevention of cardiovascular outcomes, so a dosage of 300 mg or less per day.

PATIENT AND PUBLIC INVOLVEMENT

We did not involve patients or the public in this study.

RESULTS

Four thousands and ninety liver specialists were invited per email to participate. A total of 466 completed the questionnaire, which corresponds to a response rate of 11.5%. Not all of them answered all the questions: 27% skipped at least one question. Geographically, 4% of respondents were form North America, 34% from Europe, 9% from Asia, 5% from South America, 4% from Australia and 2% from Middle East/Africa. A quarter of the respondents works in a centre where less than 50 biopsies are performed annually, 57% in a centre with 50 and 250 biopsies, and 18% where more than 250 biopsies are performed annually. Eighty-four percent of the survey respondents have a SOP for percutaneous liver biopsy in place at their centre. These characteristics that define our pool of experts who responded to the survey are summarized in Table 1.

TABLE 1 Respondents' characteristics

	Absolute number	Percentage (%)
Geographic repartition		
America	189	41
Europe	159	34
Asia	44	9
Canada	24	5
South America	22	5
Australia	19	4
Arabic league	9	2
Liver biopsies yearly performed		
<50	114	25
50–250	266	57
>250	86	18
Centre with a standard operating procedure (SOP)		
Yes	390	84
No	76	16

First, we aimed to determine the cut-off values related to bleeding diathesis chosen by most experts to postpone a percutaneous liver biopsy. We gave the choice in the questionnaire to answer in INR values or in Quick percentage values. Eighty-three percent responded using INR, 17 using Quick values. On average, biopsies are postponed with an absolute INR above 1.54 (±0.22 SD) and a median INR higher than 1.5. Fifty-three percent, answered with the exact same INR cut-off of 1.5. However, 11% of respondents only postpone the procedure if the INR is equal to or greater than 2. These results are shown in Figure 1a. Regarding responses given in Quick values, the procedure is postponed, on average, if the value is lower than 54 (±9) %. The median value is 50%. Again, more than half of respondents (65%) answered with the same cut-off: 50%. The results are shown in Figure 1b. These two figures show that 78% defer elective percutaneous liver biopsy if the INR is ≥ 1.5 or the PT ≤ 50%. The overall response rate for this question was 93.5%.

Regarding platelets, percutaneous liver biopsies are postponed with a mean value lower than 60,448 × 10^6/L (±17,513 × 10^6/L SD). The median value is by 50,000 × 10^6/L. Fifty-four percent answered the question with the same threshold of 50,000 × 10^6/L. Ninety-five percent deferred biopsy if the platelet count was ≤50,000 × 10^6/L. Indeed, looking at Figure 1c, there is an even distribution of response between 100,000 × 10^6/L and 60,000 × 10^6/L and a clear lower limit by 50,000 × 10^6/L of platelets. This question was ignored by only 2% of participants.

Concerning the periprocedural management of coagulation status and haemostasis risk, 75% stop low dose aspirin prior to an elective percutaneous liver biopsy. On average, the interruption was started 6.1 (±2.16) days before the intervention. The median value was 7 days. All responses are shown in Figure 1d.

The choice of management does not appear to be related to previous complications, as 86% report no bleeding in patients taking low-dose aspirin. Nonetheless, this practice has logistical consequences as 61% of respondents postponed a liver biopsy because of low-dose aspirin use.

DISCUSSION

Despite the lack of guidelines from professional societies such as the EASL or the AASLD, 84% of centres performing liver biopsies have a SOP for percutaneous liver biopsy. The Society of Interventional Radiology (SIR) published guidelines on the management of coagulation status and haemostasis risk in percutaneous image-guided Interventions. Some standards of practice are dedicated to the management of liver biopsy.[4,5] They recommend testing the INR with a preprocedure laboratory, the aPTT value only in patients receiving intravenous unfractionated heparin, and not to test platelet count and haematocrit. Regarding the periprocedural management, they recommend correcting the INR to <1.5, to transfuse platelets for count <50,000/µl and not to withhold aspirin.

Those guidelines are based on the Cardiovascular and International Radiological Society of Europe (CIRSE) Guidelines on percutaneous needle biopsy.[6]

The British society of gastroenterology, the royal college of radiologists and the royal college of pathology published their guideline on the subject in 2020.[7] They recommend stopping aspirin 3–7 days prior to elective procedures. A transvenous approach should be used where platelet count is <50 × 10^9/L or INR > 1.4. If a percutaneous procedure is required, an INR of 1.5–2.0 is no contraindication.

The AASLD[1] position paper on liver biopsy does not recommend any PT-INR and/or platelet count cut-off at or above which adverse bleeding can be predicted. The standards of practice by the Canadian association for interventional radiology and the CIRSE recommend a platelet count of >50 × 10^9/L and an INR < 1.5 as a threshold at which major surgery (including liver biopsies) can be performed safely.[5] A 2016 study involving a large volume of image-guided liver biopsies over a 12-year period reinforces this idea showing a statistically significant increased risk of post-biopsy bleeding with platelets count of 50,000/µl or less. Another large retrospective review of percutaneous biopsies of solid organs (renal, liver, pancreas and others) shows a significantly higher mean INR of 1.2 in the 65 patients with major bleeding complications compared to the mean INR of 1.0 in the 15,116 patients without complications.[8] However, the 1.2 INR of patients with bleeding complications remains below the cut-off of more than 90% of our respondents as well as most recommendations and studies cited so far.

Three quarters of respondents report stopping low dose aspirin before performing an elective percutaneous liver biopsy. This demonstrates a clear trend despite the lack of guidelines and literature's evidence. A large retrospective review by Atwell et al.[8] with more than 3,500 percutaneous liver biopsies shows that recent aspirin therapy does not seems to significantly increase the risk of

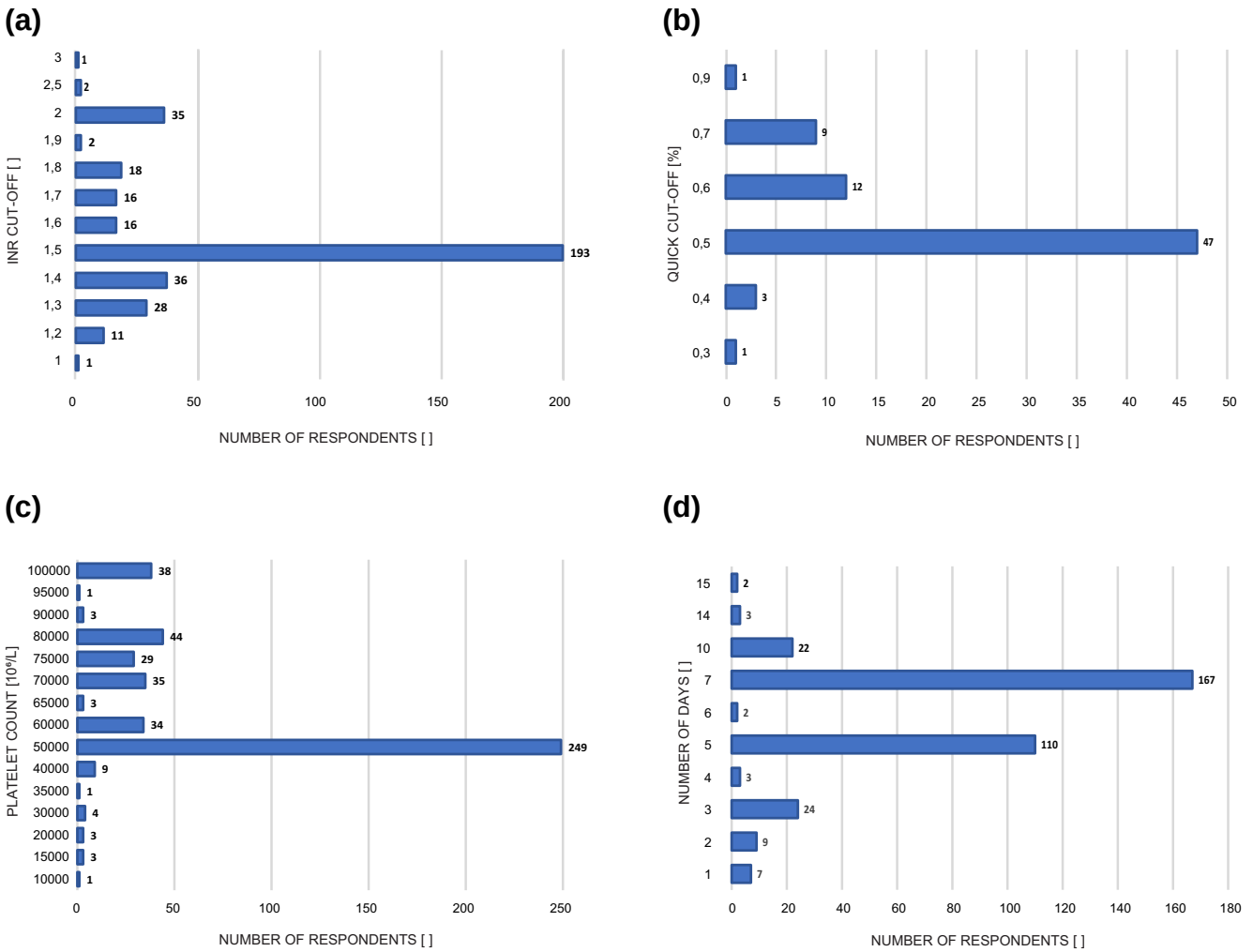

FIGURE 1 Overview of the responses to the survey questions. (a) INR cut-off to postpone the percutaneous liver biopsy. (b) Quick cut-off to postpone a percutaneous liver biopsy. (c) Platelet count cut-off to postpone a percutaneous liver biopsy. (d) Number of days between stopping aspirin and performing biopsies

bleeding complications. A meta-analysis from Burger et al.[9] on different kind of procedure including biopsies, reveals that aspirin increases the frequency of bleeding complications by approximately 50%. However, the increase is only on the frequency of bleeding complications not on their gravity. Low-dose aspirin may just be an indicator for increased comorbidity with increased bleeding risk per se. A retrospective review of 30,000 percutaneous biopsies (including 6000 of the liver) by Potretzke et al., analysed bleeding complication related with aspirin intake. A significant increased risk of bleeding with recent aspirin use, most significantly of aspirin is taken the day of biopsy has been highlighted.[10] A hypothetical bleeding risk must be contrasted with the risk of coronary and cerebrovascular events. Some studies clearly show an increased risk of non-fatal myocardial infarction after stopping low dose aspirin compared to those who continued it.[11–13] Here it is important to specify that percutaneous liver biopsies, due to the proximity of the great vessels, are classified as high-risk procedures for bleeding which may encourage experts to discontinue aspirin. However, that severe haemorrhage, defined as a change in vital sign and the likelihood of blood transfusions or even surgery, occurs only in 1:2500 to 1:10,000 biopsies.[1]

The survey finds that aspirin is usually stopped a week prior to the procedure. It is well established that a single dose of 20 mg of aspirin suppresses TXA2 production for 1 week and by this process the activation of the platelets and clots formation. The full restauration of platelets supply with normal Cyclooxygenase (COX) activity may take up to 10 days after discontinuing aspirin.[14] However, Bradlow BA pointed out that with only 20% of platelets with maintained COX activity, normal haemostasis can be maintained.[15] Other studies show restoration of platelet haemostatic function as early as day 1[16] and in most young healthy subjects after only 3 days of aspirin withdrawal.[17] Clinical studies on the subject suggest period for aspirin to be stopped from several to 10 days before interventional procedure.[1,5,18]

STRENGTHS AND LIMITATIONS OF THIS STUDY

The questionnaire was made to be anonymous, short, and concise. With the worldwide mailing and the high number of participants, this is the first study to properly document current practice of management of patients scheduled for an elective percutaneous biopsy and taking low dose aspirin. One-third of the respondent took time to give their feedback using the commentary box, showing high interest for the study. Response are predominantly driven by American experts, which could significantly bias the results. However, if we analyse this sub-population closely, the results are in line with the rest of the group. Their practice is to postpone the procedure if the platelets counts is below 60,000 $\times$ 10^6/L or the INR above 1.6. Seventy percent of them stopped low dose aspirin 6 days before the procedure.

Our study has some limitations. The physician's experience and specific adaptations for complicated patients cannot be reported in a questionnaire that is intended to be shot and concise. This can lead to generalizations and reporting bias. Mailing AASLD members, a majority of hepatologist has been selected. Our study would depict predominantly hepatologist's way of management rather than a global one. We decided to focus our study on transcutaneous liver biopsies only. We are aware that this may lead to interpretation bias, such as experts not stopping aspirin while changing their liver biopsy procedure (from transcutaneous to transjugular, for example). Nevertheless, we believe that the number of responses, their geographical distribution, and the varied size of the respondent's centers reflect a common practice of peri-procedural management during percutaneous liver biopsy. Finally, our questionnaire showed what is common practice and not what is the best practice.

CONCLUSIONS

Our survey shows that in clinical practice an elective percutaneous liver biopsy in postponed if the platelets counts is below $\leq$50,000 $\times$ 10^6/L or the INR above 1.5. Despite absence of guidance in guidelines, three quarter of the respondents stopped low dose aspirin a week before the procedure.

AUTHOR CONTRIBUTIONS

All authors contributed to the design of this protocol. All authors contributed to the manuscript and read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Dataset and details of statistical analysis will be available from the corresponding author at reynard.maxence@gmail.com. The presented data are anonymised and risk of identification is low.

ETHICS APPROVAL

This study involves human participants but was not approved by an Ethics Committee(s) or Institutional Board(s).

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