Outpatient Percutaneous Liver Biopsy is a Low-risk Procedure and has Steatosis as a New Indication Trend

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Abstract

BACKGROUND. Histological evaluation has a crucial role in diagnosing hepatic diseases and percutaneous liver biopsy (PLB) is widely chosen for this purpose. We aim to describe its indications, the rate and severity of adverse events (AEs) in an outpatient and ultrasound (US)-guided setting over 5 years. METHODS. This observational, single-center, and retrospective study included patients submitted to PLB between 2015 and 2019. We collected age, gender, coagulation tests, comorbidities, and number of needle passes. The association between the variables and outcomes (pain, mild and serious AEs, hospital admission, surgical treatment, and death) was evaluated using the generalized estimating equations method. RESULTS. We analyzed 532 biopsies in 524 patients (55.3% male) aged 49y (13–74y). Almost 39% had cardiovascular comorbidities and 18% had overweight/obesity. Hepatitis C virus (HCV) chronic infection was the major indication for PLB (47%), followed by autoimmune hepatitis/cholestasis (12.6%), and metabolic dysfunction-associated fatty liver disease (MAFLD) (12.1%). The number of HCV-related biopsies had a remarkable reduction, while MAFLD-related procedures have progressively raised over time. Around 54% of the patients reported pain, which was significantly associated with the female gender (p=0.0143). Serious AEs occurred in 11 patients (2.1%); hospital admission was necessary in 10 cases (1.9%), but no patient required surgical approach and there were no deaths. No significant association was found between the occurrence of AEs and the studied variables (clinical, laboratory, and number of needle passes). CONCLUSION. Real-time US-guided PLB is safe to perform in an outpatient setting and its indications have notably undergone a transition from HCV to MAFLD over the years. New strategies to prevent biopsy-related pain are still needed, especially for females.

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Steatosis as a New Reason for Liver Biopsy

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RESULTS . We analyzed 532 biopsies in 524 patients (55.3% male) aged 49y (13–74y). Almost 39% had cardiovascular comorbidities and 18% had overweight/obesity. Hepatitis C virus (HCV) chronic infection was

the major indication for PLB (47%), followed by autoimmune hepatitis/cholestasis (12.6%), and metabolic dysfunction-associated fatty liver disease (MAFLD) (12.1%). The number of HCV-related biopsies had a remarkable reduction, while MAFLD-related procedures have progressively raised over time. Around 54% of the patients reported pain, which was significantly associated with the female gender (p=0.0143). Serious AEs occurred in 11 patients (2.1%); hospital admission was necessary in 10 cases (1.9%), but no patient required surgical approach and there were no deaths. No significant association was found between the occurrence of AEs and the studied variables (clinical, laboratory, and number of needle passes).

CONCLUSION. Real-time US-guided PLB is safe to perform in an outpatient setting and its indications have notably undergone a transition from HCV to MAFLD over the years. New strategies to prevent biopsy-related pain are still needed, especially for females.

KEYWORDS: Liver biopsy, Hepatitis C, Steatosis, Fatty liver disease, Liver enzymes.

WHAT'S KNOWN? (What is already known about this subject?)

Percutaneous liver biopsy (PLB) remains essential to elucidate the etiology and severity of indeterminate liver diseases. It is generally a safe procedure with a low rate of serious complications. Most previous studies have assessed the safety of biopsies executed by radiologists and there are no large reports on the performance of gastroenterologists and hepatologists with real-time ultrasound guidance.

For many years, the indication for PLB has been viral hepatitis, but that need has been reducing in the era of non-invasive assessment of liver fibrosis and hepatitis C direct-acting antiviral drugs. So what would be the reasons for performing liver biopsies in the near future?

WHAT'S NEW? (what does this study contribute to the literature?)

In our study, real-time ultrasound guided liver biopsies were performed by senior residents in Gastroenterology and Hepatology (in an outpatient setting). We found similar results regarding the safety even in a scenario of physicians in training. In addition, the reasons for PLB have undergone a transformation over the years. It was possible to notice a remarkable drop in the amount of hepatitis C-related procedures and a progressive increase in the number of biopsies due to metabolic dysfunction-associated fatty liver disease (MAFLD), known as hepatic steatosis.

This enthusiasm for MAFLD histological evaluation is quite relevant, since new therapies are awaited and certainly, the staging of fibrosis and inflammation should help physicians in choosing the best therapeutic approach for their patients. This could delay the progression to cirrhosis and reduce the need for liver transplantation.

It is important to highlight that MAFLD has been reported as the second most common etiology of cirrhosis in explanted livers. We need to change this scenario. The first step is described in our study: this trend to perform liver biopsy in patients with steatosis.

INTRODUCTION

Histological evaluation has a crucial role in diagnosing the etiology and severity of hepatic diseases, liver tumors, and is useful in the follow-up after liver transplantation [1,2]. The effectiveness of this tool relies on a safe removal of the specimen and suitable provision of clinical and laboratory data to the pathology staff[1-3].

Several routes are available, such as laparoscopic, endoscopic, or transjugular [4] but percutaneous liver biopsy (PLB) is generally preferable since it is less invasive and less costly compared to other routes [2]. Coagulation impairment, low platelets, ascites, or anatomical changes are also important in this choice [1]. Physicians may use three different approaches: palpation/percussion-guided, image-guided, and real-time image-guided, most commonly ultrasound (US). Real-time US guidance seems to reduce the risk of adverse events (AEs) and this makes PLB safe to perform [2,3], whether by radiologists[5] or by gastroenterologists and hepatologists[6].

Although the pain has been commonly reported after PLB (30 – 50%), it is usually mild, self-limited, or has a good response to analgesics[4,7]. The incidence of serious complications is low, not exceeding 6% [8,9].

Approximately 60% of these events occur within the first 2 hours and 96% in the 24 hours following the procedure [10]. The reported incidence of bleeding ranges from 0.5 to 1.8% [11], but it can be serious and lead to death if prompt treatment is not carried out[1,10].

In recent years, the main indication for PLB has been the evaluation of hepatitis C virus (HCV) chronic infection, either to exclude other etiologies of hepatic damage or to establish the histological stage of fibrosis and set the appropriate therapy [12]. However, that need has been reducing in the era of non-invasive assessment of liver fibrosis and direct-acting antiviral drugs [13].

There are few reports on the purpose and safety of real-time US-guided PLB performed by hepatologists in a large outpatient cohort. We aim to describe the indications, as well as the rate and severity of biopsy-related AEs in a 5-year study.

METHODS

This observational, retrospective, and single-center study involved individuals submitted to outpatient PLB from January 2015 to December 2019 at the Gastrocentro of the University of Campinas (Unicamp), Campinas, Brazil. Patients were eligible according to a database record and subsequently, analysis of manual and electronic medical records was conducted. The protocol was analyzed and approved by the Ethics Committee of the University of Campinas (Unicamp) (CAAE: 29553819.9.0000.5404). An informed consent term was applied to the patients who were still on follow-up at our center.

Inclusion criteria: patients > 12 years old submitted to US-guided PLB at the Gastrocentro (Unicamp) during the study period. **Exclusion criteria:** those with incomplete data in the medical records. We analyzed gender, age, comorbidities, platelets count, INR (international normalized ratio), indication for the biopsy, number of needle passes, as well as PLB-related AEs and outcomes. Patients submitted to more than one PLB were considered as a new case.

The indications for PLB were classified as follows: HCV, hepatitis B virus (HBV), autoimmune hepatitis (AIH) / cholestasis, elevated liver enzymes, metabolic dysfunction-associated fatty liver disease (MAFLD), and post-transplant follow-up. Other indications, such as suspicion of drug-induced liver injury, were adjudicated as elevated liver enzymes.

The patients´ comorbidities were classified as 1) *cardiovascular* : high blood pressure, diabetes mellitus, dyslipidemia, heart failure; 2)*overweight or obesity* , 3) *chronic kidney disease* , 4)*neuropsychiatric disorders* , 5) *other* : thyroid, respiratory, intestinal disorders or acquired human immunodeficiency syndrome, as described in the medical records. Patients could be inserted into more than one group of comorbidities.

All the procedures were performed in a real-time US-guided setting and the operator was a senior resident supervised by a hepatologist. Patients were instructed to fast for 6 hours and to withdraw anticoagulants and anti-inflammatory drugs for at least one week before the biopsy. Insulin and oral antidiabetics were withdrawn on the day of the procedure. Continuous use medications should not be suspended.

Patients were positioned supine on the bed with his or her right arm placed above the head. A low dose of intravenous midazolam (2 to 3 mg) was usually administered. Local anesthesia was performed with lidocaine 2% after skin sterilization. A Tru-cut 14G needle was used preferably in the right hepatic lobe accessing through intercostal spaces. The number of needle passes depended on the operator´s decision. Patients remained on complete rest and fasting in a comfortable position, under the monitoring of vital signs, and were discharged after 4 to 6 hours. They were instructed to return in case of severe pain in the abdomen, chest or at the puncture site, dizziness, fainting, nausea, vomiting, or dyspnea.

The PLB-related consequences were divided as follows: 1) *pain* : complained by the patient at the puncture site, on the right shoulder, thorax, or abdomen. 2) *mild AEs* : high blood pressure (systolic blood pressure > 150mmHg), low blood pressure (systolic blood pressure < 90mmHg), nausea/vomiting, headache, and hypoglycemia (<70 mg/dL on capillary glucometer). 3)*serious AEs* : detection of perihepatic fluid at bedside

US examination, subcapsular bleeding, right-sided hemothorax, and death. The need for hospital admission and surgical treatment was assessed up to two months following the procedure.

STATISTICAL ANALYSIS

The Generalized Estimating Equations method was used to evaluate the association between the variables and pain or complications. The estimates were calculated by maximum likelihood in order to avoid bias on the difference in the number of PLB for each patient. Observations within a given patient were not independent and intra-patient correlation and variation were introduced into the analysis using a mixed generalized linear model.

The Chi-square or Fisher's exact tests were used to compare categorical variables and the Mann-Whitney test for numerical variables. Statistical analysis was performed using the SAS for Windows version 9.4 system. The level of statistical significance adopted in the analysis was 5%.

RESULTS

A total of 569 biopsies were performed during the study period. Due to a lack of data in the medical records, 37 cases were excluded. Eight subjects underwent two biopsies, so the study involved 532 biopsies in 524 patients (55.3% male) with a median age of 49 years (range: 13 to 74), as shown in Table 1.

Regarding laboratory tests, INR value and platelets count were available in 530 procedures. The median and range (minimal – maximum) were 1.01 (0.84 – 1.55) and 200,000/mm^3 (48,000 – 474,000/mm^3 Almost 40% had cardiovascular comorbidities, around 18% had overweight or obesity and 2.1% had chronic kidney disease. Half of the studied population had no comorbidities (Table 1).

HCV chronic infection assessment was the major indication for PLB (47.0%), followed by AIH / cholestasis (12.6%) and MAFLD (12.1%). The amount of HCV-related procedures has sharply reduced. On the other hand, the number of MAFLD-related biopsies has progressively raised over the years, as shown in Figure 1.

The median number of needle passes was 1 (ranging from 1 to 4). PLB-related pain was reported in 53.6% of the studied population. To relieve it, dipyrone was administered in 40.2% of patients, tramadol in 3.7%, and both medications in 8.1%. Eight patients (1.6%) that complained of pain did not require any medication. The female gender was associated with a higher complaint of pain (p=0.0143). There was no significant influence of other clinical and laboratory variables in the occurrence of pain (age, comorbidities, platelets count, INR, and number of needle passes). AEs occurred in 87/532 biopsies (16.4%); they were mild in 76 (14.3%) and serious in 11 (2.1%) procedures.

The main mild AEs (n=76) were high blood pressure (32/532 – 6.0%), headache (3.6%), nausea/vomiting (2.4%), low blood pressure (1.5%), and hypoglycemia (0.2%), as shown in Table 2. The management was oral captopril, venous dipyrone, venous metoclopramide, venous crystalloid, and glucose infusion, respectively. Regarding serious AEs (n=11), 5 patients had perihepatic fluid on US, 4 had subcapsular bleeding, and 2 had right-sided hemothorax (Table 2). Ten patients (1.9%) were admitted to the hospital due to the following conditions: perihepatic fluid on US examination (n=4), subcapsular bleeding (n=2), hemothorax (n=2), low blood pressure with nausea/vomiting (n=1) and intense pain at the biopsy site (n=1). No one patient required surgical treatment and there were no deaths, as shown in Table 2. There was no association between the occurrence of mild or serious AEs and the studied variables (clinical, laboratory, and procedure-related). Renal function was normal in all the patients that developed bleeding.

DISCUSSION

In this study, we evaluated a large sample of subjects submitted to real-time US-guided PLB in an outpatient setting over 5 years. Viral hepatitis was the main indication for biopsy, similar to previous reports [12,14,15]. As the prevalence of HBV chronic infection in our country is low [16], HCV-related biopsies were more frequent in our sample. Some studies carried out in other geographic areas enrolled more commonly HBV patients[15,17]. Likewise, post-transplant follow-up was the most common reason for PLB at transplant

centers [18]. In the pediatric population, the major reported indications were elevated liver enzymes, AIH, and cholestatic diseases[19].

In our study, the reason for PLB has undergone a transformation over the years. It was possible to notice a remarkable drop in the amount of HCV-related procedures and a progressive increase in MAFLD-related biopsies. As we have mentioned, a reduction in the need for liver biopsy due to HCV was expected, but other liver diseases still require histological evaluation to help on the management and follow-up[1] – notably, AIH, small-duct primary sclerosing cholangitis, anti-mitochondrial antibody–negative primary biliary cholangitis, drug or herb-induced liver injuries, some HBV patients, systemic diseases with hepatic involvement, and MAFLD, which is being intensely studied. As promising therapies are awaited, it is feasible to predict that histological staging will help physicians in choosing the best approach to MAFLD patients.

As supposed, pain was the most frequent consequence of PLB[1,10,19]. A study involving 54 patients described an 84% incidence of pain immediately following the PLB and 39% of the patients still complained of pain after 24 hours [14]. This symptom was associated with anxiety pre-procedure and the female gender [14]. We found a 53.6% incidence of pain and a significant association with the female gender but we have not studied patients' complaints prior to the biopsy. Although pain is generally mild and has a good response to analgesics, local anesthetics do not seem to prevent it, instead of the use of midazolam or nitrous oxide[14]. The real-time image-guided setting may reduce the incidence of pain, as it provides anatomical ascertain, reducing trauma to the subcutaneous tissue and hepatic capsule[4,17,18].

According to the literature, the patient's position after the PLB does not affect the rate and severity of complications [20], so our patients decided a comfortable position to rest. At our center, the protocol is to maintain observation for up to 4 to 6 hours after PLB, but the most appropriate period has not been well defined in the literature and it can last from 2 to 8 hours[4,9,21-23].

In our study, the incidence of low blood pressure following the PLB was low (1.5%), similar to previous reports [7,20]. It may occur due to bleeding, vasovagal reflex associated with pain, or even as a side effect of sedative drugs, such as midazolam[4,7,8]. We did not find an association between low blood pressure and bleeding or pain, possibly due to the low frequency of such complications in our sample.

The rate of bleeding was also low in our study, similar to the literature [3,4,24]. It has already been described that patients older than 50 years are more likely to progress with bleeding[25,26], but no statistical association between age and hemorrhage was found in our study. Parente et al. [8]reported a higher rate of bleeding after liver biopsies (2.3%); however, the studied population had neoplasia, which is more susceptible to hemorrhage. A higher risk of bleeding is also expected in patients with platelets count $<$ 50,000-70,000/mm^3 and/or INR $>$ 1.3-1.5 [3,10,25-27]. Most of our patients had normal INR and platelets count and there was no bleeding in the subjects with tests out of these limits, so we did not find any association between coagulation tests and bleeding.

The need for hospital admission in our sample (1.9%) was similar to previous reports, ranging from 1 to 3% [3,4,18]. In addition, there were no more serious complications, such as perforation of the gallbladder, colon, kidneys, hemobilia, abscess, and intraperitoneal bleeding. Death following a PLB is extremely rare (up to 0.1%) [1,18] and it did not occur in our study. However, it is essential to notice that, in general, serious complications and death are more frequent in patients with severe comorbidities, suspected neoplasia, and cirrhosis, and such individuals usually undergo in-hospital biopsies at our center.

The real-time US-guided setting seems to reduce the risk of PLB-related serious complications [1,3,25,26]. This is not entirely proven, since some studies have found different results[24,28-30]. Other factors must be reminded in order to improve the safety of PLB, such as the operator experience and a careful selection of individuals to undergo it in an outpatient setting[31]. Although radiologists most commonly perform US-guided liver biopsies [5], gastroenterologists and hepatologists can also safely execute it [6]. Our results showed a low incidence of serious AEs, even in a scenario of senior residents in training, supervised by a hepatologist.

This study has some limitations: 1) the single-center design may be associated with bias on patients selection,

2) the retrospective design and non-uniform descriptions in the medical records may have changed the rate of AEs, 3) the data collected exclusively from the medical records may have missed outcomes of patients eventually admitted to other hospitals, and 4) a non-standardized dose of midazolam for sedation may have affected the incidence of pain.

CONCLUSIONS

US-guided PLB in an outpatient setting has a low rate of complications and must keep been considered for selected individuals with indeterminate liver disease. The reason to perform it is undergoing a notable transition, where HCV chronic infection has been replaced by MAFLD. New strategies to prevent biopsy-related pain are still needed, especially for females.

Figure legends :

Figure 1 – Number of indications-related liver biopsies from 2015 to 2019 . AIH: autoimmune hepatitis; MAFLD: metabolic dysfunction-associated fatty liver disease.

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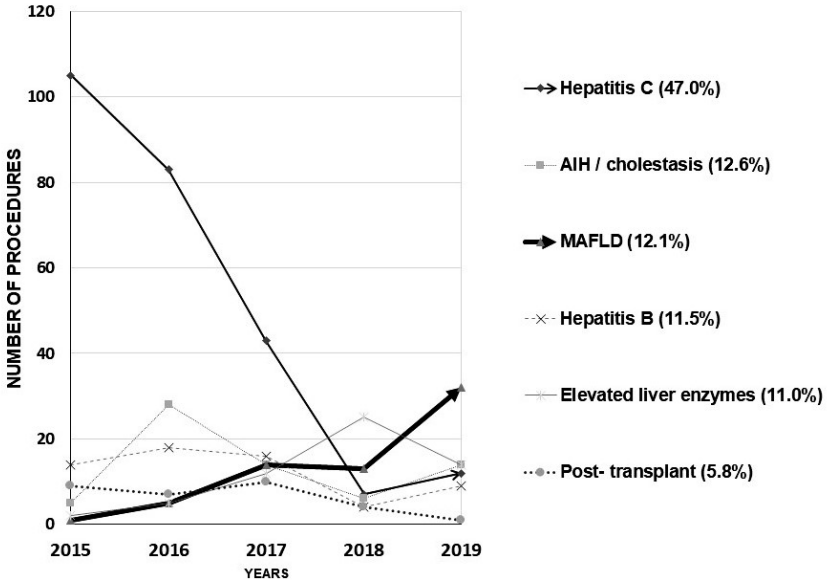

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