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HEPATOBILIARY-PANCREAS

Targeted and non-targeted liver biopsies carry the same risk of complication

Anna Maheux[1] · Yvonne Purcell[1] · Sana Harguem[1] · Valérie Vilgrain[1,2,3] · Maxime Ronot[1,2,3]

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Abstract

Objectives To reappraise the rate of and risk factors for complications of targeted and non-targeted US-guided liver biopsy in a large series.

Methods We analyzed 2405 liver biopsies performed in 2137 patients (58% males, mean age 54 ± 15 years old) between January 2010 and December 2015. Biopsies were performed for focal liver lesions characterization (targeted) or chronic liver disease assessment (non-targeted). Clinical, laboratory, and technical data were recorded. For targeted biopsies, we also recorded the largest diameter, location, enhancement pattern, and pathology. Advert events were divided into marked symptoms and complications. Those requiring specific treatment (embolization or surgery) were considered as severe.

Results A total of 1283 (53%) targeted and 1122 (47%) non-targeted biopsies were performed. Marked symptoms occurred after 134 biopsies (5.6%) (95 (7.4%) targeted and 39 (3.5%) non-targeted, $p < 0.001$), the most common being pain (109/134). Complications occurred after 38 biopsies (1.6%) (24 (1.9%) targeted and 14 (1.2%) non-targeted, $p = 0.253$) and were severe in 13 patients. In univariate analysis, prothrombin time ($p = 0.006$), serum creatinine level ($p < 0.001$), largest lesion diameter ($p < 0.001$), and tumor pathology ($p = 0.040$) were associated with the occurrence of complications but not platelet count or lesion enhancement pattern. In multivariate analysis, only the largest lesion diameter was retained (OR 1.014 [1.002–1.026], $p = 0.018$).

Conclusion The rate of advert events after US-guided liver biopsy was low, with no difference between targeted and non-targeted biopsies. When focusing on targeted biopsies, the largest lesion diameter but not enhancement pattern appeared as the main risk factor.

Key Points

- *Targeted and non-targeted liver biopsies are associated with the same observed risk of complication.*
- *Arterial phase hyperenhanced tumors on contrast-enhanced CT or MRI are not associated with a higher risk of complication when compared with non-hyperenhanced ones.*
- *A high serum creatinine level is associated with a higher risk of complication and should motivate strict post-biopsy surveillance.*

Keywords Image-guided biopsy · Risk factors · Liver neoplasms

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✉ Maxime Ronot
maxime.ronot@aphp.fr

[1] Department of Radiology, APHP, University Hospitals Paris Nord Val de Seine, Beaujon, 100 Boulevard du Général Leclerc, 92118 Clichy, Hauts-de-Seine, France

[2] University Paris Diderot, Sorbonne Paris Cité, Paris, France

[3] INSERM U1149, CRI, Paris, France

Abbreviations

APTT	Activated partial thromboplastin time
CT	Computed tomography
FNA	Fine needle aspiration
INR	International normalized ratio
PT	Prothrombin time
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
VEGF	Vascular endothelial growth factor

Introduction

Liver biopsy is of importance for the management of patients with liver disease or tumors. In patients with chronic liver disease, pathological assessment is often required to stage the severity of fibrosis and inflammatory activity or to quantify the degree of fat storage [1, 2]. In patients with focal liver lesions, biopsy is required to reach a definitive diagnosis when imaging-based non-invasive diagnosis is not feasible or inconclusive [3–5]. Furthermore, liver biopsy is also used for treatment monitoring [3].

Liver biopsy uses imaging guidance or assistance in the vast majority of the cases [1, 2, 6]. It is a safe procedure, with a complication rate reported in the range of 0.4–1.7% [7–12] and an estimated mortality of 0.11% [8]. Most complications are related to post-biopsy bleeding. Several precautions may be taken to decrease or prevent the risk of complications, the most important being strict assessment of coagulation parameters of patients, the use of real-time imaging guidance [9, 13], and the expertise of the specialist [9, 11]. However, there is no consensus on the cut-off values for coagulation parameters prior to biopsy. The American Association for the Study of Liver Disease guidelines for liver biopsy do not give specific thresholds for acceptable platelet count and coagulation parameters [1]. Liver biopsy is contraindicated with a platelet count less than 60.10^9/L in the guidelines of the British Society of Gastroenterologists but a threshold for the international normalized ratio (INR) is not specified [6]. The consensus guidelines from the Society of Interventional Radiology (SIR) recommends that an INR less than 1.5 and platelet count more than 50.10^9/L are acceptable for performing liver biopsy [14].

Published literature on liver biopsies suffers from several limitations. First, most studies addressing the risk of complications focus on coagulation parameters. These studies are either old or include small patient populations, or consist of case reports [9, 12, 15, 16], with conflicting results [7, 17]. Second, and importantly, studies rarely target specifically biopsy of focal lesions. Indeed, most are either cohorts of patients with liver diffuse disease [7, 13, 16, 18–22] or do not individualize targeted (focal lesions) and non-targeted (chronic liver disease) biopsy [8, 10, 23–25]. For those that do differentiate the two, published data are conflicting. For instance, Howlett et al [9], Strobel et al [23], and Sandrasegaran et al [17] established a link between complications and biopsy directed at a focal lesion while Mueller et al [12] did not. Others, such as Mcvay et al [24] and Chi et al [25], suggested a higher rate of complications in malignancies, which was not noted elsewhere. Importantly, these studies rarely include focal lesion features in the analysis of risk factors of complications, or do it partially, mainly enhancement pattern [9, 12, 17, 23, 24]. While Yu et al [26] studied a population with hepatocellular carcinoma, they reported no relationship of complication rate and lesion size, and the degree of vascularity of the lesions was not evaluated.

Therefore, the aim of this study was to reappraise the rate of and the risk factors for complications of percutaneous ultrasound-guided liver biopsy, comparing targeted and non-targeted biopsies in a large consecutive cohort of patients.

Materials and methods

Patient selection

This single-center retrospective study protocol was approved by our institution's human research committee that waived the requirement for informed consent. Between January 2010 and December 2015, all patients undergoing percutaneous liver biopsy in our institution were retrospectively identified from a digital database. Indications for percutaneous liver biopsy were (1) characterization of a focal liver lesion when the diagnosis was not established by imaging and when biopsy results might change patient care or (2) assessment of suspected/known chronic liver disease. Absolute contraindications for percutaneous biopsy included (i) INR > 1.5 or prothrombin time < 50%, (ii) activated partial thromboplastin time (APPT) > 1.3, and (iii) platelet count < 50.10^9/L. Biliary dilatation, ascites, and lack of cooperation of the patient were considered only partial contraindications.

In our institution, discontinuation of antiplatelet medication is advised at least 5 days before liver biopsy. Discontinuation of anticoagulants is also requested (warfarin at least 5 days prior to liver biopsy, heparin and related products 12–24 h prior to biopsy [14]). In all patients, the risk of discontinuing anticoagulant/antiplatelet medication was weighed against the potential risk of bleeding during/after liver biopsy. When discontinued, antiplatelet therapy was restarted 48–72 h after liver biopsy, and warfarin was restarted the following day.

For all patient demographics, clinical and laboratory data in the period starting 4 weeks prior to up until 4 weeks after biopsy were extracted from medical charts.

Percutaneous liver biopsy

Percutaneous liver biopsies were ultrasound-guided and performed under local anesthesia, using 16- or 18-gauge cutting needles. Details of percutaneous procedure (biopsy and possible associated fine needle aspiration (FNA)), as well as pathological analysis, are provided as Supplemental material.

For all biopsies, the following items were noted: type of biopsy (focal liver lesion or liver parenchyma), sampling method, type of needle, and the number of samples. For focal liver lesions, the following elements were also recorded: largest diameter (in mm), location (following the Couinaud anatomical system), and enhancement characteristics on arterial

phase images when compared with pre-contrast images (hypo-, iso-, or hyperenhanced when compared with the surrounding liver) on computed tomography (CT) or magnetic resonance (MR) imaging.

Outcome and adverse events

Outcomes were retrieved from clinical charts. Any untoward medical occurrence following liver biopsy was defined as "advert event." Advert events were then stratified in three levels of severity: marked symptoms, complication, and severe complication.

We defined "marked symptoms" as any post-biopsy complaint that motivated complementary imaging (ultrasound or CT). This definition was considered to be objective and chosen to compensate for the retrospective design of the study, lacking a standardized and prospective recollection of all symptoms.

A "complication" was defined as the occurrence of an abnormality on post-biopsy imaging considered imputable to biopsy. Among complications, a bleeding event was deemed to occur if the patient had acute hemoperitoneum or liver hematoma on a post-biopsy CT or ultrasound, a drop in hematocrit > 2 g/dL requiring inotropic or blood transfusion support, or need for embolization of hepatic arterial branches. A complication requiring specific treatment (including but not limited to arterial embolization or surgery) was considered as "severe."

This separation between "marked symptom" and "complication" was based on clinical considerations. Indeed, "marked symptoms" do not require treatment or follow-up, while complications do require follow-up and dedicated treatment when severe. Follow-up outpatient assessment was scheduled for day 15 post procedure.

Statistical analysis

Categorical data were expressed as frequencies and percentages, and continuous variables were expressed as means and standard deviations, or medians and ranges, as suitable. A Fisher exact test or a chi-square test was used for comparison of frequencies. The Student *t* test or the Mann-Whitney test was used to compare continuous variables according to the distribution of data. Univariate analysis was performed to factors associated with the occurrence of significant symptoms, complications, and severe complications. Multivariate analysis of the risk factors of complications and severe complications were performed using a backward stepwise logistic regression model including pertinent variables with a p value of < 0.10 in univariate analysis. Results of the multivariate analysis are shown as odds ratio (OR) (95% confidence interval). A p value of 0.05 was considered to be significant and all tests were two-sided. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 20.0. SPSS Inc.).

Results

Study population and biopsies

A total of 2405 biopsies were performed in 2137 patients (1254 males (58%), mean age 54 ± 15 years old) during the study period and included in the present study (Fig. 1).

The baseline characteristics are shown in Tables 1 and 2. A total of 1283 biopsies (53%) targeted focal lesions and 1122 (47%) were performed for suspected liver disease. Core biopsies were performed with a 16-G (n = 1181) and 18-G needle (n = 1224) at the discretion of the operator. Focal lesions had a mean diameter of 45.4 ± 36.4 mm and were mostly located in segments VIII (20.4%) and V (20.1%). On imaging, 41.8% of them showed arterial enhancement.

Pathological analysis was not contributive for 256 biopsies (20%) performed for the characterization of focal liver lesions. Among the 1027 biopsies with a contributive result, 858 (66.9%) showed malignancies, most being hepatocellular carcinoma (355/34.6%) and metastasis from adenocarcinomas (288/28%), and 169 (13.1%) revealed benign lesions, most being focal hyperplasia (72/169, 43%) and hepatocellular adenoma (58/169, 34%).

METAVIR fibrosis score was available in 2005 patients, and 364 (18.2%) had cirrhosis.

Post-biopsy symptoms

Post-biopsy symptoms are summarized in Table 3. Overall, symptoms were observed after 134 biopsies (5.6%). The most common symptom was pain (n = 109/134). Imaging performed for the exploration of these symptoms was US (n = 83/134), CT (n = 41/134), or both (n = 10/134). Results of univariate analysis performed for the identification of risk factors are shown in Tables 4 and 5. When all biopsies were considered, a lower mean prothrombin time was associated

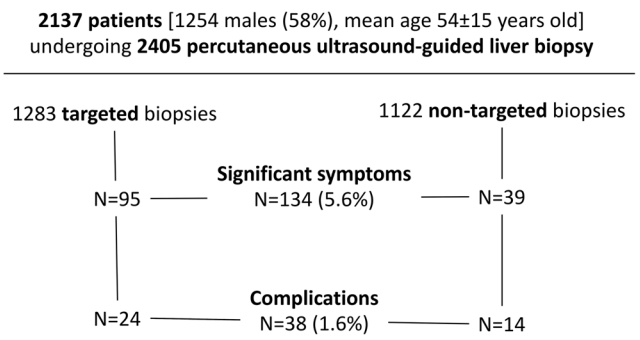

Fig. 1 Flow chart of the study population

Table 1 Baseline patient and biopsy characteristics

Patients	*N* = 2137
Male	1254 (58)
Female	883 (42)
Age	54 ± 15 (14–96)
Laboratory tests (mean ± SD (range))	
PT (%)	89.6 ± 18.1 (52–138)
APTT ratio	1.03 ± 0.2 (0.6–3.1)
INR	1.1 ± 0.2 (0.6–3.1)
Platelet count (10^9/L)	220.9 ± 115.4 (13–1144)
Creatinine (μmol/L)	79.2 ± 41 (34–855)
Tissue sampling	*N* = 2405
Type of biopsy	
Targeted	1283 (53)
Non-targeted	1122 (47)
Sampling method	
Core biopsy	
16G	1181 (49)
18G	1224 (51)
FNA when associated	200 (8.3)
20G	120 (5)
22G	80 (3.3)
Number of samples	Available for *N* = 1288
1	907 (70.4)
2	307 (23.8)
3 to 5	74 (5.7)
Pathological analysis	
METAVIR score	
Activity	Available for *N* = 1982
0	883 (44.6)
1	672 (33.9)
2	345 (17.4)
3	82 (4.1)
Fibrosis	Available for *N* = 2005
0	853 (42.5)
1	385 (19.2)
2	227 (11.3)
3	176 (8.8)
4	364 (18.2)
Steatosis	Available for *N* = 1991
0	1298 (65.2)
1	282 (14.2)
2	159 (8)
3	252 (12.7)

Numbers in brackets are percentages. *APTT*, activated partial thromboplastin time; *FNA*, fine needle aspiration; *INR*, international normalized ratio; *PT*, prothrombin time; *SD*, standard deviation

Table 2 Baseline characteristics of focal liver lesions

Focal liver lesions characteristics	*N* = 1283
Mean largest diameter (mm) ± SD (range)	45.4 ± 36.4 (5–240)
Location*	
I	21 (1.6)
II	98 (7.6)
III	82 (6 4)
IV	175 (13.7)
V	259 (20.1)
VI	197 (15.4)
VII	187 (14 .6)
VIII	261 (20.4)
IX	3 (0.2)
Enhancement characteristics on arterial phase CT or MRI	
Hypoenhancement	515 (40.1)
Isoenhancement	232 (18.1)
Hyperenhancement	536 (41.8)
Pathological analysis	
Non-contributive	256 (20)
Malignant	858 (66.9)
Hepatocellular carcinoma	355 (27.7)
Cholangiocarcinoma	109 (8.5)
Hyperenhanced metastasis**	89 (6.9)
Hypoenhanced metastasis***	288 (22.4)
Sarcoma	4 (0.3)
Hematological	13 (1)
Benign	169 (13.1)
Focal nodular hyperplasia	72 (5.6)
Hepatocellular adenoma	58 (4.5)
Hemangioma	6 (0.5)
Abscess	7 (0.5)
Granuloma	2 (0.2)
Other	24 (1.9)

SD, standard deviation

*Numbers in brackets are percentages

**Metastasis from neuroendocrine tumor, kidney metastasis, and melanoma metastasis

***Metastasis from colorectal, breast, and stomach tumors

with the occurrence of symptoms (85.2% ± 20.1 in the group with symptoms vs. 90.0% ± 17.9 in the group with no symptoms, $p = 0.005$). The type of biopsy (targeted vs. non-targeted), the size of core biopsy needle, and the number of samples were also identified as risk factors ($p < 0.001$, $p < 0.001$, and $p = 0.004$, respectively). When considering only those biopsies targeting focal lesions, the largest diameter was associated with the occurrence of symptoms (mean 62.0 ± 43.5 in patients experiencing symptoms vs. 44.1 ± 35.5 mm in others, $p < 0.001$). In multivariate analysis, largest diameter (OR = 1.009 [1.004–1.015], $p < 0.001$), prothrombin time (OR = 0.986 [0.973–0.999], $p = 0.040$), and malignant character (OR = 0.416 [0.217–0.797], $p = 0.008$) were retained as risk factors for significant post-biopsy symptoms.

Table 3 Post-biopsy adverse events

	N (%)
Post-biopsy imaging	134 (5.6)
US	83 (3.4)
CT	41 (1.7)
Both	10 (0.4)
Post-biopsy-marked symptoms	134 (5.6)
Pain	109 (4.5)
Drop in hemoglobin	9 (0.4)
Fever	8 (0.3)
Hypotension	3 (0.1)
Cutaneous bleeding	2 (0.04)
Upper digestive hemorrhage	2 (0.1)
Hepatic cytolysis or cholestasis	1 (0.1)
Mean period between biopsy and imaging (days, ± SD (range))	2.4 ± 3.1 (0–19)
≤ 1 day	80 (60)
> 1 day	54 (40)
Post-biopsy complications*	38 (1.58)
Hemoperitoneum	21 (0.9)
Subcapsular liver hematoma	11 (0.5)
Liver hematoma	6 (0.2)
Collection	1 (0.04)
Hemobilia	3 (0.1)
Biliary peritonitis	1 (0.04)
Pseudoaneurysm	2 (0.1)
Pneumothorax	3 (0.1)
Death	1 (0.04)
Mean period between biopsy and imaging (days, ± SD (range))	2.1 ± 3.6 (0–19)
≤ 1 day	24 (63)
> 1 day	14 (37)
Severe complications	*N* (%)
Angiography and embolization	11 (0.5)
Surgery	2 (0.1)

CT, computed tomography; *SD*, standard deviation; *US*, ultrasound imaging

p values in italic correspond to significant ones

*Some patients had more than one complication

Post-biopsy complications

A total of 38 patients (1.6%) had at least one complication detected by imaging (Table 3). One patient died. Among these patients, 13 had a severe complication, and 11 underwent embolization, while two underwent hemostatic surgery.

Results of univariate analysis performed for the identification of risk factors for complication are shown in Tables 6 and 7. When all biopsies were considered (Table 6), mean prothrombin time (81.5% ± 22.6 in the group with complications vs. 89.8% ± 18.0 in the group without complications, $p = 0.006$) and serum creatinine level (101.3 ± 97.0 μmol/L in the group with complications vs. 78.8 ± 39.3 μmol/L in the group without complications, $p < 0.001$) were significantly associated with the occurrence of complications. Other factors such as platelet count ($p = 0.500$), APTT ($p = 0.619$), age ($p = 0.481$), or gender ($p = 0.405$) were not associated with an increased risk of complications (Fig. 2). The type of biopsy (targeted vs. non-targeted) was not associated with the occurrence of complications ($p = 0.253$).

When considering only biopsies targeting focal lesions (Table 7), the largest diameter (71 ± 54 mm in the group with complications vs. 44.9 ± 35.9 mm in the group without complications, $p < 0.001$) and tumor pathology ($p = 0.040$) were associated with the occurrence of complications. Other factors including arterial phase hyperenhancement, fibrosis score, or sampling method were not associated with the occurrence of complications. In multivariable analysis, only the largest lesion diameter was associated with the occurrence of complications (OR = 1.014 [1.002–1.026], $p = 0.018$) (Figs. 3 and 4).

Discussion

In this cohort study including 2405 consecutive percutaneous liver biopsies, 5.6% of the 2137 patients experienced a post-biopsy-marked symptom and 1.6% had a complication. We confirmed the importance of coagulation parameters, especially prothrombin time. Noticeably, platelet count was not associated with complications, and a higher creatinine value was retained as a risk factor for bleeding. Interestingly, neither the type of biopsy (i.e., targeted or not) nor the technical factors (needle size and number of samples) influenced the complication rate. Finally, in targeted biopsies, larger tumors had a higher risk of complications but lesions showing hyperenhancement on the arterial phase did not.

Our series, which is one of the largest, has a similar advert event rate compared with previous studies [7–12]. A recent study including 1806 patients reported a rate of 5.6% [25], but "complications" were defined as any post-biopsy event, similar to our definition of marked post-biopsy symptoms. Our separation between "marked symptom" and "complication" was based on clinical considerations. Indeed, "marked symptoms" do not require treatment or follow-up, while complications do require follow-up and dedicated treatment when severe. Following a similar definition of "complication," the study by Mueller et al including 1961 patients over a period of 10 years reported a rate of 1.2% [12]. The rate of severe complications and the occurrence of one death are also similar to previously reported rates ranging from 0.5 to 1.7% [12, 19, 25]. This not only further validates the overall safety of percutaneous ultrasound-guided liver biopsy but also stressed that it may be a risky method requiring much attention in patient selection and deep analysis of risk factors.

Table 4 Factors associated with the occurrence of post-biopsy symptoms

	Symptom $N = 134$*	No symptom $N = 2270$	p value
Demographics			
Male/female	71/63 (53/47)	1370/900	0.124
Mean age ± SD	51.8 ± 17.0	53.7 ± 14.6	0.140
Laboratory tests (mean ± SD)			
PT (%)	85.2 ± 20.1	90.0 ± 17.9	*0.005*
APTT ratio	1.03 ± 0.2	1.03 ± 0.2	0.774
INR	1.16 ± 0.4	1.11 ± 0.2	0.123
Platelet count (10^9/L)	235.7 ± 107.6	219.8 ± 115.9	0.131
Creatinine (μmol/L)	81.5 ± 55.0	79.0 ± 39.9	0.497
Tissue samplings			
Type of biopsy			
Targeted/non-targeted	95/39 (70.8/29.1)	1187/1083 (52.3/47.7)	< *0.001*
Sampling method			
FNA when associated			0.481
20G	9 (6.7)	111 (4.9)	
22G	6 (4.4)	74 (3.2)	
Core biopsy			< *0.001*
16G	41 (31.0)	1140 (49.9)	
18G	93 (69.0)	1130 (49.5)	
Number of samples	96	1191	*0.004*
1	63 (65.6)	843 (70.8)	
2	25 (26.1)	282 (23.7)	
3 to 5	8 (8.3)	66 (5.5)	
Pathological analysis			
METAVIR score			
Activity	106	1876	0.858
0	50 (47.2)	833 (44.4)	
1	34 (32.1)	638 (34.0)	
2	19 (17.9)	326 (17.3)	
3	3 (2.8)	79 (4.2)	
Fibrosis	107	1898	0.266
0	53 (49.5)	800 (42.1)	
1	19 (17.8)	366 (19.3)	
2	10 (9.3)	217 (11.4)	
3	4 (3.7)	172 (9.1)	
4	21 (19.6)	343 (18.1)	
Steatosis	105	1886	0.540
0	70 (66.7)	1228 (65.1)	
1	15 (14.3)	267 (14.2)	
2	10 (9.5)	149 (7.9)	
3	10 (9.5)	242 (12.8)	

APTT, activated partial thromboplastin time; *FNA*, fine needle aspiration; *INR*, international normalized ratio; *PT*, prothrombin time; *SD*, standard deviation

p values in italic correspond to significant ones

*Patient who died was not included in this analysis because death is not a symptom per se. This patient was included in the "complication" analysis

**Numbers in brackets are percentages

Table 5 Factors associated with the occurrence of post-biopsy symptoms: results for targeted biopsies

	Symptom ($n = 95$*)	No symptom ($n = 1187$)	p value
Mean largest diameter (mm) ± SD (range)	62.0 ± 43.5	44.1 ± 35.5	*< 0.001*
Location	93	1187	0.699
I**	1 (1.1)	20 (1.7)	
II	5 (5.4)	93 (7.8)	
III	2 (2.1)	80 (6.7)	
IV	12 (12.9)	163 (13.7)	
V	23 (24.7)	234 (19.8)	
VI	15 (16.1)	182 (15.3)	
VII	16 (17.2)	171 (14.4)	
VIII	19 (20.4)	241 (20.3)	
IX	0 (0)	3 (0.3)	
Enhancement	94	1187	0.882
Hypoenhancement	39 (41.5)	475 (40.0)	
Isoenhancement	18 (19.1)	214 (18.0)	
Hyperenhancement	37 (39.4)	499 (42.0)	
Pathological analysis			
Malignant/benign	64/20 (67.4/21.1)	793/149 (66.8/12.6)	0.091
Tumor type			0.217
Non-contributive	11 (11.5)	245 (20.6)	
Hepatocellular carcinoma	27 (28.4)	328 (27.6)	
Cholangiocarcinoma	10 (10.5)	99 (8.3)	
Hyperenhanced metastasis	4 (4.2)	84 (7.1)	
Hypoenhanced metastasis	22 (23.2)	266 (22.4)	
Sarcoma	0 (0)	4 (0.3)	
Hematological	1 (1.1)	12 (1.0)	
Focal nodular hyperplasia	8 (8.4)	64 (5.4)	
Adenoma	8 (8.4)	58 (4.9)	
Hemangioma	1 (1.1)	5 (0.4)	
Abscess	2 (2.1)	5 (0.4)	
Granuloma	0 (0)	2 (0.2)	
Other	1 (1.1)	23 (1.9)	

SD, standard deviation

p values in italic correspond to significant ones

*Patient who died was not included in this analysis

**Numbers in brackets are percentages

Mean prothrombin time was significantly associated with the occurrence of complications, but INR value was not, probably because of the amount of missing data (INR available for only 838 patients). This is in line with previously published data [9, 12, 27, 28]. Other coagulation parameters such as APTT ratio or platelet count were not associated with an increased risk of complications. Of course, this is only true within the frame of contraindications of liver biopsy in the current study (i.e., $> 50.10^9$/L) and does not mean that the platelet count shall not be taken into consideration. This being said, this point remains controversial in the literature. The HALT-C trial [7] showed an increased risk of bleeding in patients with platelet count less than 60.10^9/L. Yet, in this study, all patients had hepatitis C virus infection, and biopsies were performed by hepatologists with ultrasound guidance in 80% of the cases only. Several other studies, including the most recent ones, are in line with our results and did not observe any influence of the platelet counts on complications [8, 10, 12, 17, 29]. The recent study by Sandrasegaran et al also suggested that platelet transfusion before biopsy might be ineffective [17]. More recently, a study by Kichin et al [30] showed that less stringent pre-procedural coagulation parameter guidelines (INR ≤ 2.0, platelets $\geq 25.10^9$) did not result in an increase in hemorrhagic complications and significantly decreased pre-procedural blood product administration (platelets and fresh frozen plasma).

Table 6 Factors associated with the occurrence of post-biopsy complications

	Symptom $N = 134$*	No symptom $N = 2270$	p value
Demographics			
Male/female	71/63 (53/47)	1370/900	0.124
Mean age ± SD	51.8 ± 17.0	53.7 ± 14.6	0.140
Laboratory tests (mean ± SD)			
PT (%)	85.2 ± 20.1	90.0 ± 17.9	*0.005*
APTT ratio	1.03 ± 0.2	1.03 ± 0.2	0.774
INR	1.16 ± 0.4	1.11 ± 0.2	0.123
Platelet count (10^9/L)	235.7 ± 107.6	219.8 ± 115.9	0.131
Creatinine (μmol/L)	81.5 ± 55.0	79.0 ± 39.9	0.497
Tissue samplings			
Type of biopsy			
Targeted/non-targeted	95/39 (70.8/29.1)	1187/1083 (52.3/47.7)	< *0.001*
Sampling method			
FNA when associated			0.481
20G	9 (6.7)	111 (4.9)	
22G	6 (4.4)	74 (3.2)	
Core biopsy			< *0.001*
16G	41 (31.0)	1140 (49.9)	
18G	93 (69.0)	1130 (49.5)	
Number of samples	96	1191	*0.004*
1	63 (65.6)	843 (70.8)	
2	25 (26.1)	282 (23.7)	
3 to 5	8 (8.3)	66 (5.5)	
Pathological analysis			
METAVIR score			
Activity	106	1876	0.858
0	50 (47.2)	833 (44.4)	
1	34 (32.1)	638 (34.0)	
2	19 (17.9)	326 (17.3)	
3	3 (2.8)	79 (4.2)	
Fibrosis	107	1898	0.266
0	53 (49.5)	800 (42.1)	
1	19 (17.8)	366 (19.3)	
2	10 (9.3)	217 (11.4)	
3	4 (3.7)	172 (9.1)	
4	21 (19.6)	343 (18.1)	
Steatosis	105	1886	0.540
0	70 (66.7)	1228 (65.1)	
1	15 (14.3)	267 (14.2)	
2	10 (9.5)	149 (7.9)	
3	10 (9.5)	242 (12.8)	

APTT, activated partial thromboplastin time; *FNA*, fine needle aspiration; *PT*, prothrombin time; *SD*, standard deviation

p values in italic correspond to significant ones

*Numbers in brackets are percentages

More interesting was the fact that patients with higher serum creatinine level had an increased risk of complications. Other studies have shown the same results. Sandrasegartan et al reported that estimated glomerular filtration rate was associated

Table 7 Factors associated with post-biopsy complications: results for targeted biopsies

	Complication ($n = 24$)	No complication ($n = 1259$)	p value
Mean largest diameter (mm) ± SD (range)	71 ± 54	44.9 ± 35.9	*< 0.001*
Location ($n = 1283$)			0.564
I*	0 (0)	21 (1.7)	
II	1 (4.2)	97 (7.7)	
III	0 (0)	81 (6.4)	
IV	5 (20.8)	170 (13.5)	
V	3 (12.5)	255 (20.3)	
VI	8 (33.3)	190 (15.1)	
VII	2 (8.3)	185 (14.7)	
VIII	5 (20.8)	257 (20.4)	
IX	0 (0)	3 (0.2)	
Enhancement			0.201
Hypoenhanced	11 (45.8)	504 (40.0)	
Isoenhanced	1 (4.2)	231 (18.3)	
Hyperenhanced	12 (50.0)	524 (41.6)	
Pathological analysis			
Malignant/benign	17/6	841/163	0.249
Tumor type			*0.040*
Non-contributive	1 (4.2)	255 (20.2)	
Hepatocellular carcinoma	8 (33.3)	347 (27.6)	
Cholangiocarcinoma	3 (12.5)	106 (8.4)	
Hyperenhanced metastasis	1 (4.2)	88 (7.0)	
Hypoenhanced metastasis	4 (16.7)	284 (22.6)	
Sarcoma	0 (0)	4 (0.3)	
Hematological	1 (4.2)	12 (1.0)	
Focal nodular hyperplasia	2 (8.3)	70 (5.6)	
Adenoma	2 (8.3)	56 (4.4)	
Hemangioma	1 (4.2)	5 (0.4)	
Abscess	1 (4.2)	6 (0.5)	
Granuloma	0 (0)	2 (0.2)	
Other	0 (0)	24 (1.9)	

SD, standard deviation

p values in italic correspond to significant ones

*Numbers in brackets are percentages

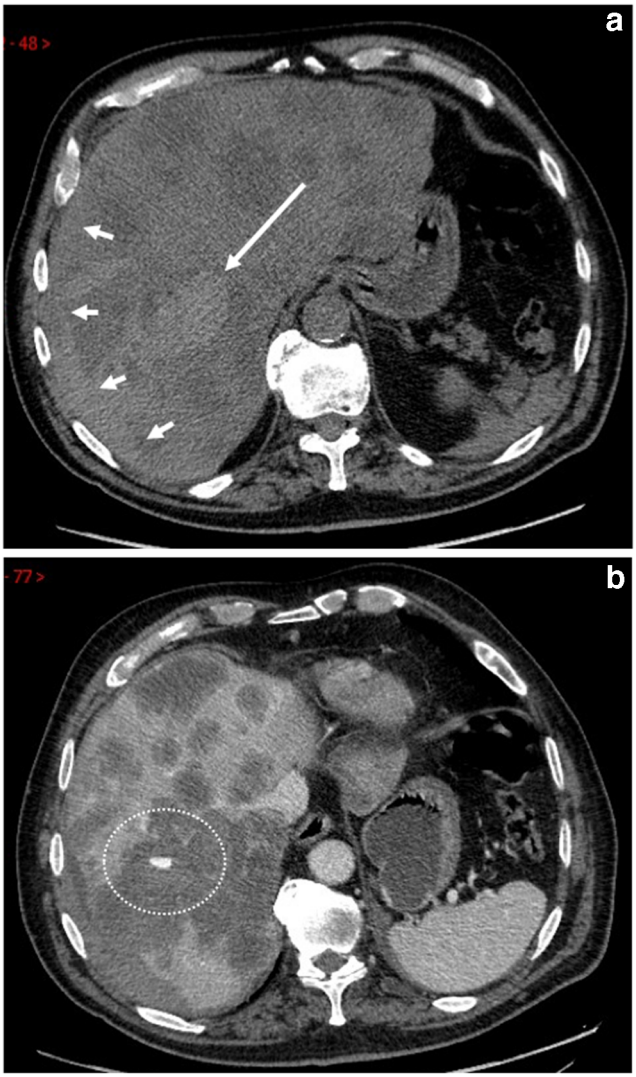

Fig. 2 A 78-year-old male patient with multiple hepatic lesions with histologically confirmed colorectal metastases. Pre-biopsy prothrombin time, activated partial thromboplastin time ratio, platelet count, and serum creatinine level were 95% ($N = 70–100\%$), 1.02 ($N < 1.2$), 294.10^9/L ($N = 150–400.10^9$/L), and 76 μmol/L ($N = 70–110$ μmol/L), respectively. One 18-gauge core biopsy was performed. The patient underwent abdominal CT 2 days after biopsy for abdominal pain. CT showed hemoperitoneum (arrowheads) and liver hematoma (long arrow) (**a**), with active bleeding (white dashed circle, **b**)

with bleeding after liver biopsy [17]. A meta-analysis by Acedillo et al showed that kidney disease was associated with perioperative bleeding [31], and it is known that patients with renal dysfunction have an increased risk of bleeding [32, 33]. This is explained by hemostatic defects due to complex platelet dysfunction. However, INR or platelet count is not associated with the risk of bleeding in patients with renal dysfunction [34]. Overall, serum creatinine level appears to be an important and underestimated parameter. This does not mean that liver biopsy shall not be performed when this level is high, but rather, patients should be closely monitored after biopsy.

The strength of our study is the comparison of targeted and non-targeted biopsies. Targeted biopsies were associated with a higher rate of symptoms, but not of complications. This is different from the study from Strobel et al and Howlett et al [9, 23]. Some might argue that these discrepancies could be explained by different types of tumors that were included, underlying the influence of tumor characteristics on complication rates. Indeed, we have shown that tumor size was positively associated with an increased risk of significant symptoms and complications. Such an association is not well established in literature. In their study, Mueller et al did not find a difference in the rate of complications when categorizing lesions by size

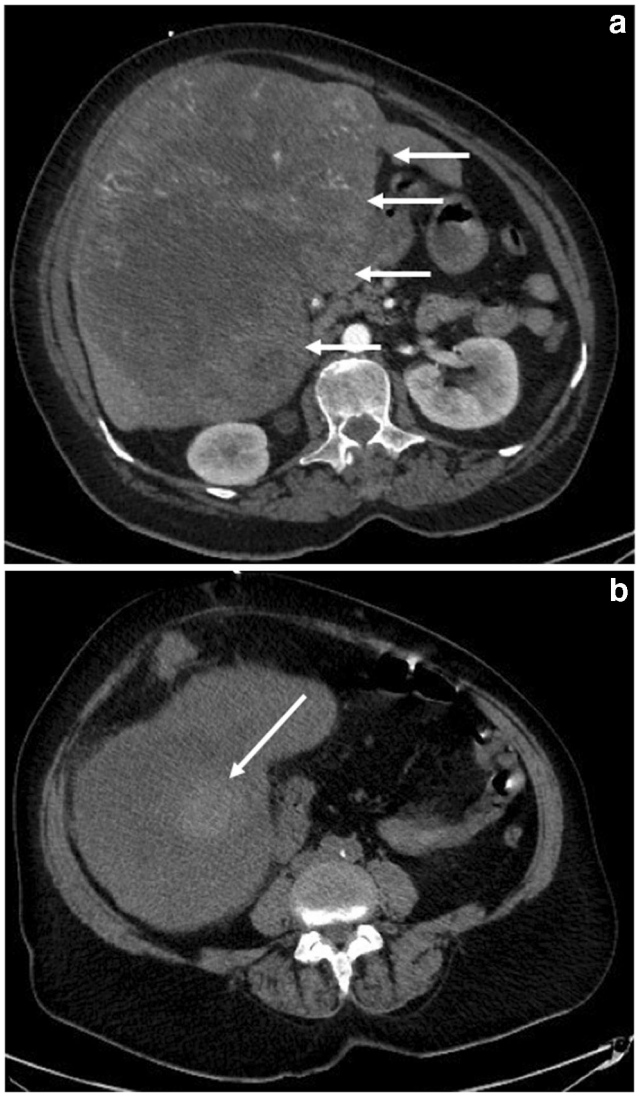

Fig. 3 A 66-year-old female patient with 170-mm right hepatic mass confirmed as hepatocellular carcinoma (arrows, **a**). Pre-biopsy prothrombin time, platelet count, and serum creatinine level were 67% ($N = 70–100\%$), 409.10^9/L ($N = 150–400.10^9$/L), and 62 μmol/L ($N = 45–84$ μmol/L), respectively. Two 18-gauge core biopsies were performed. The patient underwent abdominal CT 3 days after biopsy for abdominal pain. CT showed liver hematoma (white arrow, **b**)

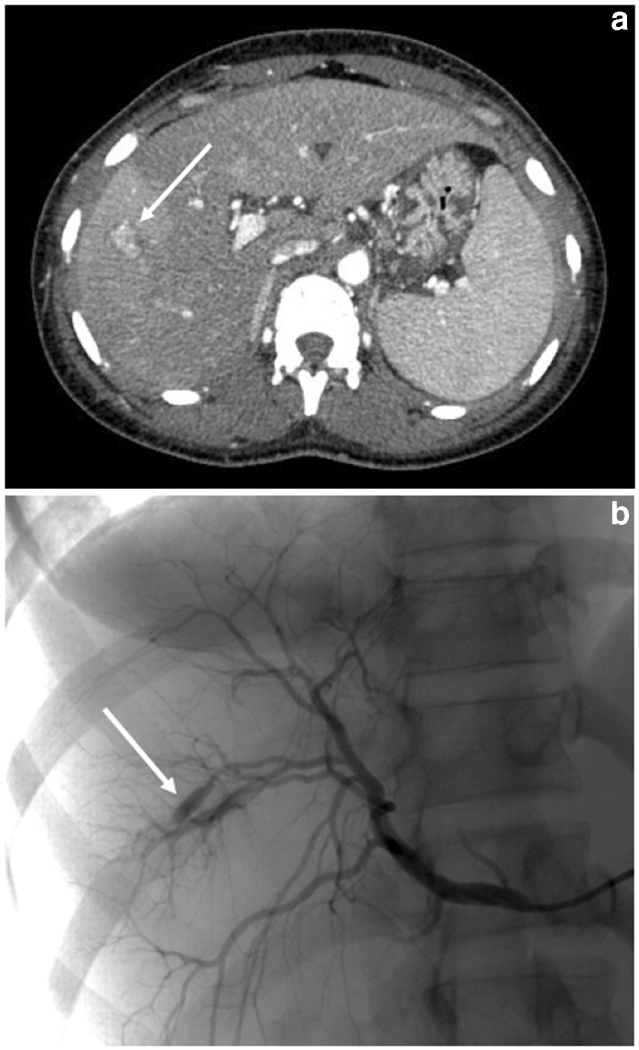

Fig. 4 A 25-year-old female patient with acute hepatitis in the setting of co-infection with hepatitis B and C viruses. Pre-biopsy prothrombin time, activated partial thromboplastin time, platelet count, and serum creatinine level were 63% ($N = 70–100\%$), 1.19 ($N < 1.2$), 121 ($N = 150–400.10^9$/L), and 60 μmol/L ($N = 45–84$ μmol/L), respectively. One 16-gauge core biopsy was performed. The patient underwent abdominal US and CT 2 days after biopsy for abdominal pain and drop in hemoglobin. CT showed an arteriovenous shunt (arrow, **a**) and hemoperitoneum (not shown). The lesion was treated by intra-arterial embolization (arrow, **b**)

(< 2 cm, 2–5 cm, and > 5 cm) [12]. Similar results were published by Yu et al using four size categories of lesions [26]. This might be explained by small weight of this risk factor, only identified in studies included a large number of patients, as in the current study. Another possible explanation is the location of tumor. Larger tumors are more frequently in direct contact with or in close proximity to the liver capsule, leading to a small or absent layer of liver parenchyma between the lesion and the capsule. This may impair local control of eventual bleeding. One study discussed this hypothesis [26] and reported two cases of complications occurring with lesions located close to the capsule. Yet, we did not include the distance from the lesion to the capsule in the analysis. This was intentional because the actual needle tract chosen by operators is highly variable and does not reflect this distance.

Patients with a histologically confirmed malignant lesion had an increased risk of post-biopsy symptoms but not of complications. Some studies reported the association between malignancy and complications [8, 10, 17, 24, 35], and authors postulated the role of tumor enhancement pattern, lesions showing arterial phase hyperenhancement being considered at higher risk. Yet, in our study, these lesions were not at higher risk of complications. Rather than the enhancement pattern of lesions per se, the risk of bleeding might instead be associated with the type of vascularization, since malignant tumors are known to undergo neoangiogenesis [36, 37].

Supporting this hypothesis, a recent study established a correlation between vascular endothelial growth factor (VEGF), an important signaling protein involved in angiogenesis, and perioperative hemorrhage in patients with gastric cancer [38]. This hypothesis was not evaluated in the current study.

Regarding biopsy technique and especially sampling method, we did not find any association between the needle size or the total number of samples and the occurrence of complications. Acquiring enough liver tissue is important for pathologists to reach a proper diagnosis. Chi et al reported that two biopsy passes did not increase the complication rate when compared with only one and that multiple biopsy passes were not associated with severe complications [25]. With thinner needles, more passes are needed to obtain an adequate amount of tissue. Yet, we did not observe any difference between 16-G and 18-G needles, as regards complications, in line with results from Atwell et al [39].

Our study is limited by the retrospective design. Moreover, a part of the population included in the study underwent liver biopsy as outpatients; they were discharged after 6 h of monitoring and instructed to contact the department if they experienced symptoms. Some post-biopsy events might have been missed, leading to an underestimation of post-biopsy symptoms or complications. Nevertheless, this was only done for patients living with relatives within 30-min distance from the department. Moreover, follow-up outpatient assessment was scheduled for day 15 post procedure. Moreover, most complications occurred between 0 and 24 h after biopsy (63% of patients). As a consequence, we believe that this bias remains limited. Another limitation is the absence of consideration of the expertise of the radiologists who performed the biopsies. In our department, only experienced consultants perform biopsies, thus limiting the possible influence of a learning curve.

In conclusion, ultrasound-guided percutaneous liver biopsy is a safe procedure, with a low rate of complications. This study confirms the importance of coagulation parameters. Noticeably, a higher creatinine level was retained as a risk factor for bleeding. Interestingly, neither the type of biopsy (i.e., targeted or not) nor the technical factors (needle size and number of samples) influenced the rate of complications. Finally, in targeted biopsies, larger tumors had a higher risk of complications, but lesions showing hyperenhancement on arterial phase imaging did not.

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Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

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