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Incidence and Predictors of Complications Following Percutaneous Liver Biopsy: A Large Italian Multicentre Study

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ABSTRACT

Background and Aims: Management of ultrasound (US)-guided percutaneous liver biopsy (PLB) lacks standardisation. Despite the low risk of major complications (< 1%), repeated blood counts and up to 4 h of in-hospital observation are typically recommended. We aimed to assess complication rates and predictors in a large cohort of patients undergoing US-PLB across three Italian tertiary centres. We included all patients undergoing US-PLB from January 2018 to December 2023. We collected clinical, biochemical and procedural features (needle type, insertions number, observation time and antiplatelet/anticoagulant regimens). Safety was assessed by the incidence of pain and major complications, including vasovagal reaction, bleeding, pneumothorax, shock, hospitalisation and death.

Approach and Results: Among 1838 patients (mean age 55.1 years, 46.1% females, mean BMI 25.1 kg/m^2, 74% parenchymal PLB), few were on anticoagulant/antiplatelet therapy (4.2%/16.2%); mean platelet count and PT INR were 209.7×10^3/mm^3 and 1.04; 17 patients (0.9%) received prophylactic therapy (blood components, thrombopoietin receptor agonists or vitamin K). Needle aspiration was predominant (92%). During a mean time of observation of 5.4 ± 2.0 h, 134/1838 patients reported pain (7.4%). Major complications were few (26, 1.4%), with 14 episodes of transient hypotension (0.8%); 10 bleeding events (0.5%); 1 pneumothorax; 1 abscess formation; 1 haemobilia; and 1 episode of chest pain. Hospitalisation was rare (12, 0.7%), primarily for

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AH, arterial hypertension; AID(s), autoimmune disease(s); BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DMt2, diabetes mellitus type 2; FFP, fresh frozen plasma; Hb, hemoglobin; HR, heart rate; INR, international normalised ratio; IQR, interquartile range; LB, liver biopsy; LT, liver transplant; MAP, mean arterial pressure; NSAIDs, non-steroidal anti-inflammatory drugs; PLB, percutaneous liver biopsy; PLT, platelets; PT, prothrombin time; SD, standard deviation; VKA, vitamin K agonist.

bleeding management. No fatalities were recorded. Pain was the sole significant independent predictor of major complications (18/26, HR 30.6, $p < 0.05$), particularly when reported within the first hour post-procedure (15/18, 83.3%).
Conclusions: Major complications following US-PLB are few and strongly associated with early post-procedural pain. In the absence of pain within the first hour, extended monitoring may be unnecessary, allowing for earlier patient discharge.

1 | Background

Liver biopsy (LB) plays a pivotal role in the diagnosis and staging of liver diseases within specific contexts settings; it also serves as a valuable tool in the assessment of liver tumours [1–4].

Percutaneous liver biopsy (PLB), when performed by expert operators, is generally well-tolerated with low rates of complications. Currently, bleeding stands out as the most common complication, with an incidence rate of 1%–2%, while the risk of mortality appears negligible at approximately 0.2% [5].

In order to promptly recognise and manage potential complications, international guidelines recommend monitoring patients following the procedure. However, there are no universally accepted protocols regarding the timing and modality of observation.

The American Association for the Study of Liver Diseases (AASLD) suggests monitoring patients for 2–4-h post-procedure without specifying the method [1], whereas the British Society of Gastroenterology, the Royal College of Radiologists and the Royal College of Pathology advise a minimum observation period of 3 h consisting of blood pressure and pulse measurements [6].

Identifying variables associated with complications following PLB could allow individualized monitoring schedules with important clinical and healthcare cost benefits.

Key determinants of complications can be categorized as procedure-related, including type of needle (cutting vs. fine-needle aspiration) and number of passes; operator-related, such as operator expertise and potential adoption of ultrasound (US) guidance; and patient-related, encompassing coagulation status, comorbidities and the use of anticoagulant or antiplatelet therapy [7].

The aim of our study was to describe the rates of US-guided PLB-related complications in a wide cohort of patients and to identify potential baseline and dynamic risk factors to tailor patients' management while balancing safety and resources utilisation.

2 | Materials and Methods

A multicentric, retrospective, observational study including all consecutive patients who underwent US-assisted or US-guided percutaneous liver biopsy between January 2018 and December 2023 was conducted. Participating centres were IRCCS Humanitas Research Hospital (Rozzano), San Giuseppe Hospital (Milano) and ASST Papa Giovanni XXIII Hospital (Bergamo). Both parenchymal and lesion-targeted liver biopsy were included in the study.

Local post-procedure monitoring protocols adopted in the participating centres are heterogeneous. Repeated blood count 3/4 h following PLB is performed both at IRCCS Humanitas Research Hospital and San Giuseppe Hospital, and a decrease in haemoglobin of more than 1.5 g associated with abdominal symptoms (pain) prompts ultrasound of the abdomen and, eventually, CT scan. On the other hand, clinical observation alone is performed at Papa Giovanni XXIII, with further investigations considered in cases of severe pain or impairment of clinical parameters.

The data collection included demographic information at liver biopsy (age, sex at liver biopsy, weight and height for BMI calculation), concurrent comorbidities (such as arterial hypertension, type 2 diabetes mellitus, dyslipidaemia, chronic kidney disease and autoimmune diseases) and concomitant medications with specific focus on anticoagulant and antiplatelet regimens; the timing of withdrawal of anticoagulant/antiplatelet was recorded, whenever available.

Coagulation status, defined by prothrombin time (PT) and platelet (PLT) count was documented, along with haemoglobin (Hb) levels before and after the procedures, if blood count was repeated according to local protocol. Furthermore, vital signs before and after the procedures, including heart rate (HR) and mean arterial pressures (MAP), were recorded.

The procedure-specific data were the type of PLB (core or lesion-targeted), type and size of the needle (needle aspiration or cutting biopsy) and number of passes.

Pain was recorded as a minor complication, whereas major complications included vasovagal syncope, bleeding, shock, pneumothorax, hospitalisation and mortality. Bleeding consisted of the presence of intra-hepatic or subcapsular hematoma accompanied by either active or non-active blush, ranging from minor to severe or haemoperitoneum/haemothorax. The duration of post-PLB observation and the timing of the onset of complications were documented.

Statistical analysis was performed using STATA software (STATA/SE 17). Continuous variables with a normal distribution are presented as mean ± standard deviation (SD), whereas those without a normal distribution are presented as median with the interquartile range. Categorical variables are represented by frequencies and percentages. Continuous measures were compared using *t*-tests or Wilcoxon rank-sum tests when appropriate. Categorical measures were compared using chi-square tests.

Logistic regression analysis was used to assess the specific relationship between baseline patients' or procedural characteristics and the outcomes (major complications). A p value lower than 0.05 was considered statistically significant.

The study was approved by the local ethics committee. Informed consent was waived due to the use of deidentified retrospective data; however, all patients signed a consent form allowing the use of retrospective data at the time of admission according

Summary

- Ultrasound-guided percutaneous liver biopsy lacks standardized protocols, leading to prolonged hospital stays and inefficient resource use.
- In our large cohort-based study, major complications occurred in 1.4% of cases, with transient hypotension and bleeding being the most common, and no deaths. Post-procedural pain within the first hour was the only significant predictor of complications.
- In the absence of significant pain within the first hour, extended monitoring and hospital stay may be unnecessary.

to local protocols. This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

3 | Results

From January 2018 to December 2023, 1838 patients underwent US-guided PLB in the participating centres. Demographic, clinical and baseline biochemical characteristics are summarised in Table 1.

The mean age of the cohort was 55.1 years (range 16–89), with 848 (46.1%) being female. In approximately one-third of the patients, the indication to PLB was liver function test alterations (1261, 68.6%), while in 471, a lesion-targeted liver biopsy for focal masses was performed. A comparison of baseline features between the core biopsy and lesion-target biopsy group is provided in Table S1.

One third of the overall population (32.4%, 596) had comorbidities: arterial hypertension (325, 17.7%), type 2 diabetes (325, 17.7%), chronic kidney disease (52, 2.8%) and chronic obstructive pulmonary disease (41, 2.2%). Metabolic comorbidities were more prevalent in patients undergoing PLB for focal lesions ($p < 0.05$), except for CKD. A substantial percentage of patients had autoimmune disorders (374, 20.4%), and 252 (13.7%) were liver transplant (LT) recipients. As expected, the latter were predominantly patients undergoing parenchymal biopsy; similarly, of the 446 patients (24.3%) on post-LT immunosuppressive therapy, only 27 performed a lesion-target LB.

Anticoagulant therapy was reported in 78 patients (4%), while antiplatelet therapy was documented in 298 patients (16%), including five on a dual antiplatelet regimen. Among those receiving antiplatelet therapy, 286 were on aspirin, four on ticagrelor and the remaining eight on clopidogrel. Additionally, a minority of patients (26, 1.4%) reported the use of non-steroidal anti-inflammatory drugs (NSAIDs).

Mean PLT count, Hb and PT INR pre-procedure values were $209.7 \times 10^3/mm^3 \pm 80.74$, 13.6 ± 1.7 g/dL and 1.04 ± 0.12, respectively; interestingly, no patient had a value of INR higher than 1.8, whereas 18 (16 in the core biopsy and 2 in the lesion-targeted group) displayed values between 1.5 and 1.8. Pre-procedure prophylactic therapy was administered in 17 patients (0.9%) with no significant differences between the parenchymal and lesion-target groups ($p = 0.023$): seven received fresh frozen plasma

TABLE 1 | Baseline characteristics of the total cohort.

	Total PLB ($n = 1838$)
Age (years) (mean, range)	55.1 (16–89)
Sex *n*, %	
Male (M)	990 (53.9%)
Female (F)	848 (46.1%)
BMI (kg/m^2) mean ± SD	25.1 ± 4.8
Reason for LB	
Impairment LFTs	1261 (68.6%)
Acute hepatitis	106 (5,8%)
Focal lesion	471 (25.6%)
Liver transplantation *n*, %	252 (13.7%)
Arterial hypertension *n*, %	596 (32.4%)
DMt2 *n*, %	325 (17.7%)
COPD *n*, %	41 (2.2%)
CKD *n*, %	52 (2.8%)
AID *n*, %	374 (20.4%)
Alcohol intake *n*, %[a]	
Yes	308 (16.76%)
Moderate	78 (25.32%)
Heavy drinkers	37 (12.01%)
Anticoagulant therapy[b]	78 (4.2%)
Antiplatelet therapy[b]	
Yes	298 (16.2%)
DAPT	5 (0.1%)
NSAIDs	26 (1.4%)
PLT ($\times 10^3/mm^3$) mean ± SD	209.7 ± 80.74
INR mean ± SD	1.04 ± 0.12
Hb (g/dL) mean ± SD	
Pre-PLB	13.6 ± 1.7
Post-PLB	13.1 ± 1.7
Variation pre-post	−0.3 ± 0.6
Prophylactic therapy, *n*, %	17 (0.9%)

Note: Moderate drinkers: between 2 and 5 UA daily for females, and 3 and 5 UA daily for males. A $p < 0.05$ was considered statistically significant.
Abbreviations: AH, arterial hypertension; AID(s), autoimmune disease(s); BMI, body mass index (kg/m^2); CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DMt2, diabetes mellitus type 2; F, female; Hb, haemoglobin (g/dL); INR, international normalised ratio; IQR, interquartile range; LFTs, liver function tests; LT, liver transplantation; M, male; NSAIDs, non-steroidal anti-inflammatory drugs; PLB, percutaneous liver biopsy; PLT, platelet count ($\times 10^3/mm^3$); SD, standard deviation.
[a]For seven patients (0.4%) alcohol intake was not reported.
[b]For one patient, data concerning anticoagulant, antiplatelet, immunosuppressive or other therapies were not available.

(FFP), five with a PT INR value greater than 1.5; nine were transfused with platelets due to PLT count lower than 50 000/mm^3, one of them in association with FFP; the remaining two were administered either thrombopoietin receptor agonist or vitamin K agonist.

Needle aspiration was the preferred modality, with the Menghini needle used in 1690 cases (92%) (Table S2). Core biopsy was mainly performed using 16G (376 patients, 27.5%) or 18G (951, 69.6%) needles, whereas focal-target biopsy adopted dimensions ranging from 18G (142, 30.2%) to 20G (132, 28.0%) to 21G (144, 30.6%). Overall, 640 biopsies (36%) required more than 1 pass, predominantly in the lesion-target LB group. To note, biopsies were performed with a US-guide mounted on the transducer (US-guided).

Adequate samples for histological analysis were obtained in 1771 patients (96.4%), with a higher proportion in the core biopsy group compared to focal lesion ($p < 0.05$). Of the remaining 66 patients, only 28 underwent a second liver biopsy within 3 months.

The overall rate of complications within our cohort is described in Table 2.

After a mean time of observation of 5.4 ± 2.0 h, 134 patients (7.4%) reported pain (=minor complication), with a median onset within 1 h following the procedure. To note, 129 of them (96.3%) reported pain either immediately after or within 1 h following the procedure; four between 1 and 3 h and the remaining one at 72 h, when at home and eventually resulting in a diagnosis of abscess formation (=major complication) (Figure 1). Pain was managed with analgesic therapy in 102 (76.1%).

A total of 26 (1.4%) major complications were observed, including 10 bleeding events (0.5%), of which four active bleeding at CT scan, one of them with haemorrhagic shock; 12 episodes of vasovagal syncope; 1 pneumothorax; 1 abscess formation; 1 haemobilia; and 1 episode of chest pain. No death occurred, and 12 (0.7%) hospitalisations were reported, all corresponding to major complication events, seven of which were due to bleeding.

Univariate analysis showed that only PT INR and pain were associated with an increased risk of major complications. Multivariate analysis confirmed pain to be independently associated with major complications, with a hazard ratio of 30 (CI 12.6–74.1).

TABLE 2 | Minor and major complications observed in the overall cohort, the core percutaneous liver biopsy group and focal target.

	Total ($n = 1838$)	Core PLB ($n = 1367$)	Focal-target PLB ($n = 471$)	p
Complications, *n*, %				
Pain	134 (7.3%)	109 (8%)	25 (5.3%)	**0.05**
Major	26 (1.4%)	18 (1.3%)	8 (1.7%)	0.54
Bleeding	10 (0.5%)	6 (0.4%)	4 (0.8%)	
Abscess	1 (0.1%)	0	1 (0.2%)	
Haemorrhagic shock	1 (0.1%)	1 (0.1%)	0	
Haemobilia	1 (0.1%)	0	1 (0.2%)	
Pneumothorax	1 (0.1%)	1 (0.1%)	0	
Vasovagal syncope	1 (0.1%)	1 (0.1%)	0	
Chest pain	14 (0.8%)	12 (0.9%)	2 (0.4%)	
Hospitalisation	1 (0.1%)	1 (0.1%)	0	
Death	12 (0.7%)	8 (0.6%)	4 (0.8%)	
Timing (h)				
Observation (mean, SD)	5.4 ± 2.0	5.4 ± 1.8	5.6 ± 2.4	**0.04**
Complications				
0 < pain ≤ 1 h	129 (96.2%)	106 (97.3%)	23 (92%)	0.212
1 < pain ≤ 4 h	4 (3%)	3 (2.8%)	1 (4%)	0.741
4 < pain ≤ 6 h	0	0	0	\
Pain > 6 h	1 (0.8%)	0	1 (4%)	\
Major (median, IQR, range)	1, 0–1, 0–96	1, 0–1, 0–24	1, 0–36.5, 0–96	**0.0215**

Note: Bold values indicate statistical significance $p < 0.05$.
Abbreviations: IQR, interquartile range; PLB, percutaneous liver biopsy.

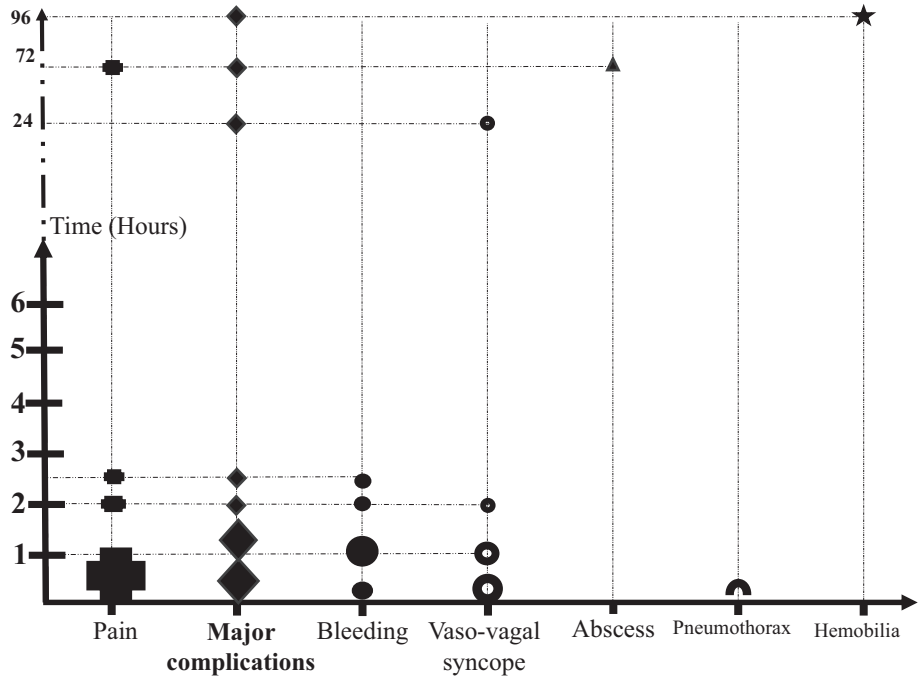

FIGURE 1 | Timing of minor and major complications. ■ One hundred and twenty-nine patients reported pain at the moment of PLB, three at 2 h, one at two and a half hours, one at 72 h following the procedure. ○ Seven episodes of vasovagal syncope occurred at the moment of PLB, five within 1 h, one within 2 h and one 24 h following the procedure. ● Two bleeding events occurred at the time of the PLB, two within 1 h, one 2 h and one 2 and a half hours following the procedure. ▲ One episode of abscess formation occurred 72 h following PLB. ◠ One episode of pneumothorax occurred at the moment of PLB. ★ One episode of haemobilia occurred 96 h following PLB.

No other features emerged as risk factors, including type (cutting vs. aspiration) or size of the needle, number of passes, PLT count before the procedure or the presence of any clinical comorbidities (Table 3).

When analysing Hb variation following the procedure, only 4 out of the 10 patients experiencing a major bleeding event were monitored with repeated blood count as per local protocol, with three of them having a drop in Hb levels of 1 g/dL, not prompting further testing. Among the remaining six patients, one was identified due to hypotensive shock immediately after the procedure, while the other five reported significant pain necessitating analgesic therapy and prompting additional urgent investigations (ultrasound, CT scan).

However, we have to highlight that no major complications were associated with a significant drop of Hb following the procedure, with a mean overall value in the cohort of -0.3 ± 0.5 g/dL.

Among patients with available repeated blood count 3 h following the procedure (973 patients), nine showed a drop in haemoglobin greater than 1.5 g/dL; interestingly, none of them reported pain or a major complication event, which was excluded with abdominal US scan as per local protocols.

Vital parameters including MAP and HR following the procedure could be retrieved only for 551 and 583 patients enrolled in one centre, respectively. At univariate analysis, neither the former (mean 92.9 ± 13.8 mmHg) nor the latter (70.1 ± 11.5 beats per minute) emerged as significantly associated with major complications ($p = 0.9576$ and $p = 0.2116$, respectively).

4 | Discussion

Despite significant advancements in non-invasive techniques for the diagnosis and prognosis in liver diseases, PLB remains essential in various clinical scenarios.

While the indications for PLB have evolved, with liver function abnormalities becoming increasingly common, most available data on its safety and tolerability are outdated [8, 9]. The impact of both clinical and procedural-related factors on the prediction of minor and major complications including bleeding, pneumothorax and haemobilia is still unclear. Indeed, post-PLB follow-up protocols lack standardisation, with considerable variability in monitoring modalities in terms of repeated blood count, ultrasound evaluation and clinical observation only.

In our study, a large cohort of patients ($n = 1838$) who underwent PLB across three referral centres in northern Italy was analysed. No procedure-related deaths were observed, and major complications occurred in 26 cases (1.4%). Pain, defined as a minor complication, was reported in 7.5% of patients (134/1838), with approximately three-quarters requiring analgesic treatment.

Bleeding events were rare (10/1838, 0.5%), consistent with previous reports involving smaller adult cohorts and far below the observations among the paediatric population, where bleeding rates can reach up to 5% [5, 10–12]. Among the 10 cases of bleeding, seven required hospitalisation, with one of them undergoing embolisation and another receiving blood transfusion. The remaining three cases were minor and resolved spontaneously with clinical monitoring alone.

TABLE 3 | Univariate and multivariate analyses.

	No complications	Complications	*p*	HR	*p*
	***N* = 1812**	***N* = 26**			
Age (years) mean ± SD (range)	55.1 ± 15.3 (16–89)	56.6 ± 12.3 (28–81)	0.315		
Sex *n*, %					
Male (M)	975 (53.8%)	15 (57.7%)	0.693		
Female (F)	837 (46.2%)	11 (42.3%)			
BMI (kg/m^2) mean ± SD	25.1 ± 4.8	25.7 ± 4.1	0.254		
LT *n*, %	250 (13.8%)	2 (7.7%)	0.369		
AH *n*, %	586 (32.4%)	10 (38.5%)	0.509		
DMt2 *n*, %	321 (17.7%)	4 (15.4%)	0.756		
COPD *n*, %	41 (2.3%)	0	0.438		
CKD *n*, %	51 (2.8%)	1 (3.9%)	0.753		
AID *n*, %	371 (20.5%)	3 (11.5%)	0.261		
Alcohol intake *n*, %					
Yes	303 (16.8%)	5 (19.2%)	0.741		
Moderate	77 (25.4%)	1 (20%)	0.847		
Heavy drinkers	36 (11.9%)	1 (20%)			
Anticoagulant therapy	77 (4.3%)	1 (3.9%)	0.919		
Antiplatelet therapy	293 (16.2%)	5 (19.2%)	0.675		
Type of needle					
Aspiration needle	1670 (92.2%)	22 (84.6%)	0.200		
Cutting needle	142 (7.8%)	4 (15.4%)			
Needle dimension[a]					
16G	398 (22.3%)	9 (36%)	0.123		
20G	162 (9.1%)	4 (16%)	0.233		
18G	1081 (60.4%)	12 (48%)	0.205		
21G	146 (8.2%)	0	0.136		
Number of passes[b]					
N = 1	1.122 (64%)	17 (65.4%)	0.884		
N > 1	631 (36%)	9 (34.6%)			
PLT (×10^3/mm^3) mean ± SD	209.460 ± 80.6	224.692 ± 92.3	0.169		
50 < PLT < 100	125 (6.9%)	1 (3.9%)	0.541		
PLT < 50	15 (0.8%)	0	0.641		
INR mean ± SD	1.04 ± 0.11	1.09 ± 0.18	**0.026**		0.452
INR > 1.5	16 (0.9%)	2 (8.3%)	**0.0000**		0.255
Hb (g/dL) mean ± SD					
Pre-LB	13.6 ± 1.7	12.7 ± 2.2	0.998		
Post-LB	13.1 ± 1.7	12.9 ± 1.8ù	0.753		
Variation pre-post	−0.3 ± 0.7	−0.3 ± 0.5	0.485		

(Continues)

TABLE 3 | (Continued)

	No complications	Complications	*p*	HR	*p*
	N = 1812	*N* = 26			
Prophylactic therapy	16 (0.9%)	1 (3.9%)	0.117		
Pain	116 (6.4%)	18 (69.2%)	**0.000**	**30.6**	**0.000**
0 < pain ≤ 1 h	114	15	**0.002**		
1 < pain ≤ 4 h	2	2	**0.029**		
4 < pain ≤ 6 h	0	0	\		
Pain > 6 h[c]	0	1	**0.011**		

Note: Bold values indicate statistical significance $p < 0.05$.

Abbreviations: AH, arterial hypertension; AID(s), autoimmune disease(s); BMI, body mass index (kg/m^2); CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DMt2, diabetes mellitus type 2; F, female; G, gauge; Hb, haemoglobin (g/dL); HR, hazard ratio; INR, international normalised ratio; IST, immunosuppressive therapy; LT, liver transplantation; M, male; NSAIDs, non-steroidal anti-inflammatory drugs; PLB, percutaneous liver biopsy; PLT, platelet count (×10^3/mm^3); SD, standard deviation.

[a]For 26 procedures (1 with major complications) needle dimension was unknown.

[b]For 59 procedures, the number of passes was unknown.

[c]Patients reporting pain after 6 h (72 h) from procedures were then hospitalised.

Vasovagal syncope emerged as the most frequent major complication, occurring in 14 out of 1838 patients (0.8%), with an association with bleeding events in two cases. Notably, one episode of vasovagal syncope manifested the day after discharge and was reported through an email contact.

In line with previous reports, 12 patients (0.8%) required hospitalisation, primarily due to bleeding events ($n = 7$), followed by vasovagal syncope ($n = 2$) and pain ($n = 2$). Importantly, one of these hospitalisations occurred 4-day post-procedure, following the onset of severe pain leading to an emergency department visit where radiological evaluation showed haemobilia [13].

Our study did not allow the identification of pre-procedural (baseline) demographic or clinical factors associated with an increased risk of minor or major complications.

Unlike previous findings, neither procedural nor patient-related variables correlated with major complications in our analysis. Specifically, our results do not support prior reports suggesting an association between bleeding episodes and the type or size of the needle or the number of passes [14, 15].

Furthermore, coagulation profile abnormalities, including moderate to severe thrombocytopenia, were not consistently predictive of complications. However, we do acknowledge that only 15 patients (0.8%) underwent PLB with a platelet count below 50 000/mm^3, which is considered the threshold for high-risk bleeding procedures.

While an INR value > 1.5 emerged as statistically significant at univariate analysis—in line with previous reports—this association was not confirmed in logistic regression [14]. It is worth mentioning that only 18 patients (1%) underwent PLB with an INR > 1.5, and among them two experienced bleeding. The first patient (INR 1.5) did not receive any pre-procedural treatment and did not require any hospitalisation. The second patient (INR 1.61) received plasma transfusion before the procedure but subsequently developed a mild perihepatic fluid collection without evidence of an intraparenchymal hematoma. Although the absolute numbers remain low, the proportion of bleeding events in this subgroup is not negligible, suggesting that caution should be exercised when considering PLB in such cases.

Interestingly, neither pre- nor post-procedural Hb levels, nor their variations were associated with complication events. This raises concerns about the cost-effectiveness of repeated blood count as a predictive tool for post-procedural complications.

One of the most widely debated issues regarding liver biopsy is the optimal duration of post-procedural follow-up. Since up to 60% of complications occur from 2 to 4 h after the procedure, this range represents the recommended time of clinical observation in most guidelines [16]. Nevertheless, available data indicate that bleeding events can occur up to 12 h after PLB, with 90% occurring within 24 h [7].

In our study, five major complications occurred more than 1 h following the procedure. Notably, three of them, consisting of one case of haemobilia (96 h), one abscess formation (72 h) and one vasovagal syncope (24 h), developed more than 24 h after PLB; thus, they could not have been predicted even if routine observation was performed. Nonetheless, referral of pain associated with fever even up to 3 days after discharge should prompt further investigation to exclude delayed complications such as infection of the biopsy site or haemobilia. The remaining two cases (both bleeding events) were observed within 3 h (2-h post-procedure) and occurred in patients with normal platelet levels, no coagulation impairment and no anticoagulant or antiplatelet regimen prior to the biopsy. The first case involved a focal-mass biopsy that resulted in bleeding with active blush. The second case occurred in a patient with Grade 1 obesity who underwent a core biopsy, leading to bleeding without active blush, which resulted in a hepatic hematoma. In both cases, no significant haemoglobin decrease was observed on repeated blood counts at 3 h (less than 1 g/dL), meaning that even in these instances, major complications could not have been predicted. Both events were detected due to the onset of pain prompting evaluation

with ultrasound; a practice that is both feasible and effective, and required hospitalisation.

To note, in our study pain emerges as the only significant predictive factor of major complications at multivariate analysis; interestingly, up to 96% of patients (129/134) reported pain within 1 h, thus representing an easy and handy tool for the effective identification of patients at the risk of major complications.

Our study has several limitations. First, its retrospective design restricted comprehensive data collection, and when available, the measurement of vital parameters was unprecise in terms of timings. Second, the study population consisted of patients undergoing liver biopsy in a day-hospital setting, thus introducing a selection bias related to comorbidities and general performance. Furthermore, it is important to highlight that all PLBs were performed under ultrasound guidance using a transducer-mounted guiding system rather than mere ultrasound assistance. This approach enhanced procedural safety and facilitated immediate post-procedural evaluation of the biopsy site, allowing for prompt detection of acute bleeding.

Nevertheless, this study includes a wide cohort of patients who consecutively underwent liver biopsy over the past 5 years in tertiary care hospital settings, thus offering valuable clinical insights.

In conclusion, complications following US-guided percutaneous liver biopsy are rare. Early-onset pain warrants attention, potentially representing a useful predictive clinical marker for major complications. Additional prospective and randomised studies would be of major help in standardising post-biopsy protocols with the optimisation of patients' safety and resources utilisation.

Author Contributions

All the authors have given substantial contributions to the completion of this work and have seen and approved the text in the current version.

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Ethics Statement

The study was approved by the local ethics committee.

Consent

Informed consent was waived due to the use of deidentified retrospective data; however, all patients signed a consent form allowing the use of retrospective data at the time of admission according to local protocols.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. D. C. Rockey, S. H. Caldwell, Z. D. Goodman, R. C. Nelson, A. D. Smith, and American Association for the Study of Liver Diseases, "Liver Biopsy," *Hepatology* 49, no. 3 (2009): 1017–1044.

2. J. F. D. Cadranel, J. B. Nousbaum, M. Gouillou, and B. Hanslik, "Major Changes in the Number and Indications of Liver Biopsy for Chronic Liver Diseases Over One Decade in France," *European Journal of Gastroenterology & Hepatology* 28, no. 9 (2016): e26–e32.

3. A. A. Bravo, S. G. Sheth, and S. Chopra, "Liver Biopsy," *New England Journal of Medicine* 344, no. 7 (2001): 495–500.

4. E. B. Tapper and A. S. F. Lok, "Use of Liver Imaging and Biopsy in Clinical Practice," *New England Journal of Medicine* 377, no. 8 (2017): 756–768.

5. M. Midia, D. Odedra, A. Shuster, R. Midia, and J. Muir, "Predictors of Bleeding Complications Following Percutaneous Image-Guided Liver Biopsy: A Scoping Review," *Diagnostic and Interventional Radiology* 25, no. 1 (2019): 71–80.

6. J. Neuberger, J. Patel, H. Caldwell, et al., "Guidelines on the Use of Liver Biopsy in Clinical Practice From the British Society of Gastroenterology, the Royal College of Radiologists and the Royal College of Pathology," *Gut* 69, no. 8 (2020): 1382–1403.

7. J. H. Boyum, T. D. Atwell, G. D. Schmit, et al., "Incidence and Risk Factors for Adverse Events Related to Image-Guided Liver Biopsy," *Mayo Clinic Proceedings* 91, no. 3 (2016): 329–335.

8. M. G. Ettel and H. D. Appelman, "Approach to the Liver Biopsy in the Patient With Chronic Low-Level Aminotransferase Elevations," *Archives of Pathology & Laboratory Medicine* 142, no. 10 (2018): 1186–1190.

9. A. Khalifa and D. C. Rockey, "The Utility of Liver Biopsy in 2020," *Current Opinion in Gastroenterology* 36, no. 3 (2020): 184–191.

10. H. Matos, M. J. Noruegas, I. Gonçalves, and C. Sanches, "Effectiveness and Safety of Ultrasound-Guided Percutaneous Liver Biopsy in Children," *Pediatric Radiology* 42, no. 11 (2012): 1322–1325.

11. R. K. Azzam, E. M. Alonso, K. M. Emerick, and P. F. Whitington, "Safety of Percutaneous Liver Biopsy in Infants Less Than Three Months Old," *Journal of Pediatric Gastroenterology and Nutrition* 41, no. 5 (2005): 639–643.

12. J. G. Amaral, J. Schwartz, P. Chait, et al., "Sonographically Guided Percutaneous Liver Biopsy in Infants: A Retrospective Review," *AJR. American Journal of Roentgenology* 187, no. 6 (2006): W644–W649.

13. R. J. Firpi, C. Soldevila-Pico, M. F. Abdelmalek, G. Morelli, J. Judah, and D. R. Nelson, "Short Recovery Time After Percutaneous Liver Biopsy: Should We Change Our Current Practices?," *Clinical Gastroenterology and Hepatology* 3, no. 9 (2005): 926–929.

14. T. D. Atwell, R. L. Smith, G. K. Hesley, et al., "Incidence of Bleeding After 15,181 Percutaneous Biopsies and the Role of Aspirin," *American Journal of Roentgenology* 194, no. 3 (2010): 784–789.

15. H. Chi, B. E. Hansen, W. Y. Tang, et al., "Multiple Biopsies Passes and the Risk of Complications of Percutaneous Liver Biopsy," *European Journal of Gastroenterology & Hepatology* 29, no. 1 (2017): 36–41.

16. D. C. Rockey, S. H. Caldwell, Z. D. Goodman, R. C. Nelson, and A. D. Smith, "Liver Biopsy," *Hepatology* 49, no. 3 (2009): 1017–1044.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.