

# Complications and risk factors of a large series of percutaneous liver biopsies in patients with liver transplantation or liver disease

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**Abstract. – OBJECTIVE:** Liver biopsy is a very important investigation in Hepatology. The aim of this retrospective study was to assess the prevalence of complications after Percutaneous Liver Biopsy (PLB), performed in two groups of patients with liver transplantation or with liver disease. We compared our results with those most representative of the literature and discussed about indications, advantages and disadvantages in relation to the different modes for the execution of this procedure, with particular regard to the use of ultrasound guidance.

**PATIENTS AND METHODS:** We analyzed the results of 847 PLB performed with the Menghini technique between January 2004 and December 2013 at the Transplant Unit of the University of Rome Tor Vergata. The indications for biopsy were: follow-up liver transplantation, HBV, HCV and HBV/HCV related liver disease, alcohol related liver disease and HIV coinfecting with HBV or HCV. Our patients were classified into two groups according to specific indication: patients with liver transplantation (group A) and patients with liver disease (group B). The procedure was always performed in the Day Hospital regimen. After the biopsy, the patients remained in bed for about 4-6 hours. In absence of complications, they were then discharged in the same day.

**RESULTS:** The most frequent complication was pain after biopsy (group A n. 45, 7.9%; group B n. 85, 30.9%), requiring analgesics administration, hypotension as a result of a vasovagal reaction resolved spontaneously (group A n. 6, 1.0%; group B n. 6, 2.2%), and bleeding (group A n. 1, 0.2%; group B n. 6, 2.2%), which, however, has never necessitated surgery, except in one case of hemothorax. Two cases of pneumothorax were resolved with chest tube. Other complications did not have a significant impact.

**CONCLUSIONS:** Liver biopsy is not replaceable investigation to diagnose several liver diseases and their course and also to monitor the condition of the hepatic parenchyma after transplantation. Among the various methods we preferred the Menghini technique with percutaneous transcostal approach, because less traumatic.

This procedure presents low occurrence of various problems. We reviewed the literature regarding the major complications related to the technique and the use of ultrasound guidance. Based on our case series and data reported by the main Authors, we believe that ultrasound guidance is not decisive in the prevention of major complications. It is useful if done in the days or weeks prior to biopsy only in order to know any anatomical abnormalities or rather diseases that may pose a specific indication for the procedure with ultrasound guidance.

*Key Words:*

Liver biopsy, Biopsy needle, Liver transplantation, Liver disease, Complications.

## Introduction

Liver biopsy is a staple in diagnostic hepatological. Although today there are many imaging techniques available, histological diagnosis is still not replaceable to find some liver diseases and to monitor their course. Furthermore, the liver biopsy allows to evaluate the conditions of the liver parenchyma after transplantation. Among the various methods, Percutaneous Liver Biopsy (PLB) with the Menghini method<sup>1-2</sup> is certainly less traumatic for the small size of the needle and for the very rapid time of execution.

The aim of this study is to analyze retrospectively the results of 847 PLB performed with the technique of Menghini in two groups of patients, with liver transplantation or with liver disease, to compare our results with those most representative of the literature. We also aim to discuss about indications, advantages and disadvantages in relation to the different modes for the execution of this procedure, with particular regard to the use of ultrasound guidance.

## Patients and Methods

Between January 2004 and December 2013, at the Transplant Unit of the University of Rome "Tor Vergata", 847 PLB were performed to assess the state of health of the hepatic parenchyma. The indications for biopsy are showed in Table I. All patients divided in two groups based to specific indications: patients with liver transplantation (group A) and patients with liver disease (group B). In our study we considered the procedures. Some transplanted patients were biopsied periodically, and for this reason the number of patients and procedures was different. Instead, patients with liver disease usually underwent only to a single biopsy, with few exceptions. The mean age was calculated at the time of the first procedure.

The biopsy was always performed in the Day Hospital regimen. All patients were informed about the PLB procedure and any possible complications and have expressed the consent with their signature. Patients undergoing liver biopsy for acute rejection after liver transplantation or for serious complications were always hospitalized and, therefore, were not considered in this study.

The exclusion criteria for our analysis were considered: (1) Hemoglobin < 8.0 g/dl; (2) INR > 2; (3) Platelets count < 40.000/ $\mu$ l; (4) Other coagulation disorders; (5) Ascites; (6) Dilatation of the intrahepatic bile ducts. The patients with platelets < 40.000/ $\mu$ l (15 procedures), subjected to platelet transfusion prior to biopsy, were excluded.

At the time of convening, the patients taking anticoagulants (aspirin, etc.) were asked to discontinue therapy at least 3 days before the examination. Before starting the procedure or in the days before, all patients underwent abdominal ultrasound to exclude any anatomical or pathological conditions, that could represent a contraindication to the procedure. Also before the biopsy, all patients were subjected to blood sample tests, to evaluate coagulation and blood count parameters.

PLB with intercostal access was performed by the standard technique described by Menghini<sup>1,2</sup>, using the appropriate automatic needle (16 gauge in diameter and 15 cm in length). The patient was placed supine, slightly turned to the left and right arm behind his head. By the percussion we delimited the upper margin of the liver and by the palpation the bottom margin. Then, we identified the most suitable point for the biopsy, generally located in the intercostal space corresponding to the point of intersection between the anterior axillary line and the transverse line that passes on the xiphoid process. Local anesthesia was performed by infiltration of Ropicavaine 10 mg/ml. After practicing a small skin incision of about 2-3 mm in the set point, the needle was inserted through the intercostal space along the costal margin top to prevent accidental injury intercostal artery. In full expiration and apnea, the surgeon proceeded, with rapid maneuver, to the puncture of the liver and biopsy by suction. The hepatic frustule was usually 1 mm in diameter and approximately 20-30 mm in length. It was preserved in formalin and sent to the histologist evaluation. We performed a pressure dressing on the point of incision and was also applied a bag of ice. After the procedure, the patient remained in bed for about 4-6 hours. Before discharge, they proceeded to check vital signs and a blood sampling to assess any changes. In absence of complications, the patient was discharged.

## Results

The complications, overall considered, are shown in Table II.

In 35 cases (4.1%) it was necessary to repeat the procedure a second time, and in 11 cases (1.3%) even a third time because the sample was less than 15 mm and, therefore, not satisfactory for histological examination.

**Table I.** Indications for liver biopsy.

Indication	n. biopsies	n. patients	Males	Females	Mean age
Liver transplantation follow-up	572	290	204	86	51.0 $\pm$ 10.24
HBV related liver disease	45	43	33	10	39.5 $\pm$ 15.42
HCV related liver disease	97	94	75	19	37.2 $\pm$ 13.35
HBV/HCV related liver disease	40	39	28	11	41.6 $\pm$ 11.25
Alcohol related liver disease	49	47	24	23	53.1 $\pm$ 18.11
HIV coinfectd with HBV or HCV	44	44	32	12	26.2 $\pm$ 9.25
<b>Total</b>	<b>847</b>	<b>557</b>	<b>396</b>	<b>161</b>	

**Table II.** Total complications after liver biopsy.

Complication	Total (n. 847 procedures)	Group A Liver Transplantation (n. 572 procedures)	Group B Liver Disease (n. 275 procedures)
Pain	130 (15.3%)	45 (7.9 %)	85 (30.9%)
Hypotension	12 (1.4%)	6 (1.0%)	6 (2.2 %)
Intrahepatic bleeding	7 (0.8%)	1 (0.2%)	6 (2.2 %)
Pneumothorax	2 (0.2%)	2 (0.3%)	0
Hemothorax	1 (0.1%)	1 (0.2%)	0
Pancreatitis	1 (0.1%)	1 (0.2%)	0
Choleperitoneum	0	0	0
Intestinal perforation	0	0	0
Sepsis	0	0	0
Hematuria	0	0	0
Death	0	0	0

In a total of 28 cases it was performed the biopsy under ultrasound guidance. In addition, 21 patients in group B underwent liver biopsy under ultrasound guidance because the procedure had been unsuccessful previously in other centers. So were performed with ultrasound guidance a total of 23 biopsies in group A and 26 in group B. The complications observed in this group were similar to remaining study population and are reported in Tables III and IV.

The post-biopsy pain was the most frequent problematic; in a total of 130 cases (group A n. 45, 7.9%; group B n. 85, 30.9%) was necessary administration of mild analgesic (Paracetamol 1000 mg). Only in 17 cases the persistence of pain, mostly in anxious patients, has required further administration of Ketorolac (30 mg i.m.) or Tramadol (100 mg im). In 2 cases it was necessary precautionary hospitalization for 48 hours, during which the symptoms regressed so that the patient was regularly discharged. In 1 case the painful

symptom was associated with an increase of amylase and lipase blood levels. The patient was hospitalized for 7 days and subjected to medical therapy until normalization of values, occurred after 5 days.

In a total of 12 cases (group A n. 6, 1.0%; group B n. 6, 2.2%) we observed a vasovagal reaction with transient hypotension, which resolved spontaneously.

The intrahepatic bleeding occurred overall in 7 cases (group A n. 1, 0.2%; group B n. 6, 2.2%), but it has never been necessary surgical treatment. These patients were hospitalized, as a precautionary measure, and monitored by abdominal ultrasound and blood samples. The bleeding, however, was not important: it was always stopped spontaneously after 48-72 hours. We reported 1 case of hemothorax in a patient with liver transplantation for potus related cirrhosis, who had already been subjected to 7 of liver biopsies of control in previous years without any problem. In addition, this patient underwent regular hemodialysis

**Table III.** Complications after liver biopsy without ultrasound guidance.

Complication	Total (n. 798 procedures)	Group A Liver Transplantation (n. 549 procedures)	Group B Liver Disease (n. 249 procedures)
Pain	120 (15.0%)	43 (7.8 %)	77 (30.9%)
Hypotension	10 (1.3%)	5 (0.9%)	5 (2.0 %)
Intrahepatic bleeding	5 (0.6%)	1 (0.2%)	4 (1.6 %)
Pneumothorax	2 (0.3%)	2 (0.4%)	0
Hemothorax	1 (0.1%)	1 (0.2%)	0
Pancreatitis	1 (0.1%)	1 (0.2%)	0
Choleperitoneum	0	0	0
Intestinal perforation	0	0	0
Sepsis	0	0	0
Hematuria	0	0	0
Death	0	0	0

**Table IV.** Complications after liver biopsy under ultrasound guidance.

Complication	Total (n. 49 procedures)	Group A Liver Transplantation (n. 23 procedures)	Group B Liver Disease (n. 26 procedures)
Pain	10 (20.4%)	2 (8.7%)	8 (34.6%)
Hypotension	2 (4.1%)	1 (4.3%)	1 (3.8 %)
Intrahepatic bleeding	2 (4.1%)	1 (4.3%)	1 (3.8 %)
Pneumothorax	0	0	0
Hemothorax	0	0	0
Pancreatitis	0	0	0
Choleperitoneum	0	0	0
Intestinal perforation	0	0	0
Sepsis	0	0	0
Hematuria	0	0	0
Death	0	0	0

for chronic renal failure. At the time of discharge from the day hospital blood parameters were normal. The bleeding was manifested late after 48 hours, subsequently to the routine hemodialysis. In this case it was necessary to surgery (performed in another hospital) to stop bleeding due to accidental injury of a intercostal vessel.

In 2 cases we observed a pneumothorax, reduced in a few days with chest tube. Both patients were smokers with emphysema. Probably the biopsy needle has through the phrenic angle cost injuring some emphysematous air bubble.

We have never been observed other complications reported in the literature, such as hematuria, choleperitoneum, bowel perforation or sepsis. In our casuistry we did not record any death.

The fragmentation of the frustule occurred in a total of 80 cases (Group A n. 61, 10.7%; Group B n. 19, 6.9%) but has not proceeded to a further sampling since, however, the amount of hepatic parenchyma was considered generally adequate for histological evaluation.

## Discussion

The first liver biopsy was performed in 1883 in Germany, but it was risky because it required a run time of 15 minutes approximately.

In 1958 Menghini<sup>1</sup> devised and published an innovative method, the "One-second needle biopsy of the liver". In subsequent years, this technique has been modified and improved mainly thanks to the introduction of syringes and needles disposibles<sup>2-3</sup>.

Historically, liver biopsy was used almost exclusively as a diagnostic tool. Despite the intro-

duction of new diagnostic methods of imaging in recent years, the indications for liver biopsy for histological evaluation of the liver are increased. This can be related to three factors: (1) the large population of patients with hepatitis C, for which only the biopsy may allow staging of the disease, according to the directives of the current guidelines; (2) the increasing number of patients undergoing liver transplantation and the need to periodically monitor the status of the hepatic parenchyma; (3) the staging rather than diagnosis of diseases, recently increased, such as obesity, diabetes mellitus, hyperlipidemia etc<sup>4-5</sup>.

The British Society of Gastroenterology<sup>6</sup>, the American College of Gastroenterology<sup>7</sup> and the Canadian Association of Gastroenterology<sup>8</sup> has developed specific guidelines for liver biopsy as an outpatient procedure. The most recent guidelines of the American Association for the Study of Liver Diseases (<sup>9</sup>) still do not substantially differ from the previous ones.

Liver biopsy currently has three major roles: (1) diagnosis; (2) assessment of prognosis (disease staging); (3) assist in making therapeutic management decisions.

For many diseases, clinical and/or blood based tests suffice to establish a diagnosis (typical examples include hepatitis B or hepatitis C virus infection). Nonetheless, liver biopsy is often a critical component in establishing the diagnosis of many forms of liver disease. Although histological assessment alone may be able to make a diagnosis on occasion (i.e. a florid duct lesion in primary biliary cirrhosis), liver histology is typically and most appropriately considered in conjunction with the full gamut of clinical and laboratory data.

Acute and chronic hepatitis, cholestatic disorders, fatty liver disease, vascular diseases, infiltrative or storage diseases, some infectious and granulomatous diseases, and other disorders may be associated with characteristic histological abnormalities that are helpful in diagnosis<sup>10</sup>.

It is likely that liver biopsy will always play a role in the management of the patient with a diagnostic dilemma. This includes the patient with abnormal liver tests of unknown etiology or the patient in whom a specific liver disease has been considered, but has not yet been confirmed (i.e. hereditary disorders such as Wilson disease, alpha-1-antitrypsin disease, glycogen storage diseases, tyrosinemia, Niemann-Pick disease, amyloidosis, and others)<sup>11-24</sup> or with systemic disease in which the liver appears to be involved. Liver histology may provide important diagnostic information in patients with acute liver failure<sup>25</sup>.

A further important use of liver biopsy is in assessing disease severity, notably fibrosis, which, as a precursor to cirrhosis, may predict the emergence of complications of portal hypertension and also liver-related morbidity and mortality. Evidence in the area of HCV emphasizes the role of fibrosis assessment in determining prognosis. Assessment of liver histology may be particularly beneficial in patients with human immunodeficiency virus and HCV who have persistently normal ALT levels, because these patients may have significant fibrosis, which may be of prognostic importance. This allows the clinician to determine the extent of liver fibrosis and, consequently, to assess suitability for treatment<sup>26</sup>.

Currently, liver biopsy is used more than ever to develop treatment strategies. As previously emphasized, this has evolved because of the many new therapies available for patients with a variety of liver diseases. Not only can a treatment plan be instituted in a patient after a specific diagnosis is made (i.e. steroids in the setting of autoimmune hepatitis), but among those with established liver disease, treatment may be predicated on the specific histological lesion.

Assessment of liver histology following orthotopic liver transplantation is an essential component of management in this patient population. It is often important to make a specific diagnosis in the setting of liver test abnormalities early after transplantation to investigate allograft rejection, preservation or reperfusion injury, drug-induced liver injury, viral infection (usually recurrent) or bile duct injury. Liver biopsy is also often helpful in the setting of late allograft dysfunction<sup>27</sup> in-

cluding to investigate the possibility of recurrence of the original disease<sup>28</sup>. Some liver transplant programs, such in our transplant center, perform liver biopsy on a protocol basis after transplantation for HCV related cirrhosis (e.g., annually), even in those patients with normal liver tests, although compelling evidence to support this approach is lacking. In contrast, there is good evidence suggesting that fibrosis progression may be predicted by using liver histology in patients following transplantation<sup>29-30</sup>. In our case load liver biopsy after liver transplantation was performed in order to evaluate the feasibility of immunosuppression withdrawal<sup>31-32</sup> or complete and sustained prophylaxis withdrawal in patients liver-transplanted for HBV-related cirrhosis<sup>33</sup>.

The use of the ultrasound or computerized tomography (CT) in PLB is controversial. We must distinguish the different indications for biopsy. When the investigation is aimed at studying the state of health of the liver the biopsy sampling can be performed in any part of the parenchyma and, therefore, the use of imaging methods is unnecessary during the procedure; if anything, can be useful in previously only to exclude any particular anatomical anomalies or pathological situations (presence of angiomas, etc.). Instead, when the indication for biopsy is the necessity of a histological diagnosis of a well-defined focal lesion (focal biopsy), the CT or ultrasound guidance may be useful to allow the targeted localization of the lesion. In the latter case, also, the sampling can be performed with a cutting needle (Tru-Cut type) of greater size (14G) and with a cutting part. This technique has a better yield but is more traumatic to the Menghini needle, which instead works with a vacuum mechanism<sup>34</sup>.

Many studies have showed that the prevalence of bleeding can not be changed with the use of the ultrasound system<sup>35-37</sup>. Gilmore et al<sup>38</sup> reported an audit conducted in England and Wales by the British Society of Gastroenterology and the Royal College of Physicians of London. There was no differences in the frequency of bleeding between the different techniques (standard vs image guided). Bleeding was commoner in the patients with raised INR: 3.3% when INR was 1.3-1.5, and increasing to 7.1% above an INR > 1.5. This observation was later confirmed by Thampanitchawong and Piratvisuth<sup>39</sup>, who present his series of 484 PLB with occurrence of bleeding complications of 4.5%. They affirm that the bleeding disorders are the leading cause of bleeding in these patients. Our data do not confirm nor refute this hypothesis

because in our study we excluded all patients with severe bleeding disorders. Muir and Trotter<sup>40</sup> report an epidemiological study carried out by means of a questionnaire sent to 157 members of the Duke University Digestive Epidemiological Studies Consortium (Durham, NC, USA). There are significant data showing that the use of ultrasound reduces the occurrence of bleeding, but notes that ultrasound guidance is recommended only for trainees. Therefore, in the U.S. it is used only in 13% of biopsies. Caldwell and Northup<sup>41</sup> reported the experience of 10 centers for a total of 2.740 PLB and confirm, according to Stone and Mayberry<sup>36</sup>, that the use of the ultrasound does not reduce the occurrence of bleeding complications, arguing that the resolution of this instrument does not allow you to view, and then to avoid the small vessels which are generally the most common cause of bleeding.

Menghini, discussing about the problems and clinical applications of biopsy<sup>2</sup>, stressed the importance of speed of method execution (not coincidentally the title of this article is "One-second biopsy of the liver"). The ultrasound-guided biopsy requires longer execution times, and then a more prolonged residence time of the needle into the liver parenchyma. This would increase the risk of bleeding and, therefore, the use of ultrasound is justified only in the focal biopsies<sup>42</sup>. In our study, the occurrence of bleeding events was lower in patients in follow-up after liver transplantation. It is possible that the post-operative adhesions in the abdominal wall can contribute to reducing bleeding after liver biopsy.

The post-biopsy pain is the most frequent complication. Eisemberg et al<sup>43</sup> affirm that the pain during the procedure is present in 84% of patients and can remain in an acute form for 24 hours in 40% of cases. They also argue that there is a correlation between the levels of pre-biopsy anxiety and pain intensity. It is usually located in the intercostal space or in the right shoulder, more common in women. When the pain is not a symptom of other complications (peritoneal irritation or bleeding biliary loss for drilling, etc.) may result from stimulation of sensory receptors in the skin and the liver capsule. We believe that the denervation of the liver capsule may explain the lower prevalence of pain that we observed in patients with liver transplantation. Shoulder pain can be viscerosomatic type<sup>44</sup>. Janes and Lindor<sup>45</sup> report a case series of 405 patients of whom 5 (1.2%) required hospitalization for observation after biopsy. Controversial is the use of ultra-

sound in the prevention of pain. Al Knawy and Shiffman<sup>46</sup> affirm that the use of ultrasound guidance reduces the frequency of pain during the biopsy and after biopsy, respectively, of 10.9% and 1.8%. However, it is interesting to note that this effect is significantly reduced with the use of sedative pre-biopsy, thus confirming the observation of Eisemberg et al<sup>43</sup>. Gilmore et al<sup>38</sup> reported a 30% occurrence of pain and argues that in 40% of patients the pain subsides spontaneously without the use of analgesics. In case of persistence of symptoms is usually sufficient the administration of Paracetamol.

The trans-thoracic approach determines rare complications described in the literature. Piccinino et al<sup>47</sup> conducted a multicenter retrospective study on 68.276 biopsies and reported a 0.35% occurrence of pneumothorax and a 0.18% of hemothorax. In the latter case, the accidental injury of a diaphragmatic or intercostal vessel is responsible for the complication. The preventive use of the ultrasound is useless, because these vessels are not detectable due to their small size<sup>36,48</sup>.

Some authors describe rare cases of acute pancreatitis after liver biopsy. They agree in considering pancreatitis caused by biliary obstruction due to hemobilia following procedure. Jornod et al<sup>49</sup> considered that the risk of hemobilia is less than one per 1000 procedures. Zhou<sup>50</sup> accounts the hemobilia for approximately 3% of all major complications caused by percutaneous ultrasound guided liver biopsy. Pena et al<sup>51</sup> describe a case managed with biliary drainage stent. In our case of acute pancreatitis, probably due to hemobilia, the drainage or other procedure were not necessary because the values returned gradually to normal with medical therapy after 5 days, and after 7 days the patient was discharged. Other described complications in the literature have a much negligible. Piccinino et al<sup>47</sup> reported a prevalence of less than 0.01% for visceral perforation, biliary fistulas, septic complications and needle breakage.

A very important aspect to consider are the size and the possible excessive fragmentation of the small piece of liver parenchyma taken. The extent of fibrotic damage is an important way on the yield of the levy. Therefore, in case of unsatisfactory withdrawal after no more than three consecutive attempts by needle with suction mechanism, it is advisable to repeat the biopsy at another time using a cutting needle type "Tru-cut". In the latter case, since the larger the needle increases the risk of complications, it is useful to the use

of ultrasound guidance. The majority of pathologists considered suitable scrap of 1.5-2 cm in length taken with needle 16G<sup>52</sup>, which statistically contain at least 10 portal tracts<sup>6-8,53</sup>.

In the literature there are no precise results regarding the occurrence of mortality. The few data indicate that mortality post-biopsy can vary from 0.01% to 0.1%. However, it is difficult to establish the role of the disease rather than the biopsy<sup>6,34,38,48</sup>.

The trans-thoracic approach reduces the possibility of damage to organs or structures, differently biopsy performed through subcostal that exposes the anatomical structures of the liver hilum and the colon. For this reason, in the absence of other specific indications, only the subcostal access always requires the use of ultrasound guidance. It should be pointed out, however, that the transplanted liver is devoid of cholecyst.

However, the opinions on the usefulness of CT and ultrasound are controversial. The use of driving through imaging methods is indicated only in focal liver biopsy in the USA and UK. Lindor et al<sup>35</sup> have a total of 836 liver biopsies performed in two centers: 489 in Rochester and 347 in Barcelona. They reported that the use of the ultrasound does not alter the occurrence of all complications, but nevertheless reduces hospitalization days. Manolakopoulos et al<sup>37</sup> limit the indication of ultrasound in obese patients and also focus on the impact on costs, confirming what was previously stated by Pasha<sup>54</sup>. This is also an indication that emerges in the Guidelines of the British Society of Gastroenterology and the British Association for the Study of the Liver. Therefore, the use of ultrasound guidance is not considered the standard of care in all units in the UK<sup>55</sup>.

## Conclusions

Despite the recent advances in imaging methods, liver biopsy is not replaceable investigation to diagnose several liver diseases and their course and also to monitor the condition of the hepatic parenchyma after transplantation.

The methods that have been described in the literature for the hepatic biopsy are numerous and the results are not always concordant. Based on our case series and data reported by the main authors, we believe that liver biopsy performed according to the standard method of Menghini, with percutaneous transcostal approach, is preferable because it is less traumatic and pre-

sents low prevalence of various problems. Furthermore, we believe that the ultrasound examination is useful if done in the days or weeks prior to biopsy only in order to know any anatomical abnormalities or diseases that may pose a contraindication to examination or rather justify the use of an ultrasound-guided biopsy, but is not decisive in the prevention of major complications.

## Conflict of interest

The Authors declare that there are no conflicts of interest.

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