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Review

Fibrosis and steatosis of the liver graft: Are non-invasive tests useful? A short review

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ABSTRACT

As life expectancy of liver transplanted patients improves, new questions are arising to avoid progressive graft loss. The spectrum of chronic inflammation and fibrosis are known to be important triggers in the alteration of graft function. Liver biopsy remains the gold standard to better understand progressive, normal, and abnormal histological modifications of the graft.

In parallel, the interest for metabolic steatosis development in post-transplantation is also growing. Long-term survival of these patients involves the management of comorbidities including metabolic syndrome and cardiovascular diseases. Early detection of altered graft parenchyma, and monitoring of its evolution are undoubtedly essential.

Non-invasive methods including transient elastography and fibrosis biomarkers are attractive tools to avoid drawbacks and complications of liver biopsy. Accuracy of these methods are well-known in a pre-transplantation setting, but evidence is lacking in post-transplantation setting. We review current knowledge of progressive liver fibrosis and steatosis development after transplantation and non-invasive methods of their assessment.

Introduction

Cirrhosis causes the death of one million people worldwide each year [1]. Liver transplantation (LT) is today accepted as the best treatment for end-stage liver diseases (ESLD), acute liver failure, hepatocellular carcinoma following Milan criteria and few metabolic disorders[2]. Improvements are still needed in post LT to maximize survival rates and lead our patients to a normal life expectancy. Furthermore, re-transplantation is a great challenge in terms of surgery and immunological tolerance. Early detection and better understanding of the graft histological modifications and alterations become essential to avoid graft loss.

Progressive liver graft fibrosis is a cause of graft failure and late death in the follow-up of transplant patients. However, fibrosis in early stage can evolve and be reversible[3]. Hence, early detection and good assessment of fibrosis are crucial to improve fibrosis management and provide targeted therapies. Physiopathology and mechanisms of development of the graft fibrosis are not totally clarified. Most known publications include observational studies on pediatric population[4]. With the increasing prevalence of obesity and metabolic syndrome, the detection of steatosis (included in the spectrum of the metabolic dysfunction-associated steatotic liver disease or MASLD) and its aggressive form called non-alcoholic steatohepatitis (NASH) on the liver graft[5] and the better knowledge of its natural evolution and complications are needful.

Non-invasive methods including transient elastography (TE) and fibrosis biomarkers are attractive tools to avoid drawbacks and complications of liver biopsy. They can be useful in screening for steatosis and/or fibrosis in the situation of a native liver. The purpose of this review is to present the actual knowledge on the occurrence of fibrosis and steatosis after liver transplantation and to focus on the usefulness of non-invasive diagnostic tools in detecting and grading these alterations.

Abbreviations: ACR, acute cellular rejection; ALD, alcohol-related liver disease; ARFI, acoustic radiation force impulse; AUC, area under curve; BMI, body mass index; CAP, controlled attenuation parameter; DM, diabetes mellitus; EASL, the European Association for the Study of the Liver; ESLD, end-stage liver diseases; HCV, hepatitis C virus; HEV, hepatitis E virus; LB, liver biopsy; LSM, liver stiffness measurement; MASLD, metabolic -associated steatotic liver disease; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NASH, non-alcoholic steatohepatitis; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; SE, sensitivity; SP, specificity; SWE, shear wave elastography.

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Allograft hepatitis and fibrosis: prevalence and pathophysiology

Pediatric population

Under the appearance of healthy transplant patients and strictly normal biochemical tests, a significant proportion of patients shows histological abnormalities, including fibrosis and inflammation. These alterations are well known in the pediatric population. Table 1 summarizes the studies evaluating fibrosis and non-specific inflammation in post-LT LB. In 2006, Evans et al. presented a cohort of 158 pediatric patients. They evaluated the presence of chronic inflammation in 22%, 43% and 64% in the protocol biopsies at 1, 5 and 10 years respectively [6]. They also showed a great correlation between presence of chronic inflammation and fibrosis. At 10 years post-LT, 91% of the patients with chronic inflammation also presented fibrosis of the graft. Venturi et al. observed an incidence of fibrosis, quantified with computerized morphometric analysis, in 74% of their 54 children included in their long term follow-up (7 years)[7].

The pathophysiology linked to the development of the post-LT fibrosis was mostly investigated in this pediatric population. The risk factors for developing post-transplant fibrosis are different compared to the adult population. The main cause for these differences is the underlying etiology for end-stage liver disease. Most liver diseases in pediatric patients do not recur after LT. Several risk factors have been identified. First of all, a correlation between the presence of chronic hepatitis and the development of fibrosis was established, but no direct cause was associated with this inflammation[6]. Multiple triggers could be linked to this inflammation including recurrent and acquired viral diseases, recurrent or de novo autoimmune hepatitis and idiopathic etiology. This latter concept also called idiopathic post-transplantation hepatitis (IPTH) could be correlated with a form of late rejection[8,9]. IPTH doesn't seem to be well accepted and defined in the scientific community. Multiple histological terms are used (i.e. "non-specific inflammation", "interface hepatitis", "portal inflammation"). This leads to difficulties in harmonization and comparison. Some believe that IPTH is related to an immunological process. Few supporting arguments are present including association with autoantibodies (after exclusion of the diagnostic of de novo autoimmune hepatitis), features of rejection and its development after reducing immunosuppression[6,8,10]. Globally, it is important to keep in mind that all these concepts (IPTH, late rejection, de novo autoimmune hepatitis) are currently interconnected, being part of a large family of immune diseases with overlaps in each entities that can ultimately lead to the development of graft fibrosis[8]. The development of chronic inflammation and fibrosis should not be confused with typical, clinically, and histologically well-defined diagnosis of acute and chronic rejection.

Another interesting concept to consider in the development of fibrosis is that of the immunoregulatory capabilities of the different liver cell types that can control chronic immune injuries and release fibrotic factors including interleukin-10 and transforming growth factor-β. The regulatory effect of liver regulatory T-cells (T-regs) and their release of immunomodulatory cytokines makes the liver less susceptible to alloimmune stimulations but favours the development of fibrosis in the liver graft[11]. To support this hypothesis, Koshiba et al. showed the development of fibrosis to a greater extent in the grafts of immunotolerant patients compared to liver grafts of patients still under immunosuppressive therapies [12]. Then, other risk factors for the development of fibrosis than immunomodulatory mechanisms should be mentioned. These factors include prolonged cold ischemia time, higher donor/recipient age ratio, partial graft transplantation[13]. Subclinical biliary and venous obstruction secondary to complicated surgery can also lead to graft fibrosis[11]. Finally, the gut microbiome is also thought to play a role in the development of the fibrosis. Dysbiosis is known in ESLD patients, and this gut alteration can be partially maintained after LT. Bacterial translocation through increased intestinal permeability could stimulate pro-inflammatory pathways in the liver resulting in the activation of hepatic stellate cells producing extracellular matrix that initiate fibrogenesis[14]. The different risk factors of developing fibrosis are summarized in Fig. 1.

Table 1
Occurrence of liver abnormalities and fibrosis in pediatric liver transplant recipient.

Author, year	Population	Number of biopsies	Length of follow-up (years)	Abnormal liver biopsies	Fibrosis (all stages)
Evans [6] (2006)	pediatric	113, 135, 64	1, 5, 10	32%, 55%, 69%	52%, 81%, 91% at 1, 5, and 10 years (fibrosis in the biopsies with chronical inflammation)
Venturi [38] (2012)	pediatric	38	7	94%	94%
Angelico [37] (2022)	pediatric	320	1, 2, 5	Not indicated	70%, 77.5%, 83.8%
Fouquet [72] (2005)	pediatric	67	>10	73%	22% (centrolobular fibrosis)
Perito [73] (2022)	pediatric	78	10 and 15	Not indicated	At 10 years: 55% of LAFSc 4 to 6; 3% of LAFSc > 6 At 15 years: 62% of LAFSc 4 to 6; 5% of LAFSc > 6

Adult population

In the adult population, prevalence of fibrosis has changed over the last years. Most of prospective studies about graft fibrosis have focused on post-HCV transplantation. Last studies present an overall prevalence of 36,2% (20–68,1%) of significant fibrosis (≥ F2 in Metavir scoring system) but still include an important proportion of HCV patients[3]. Table 2 shows the few studies examining the prevalence of histological fibrosis in adult cohorts[15–19].

Regarding the pathophysiology of the development of graft fibrosis in adult patients, it is mainly driven by the recurrence of the primary disease. Recurrent or *de novo* autoimmune or viral injuries remain the most common causes of chronic hepatitis in this population, leading to fibrosis if untreated. In addition, chronic viral hepatitis including hepatitis E virus (HEV) infection or Torque teno virus (TTV) should be considered. 50–80% of the LT patients infected with HEV present chronic infection and 10% will progress to cirrhosis[20]. The genotype 3 is the main driver for chronic hepatitis. TTV, a virus which is part of the normal virus virome may play a role in allograft fibrosis without chronic hepatitis, but this has still to be confirmed[21].

Allograft steatosis: prevalence and pathophysiology

Pediatric population

Very few studies have addressed the problem of the development of steatosis on the liver graft in pediatric LT recipients. The data are mostly retrospective, and diagnosis only based on liver biopsies. In a single cohort of pediatric patients in the US, it has been shown that up to 1/3 of the patients would present with steatosis in at least one liver biopsy in the follow-up[22]. It was an early and transient finding after LT. In cystic fibrosis recipients, steatosis of the liver graft has been linked to the presence of steatosis on the explant[23]. It has been shown that the

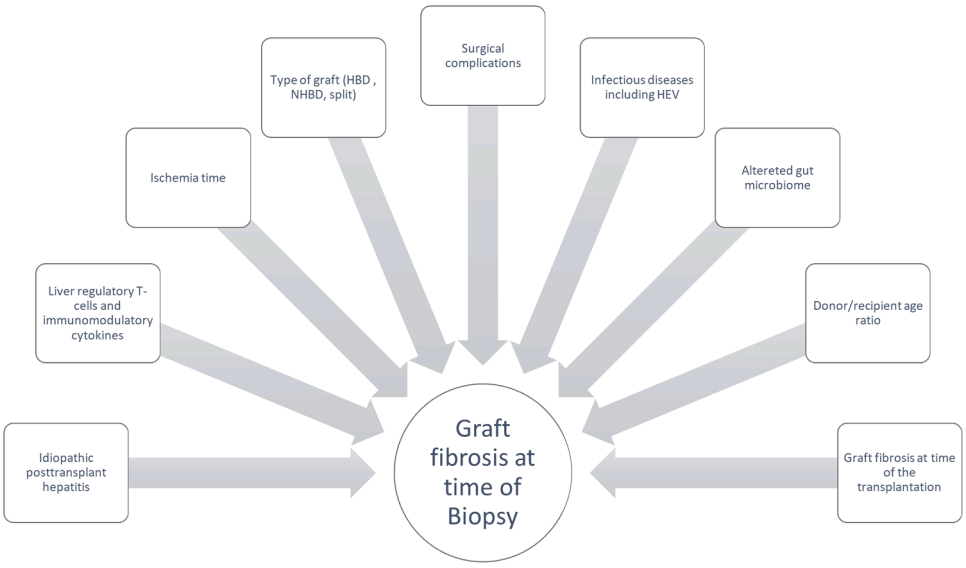

Fig. 1. Physiopathology of the graft fibrosis.

Table 2
Occurrence of liver graft fibrosis in a post-transplanted adult population.

Author, year	Population	Number of biopsies	Etiology	Time after LT	Fibrosis (≥ F2)
Barrault [15] (2013)	adult	43	HCV, alcohol, others	55.8 ± 4.9 months	F2: 15.5% - F3: 17.7% - F4: 4.4%
Beckebaum [74] (2010)	adult	157	HCV (30%) and others	80.9 ± 65.7 months	F2: 23.6% - F3: 19.7% - F4: 15.3%
Lutz[17] (2015)	adult	48	HCV (27%) and others	23±2 months	F2: 14.6% - F3: 10.4% - F4: 2.1%
Sebagh [18] (2012)	adult	91	HBV, HCV, alcohol, others	240 months	F2: 18.7% - F3: 6.6% - F4: 9.1%
Pissaia [19] (2009)	adult	94	All aetiologies	30.7 months	F2-F3-F4: 28%

presence of metabolic syndrome in children post-LT was associated with the presence of liver steatosis[24]. This was also linked to increased cardiovascular risk factors in this population. This highlights the importance of diagnosing steatosis and metabolic syndrome in this LT population to counteract the risk of developing cardiovascular diseases in the adulthood and develop liver fibrosis.

Adult population

The natural course of new-onset or recurrent MASLD after LT appears to be different, with earlier and more rapid onset for recurrent MASLD and more frequent progression to NASH. Vallim et al. published in 2014 a cohort of 91 post-LT MASLD patients, in which the new-onset MASLD subgroup presented a lower prevalence of diabetes mellitus (DM) (37.5% vs 100%, $p < 0.01$) and a lower rate of fibrosis (12.5% versus 71.4%, $p < 0.01$) and steatohepatitis (17.2% versus 71.4%, $p < 0.01$) compared to recurrent MASLD[25]. Literature presents a wide range of prevalence of post-LT steatosis from 30 to 100%, with variables periods of apparition between 6 months and 10 years[26,27]. This is explained by small retrospective studies, with variable diagnostic methods and variable durations of follow-up. Allograft steatosis seems frequent but not to have a major impact of post LT outcomes[28].

Several risk factors influence the occurrence of MASLD after LT. Risk factors include genetic, environmental, and immunosuppressive therapies. The first one is directly linked to the donor. These include genetic of the donor (allele c.499A in TM6SF2, allele c.444 G in PNPLA3 or allele rs738409 in PNPLA3)[29,30], and pre-LT graft steatosis rate[5]. Other risk factors are related to the recipient. After LT, patients are exposed to a rapid amelioration of the nutritional status. Recipient's risk factors include metabolic syndrome, post-LT body mass index (BMI), weight gain after LT, DM development, HCV infection and alcohol abuse [5,27,31]. Lastly, immunosuppressive therapies including steroids and calcineurin inhibitors have also an impact on the development of metabolic syndrome after LT by increasing insulin resistance, arterial hypertension, dyslipidemia[32].

Diagnosing liver graft fibrosis: liver biopsy is the "gold standard"

Histological modifications could be the first sign of a negative evolution in the post-transplant setting. LB is usually required to elucidate the true reasons for allograft dysfunction. LB gives precious data about quantification of steatosis, inflammation, cellular rejection and vascular or biliary alterations. Therefore, LB remains an important tool in the post LT management. However, LB has also its own drawbacks including serious complications (bleeding and pneumothorax), and weaknesses, the results depending on the quality and the size of the specimen, and its inter-observer irregularities[33].

It is not only the pathophysiology of fibrosis which remains poorly understood, but also the evolution over time, its actual implications and its outcome on patient and graft survival. Furthermore, the dynamic state of liver fibrosis and its ability to decrease is still a matter of debate. Difficulties in its understanding remain mainly due to the lack of standardization in its assessment and in its histological quantification. The main studies in pediatric and adult LT populations used semi-quantitative scoring systems, such as METAVIR or Ishak scores which have been validated in viral hepatitis on native liver [34,35], but which were not designed for LT cohort and are not able to fully quantify the allograft fibrosis and its evolution over time. The gold-standard staging method remains the computer-assisted morphometric analysis of the collagen[36], but it is difficult to apply in daily practice.

In the LT context, it is important to consider the fibrosis in the three area of the hepatic acini: the portal tract, the sinusoids and the centrilobular veins. The pattern and distribution of fibrosis are influenced

by its cause. Previous publications distinguished the development of the portal fibrosis related to a longer ischemic time, the donation after circulatory death, and the IPTH; the sinusoidal fibrosis with the biliary complications and chronic rejection; and the centrilobular fibrosis with the vascular complications, de novo auto-immune hepatitis and chronic rejection[7,10,37]. Adults' follow-up would certainly benefit from using a more precise and complete scoring system as the *liver allograft fibrosis semiquantitative scoring system* (LAFSc or *Venturi Score*) developed and validated by Venturi et *al.* to assess post LT fibrosis in a pediatric population, but studies validating this tool in adult patients are still lacking [38].

Detecting the fibrosis in LT patients: are noninvasive methods available?

No strong recommendation of non-invasive methods is currently published in the field of post LT[39,40]. Because of potentially severe complications, and high-cost procedure, alternatives to LB are attractive in the follow up of the LT recipient.

Patented serum markers such as FibroTest® or Hepatoscore®, and non-patented scores as FIB-4 have been validated in native liver in ruling-out the presence of fibrosis[41,42,43]. The main advantages of the serum markers are the easily access in daily practice, and their results obtained with online calculators. In post LT follow-up, few studies exist in the literature but with divergent results[19,44]. In 2017, Bhat et al., performed a meta-analysis to compare the accuracy of non-invasive methods in post-LT patients. They included 8 studies for APRI and 4 studies for FIB-4. The odds ratio (OR) for APRI in detecting significant fibrosis was 9.20 (95% CI 5.79–14.07, $p = 0.001$) and the OR for FIB-4 was 7.08 (95% CI 4.00–12.55, $p = 0.001$)[3]. Important limitations are still presents and curb the utilization of patented and no-patented serum markers in post-LT. Evidence are clearly lacking, with no strong data and no established cut-off. Another important problem is the influence of other post-LT parameters on biological scores. Splenomegaly and thrombocytopenia can persist after LT even if portal hypertension is resolved, and can influence negatively the evaluation of liver fibrosis[26]. Patented scores could also be distorted (chronical inflammation on alpha-2-macroglobuline, drugs induction on GGT and haemolytic anemia on haptoglobin[3]).

Transient elastography (TE) was developed for the measurement of liver stiffness (LSM) with excellent correlation with fibrosis grades in pre-LT. The strength of TE is its capability to evaluate a large region of the hepatic parenchyma, one hundred times larger than a simple LB[26]. It should be noted that certain situations such as transaminases flares, liver infiltration by tumor cells, liver steatosis or necroinflammation, recent food intake, hepatic congestion, high body mass index can be associated with high elasticity results that overestimate the degree of fibrosis[45]. TE shows also new perspectives in term of detecting complications and prognostic in pre-LT chronic liver diseases including prediction of portal hypertension, and risk of decompensation and death [46]. However, in transplant patients' cohorts, data are lacking in evaluating the efficacy of TE. Only a few studies about the role of TE in the screening and the diagnosis of the fibrosis recurrency have been published.

In pediatric patients, a good correlation between METAVIR score and the results of TE was observed, with liver stiffness cut-off value of 5,6 kPa for the detection of advanced fibrosis (METAVIR score >2), with a 75% sensitivity, a 95.8% specificity, a 90% positive predictive value, and an 88.5% negative predictive value[47]. Another retrospective study confirmed these data, with a higher cut-off of 6.5kPa[48]. This study confirmed a better correlation between TE and liver biopsy than with APRI of FIB4 biological scores. Importantly, the noninvasive evaluation was feasible regardless of the graft type.

In adult patients, the first studies were based on HCV post-LT populations. Bhat et al. wrote a meta-analysis based on 24 single studies (8 studies assessing APRI, 4 assessing FIB-4 and 12 assessing TE)[3]. If we focus on TE, a total of 1196 patients were included, with a mix of etiologies and with a prevalence of fibrosis ≥ F2 of 37.4%. This meta-analysis shows that TE correlates well with LB in the diagnostic of fibrosis ≥ F2 with an AUROC at 0.75 to 0.96. The other strength of this meta-analysis is the comparison with biomarkers tests, showing a significant difference between TE and FIB4 and between TE and APRI ($p < 0.05$). One of the major limitations of this analysis is the large range of cut-offs (from 4.3 kPa to 12.3 kPa) in the definition of significant fibrosis (≥ F2) post-LT. However, limitations known in pre-LT[49] are also present in post-LT. Biliary complications and secondary cholestasis are frequent in post-LT, with an estimated incidence of 5%−32%[50]. Outflow obstruction, including stenosis or thrombosis of the inferior vena cava or the hepatic vein, are less common, with an incidence of less than 3%[51]. Hepatic inflammation secondary to low grade rejection, or real acute or chronic rejection, without significant fibrosis is also a major and frequent issue after LT and increases LSM results. Other difficulties are specifically related to post-surgery including the type of graft (split, left lobe), the diaphragm elevation, the mismatch between the graft and the abdominal cavity.

Other imaging techniques such as acoustic radiation force impulse (ARFI) or shear wave elastography (SWE) are now available. These techniques, which are more recent than TE, do not have accepted and validated cut-offs in the various etiologies of chronic liver disease, nor do they have quality criteria[52]. A few studies are available in post-LT, with small numbers of patient[53–56]. Vo et al. recently proposed to combinate SWE with serum markers to improve fibrose detection in LT [57]. Magnetic resonance elastography (MRE) is the most accurate non-invasive method to stage fibrosis in MAFLD population[33,58]. The main advantage of the MRE is the absence of BMI interference on the result. MRE was analysed in post LT in a meta-analyze including 6 studies and 141 patients[59]. The AUROC for detecting fibrosis ≥ F1 was 0.73, ≥ F2 was 0,69 and ≥ F3 was 0.83 54. They have therefore obtained excellent results for advanced fibrosis, but with less accuracy

Table 3
Non-invasive methods for detecting fibrosis after LT.

Trials Author, year	Number of patients (n)	Method of detection	Cut-off	Accuracy	
Pissaia [19] (2009)	50	FIB-4	3.25	PPV: 67%	NPV: 77%
		APRI	0.5	PPV: 62%	NPV: 91%
Kamphues [44] (2010)	135	FIB-4	2.8	PPV: 88%	NPV: 42%
		APRI	0.4845	PPV: 80%	NPV: 80%
Imai [75] (2018)	203	FIB-4	3.64	Se: 57.7%	Sp: 69.6%
		APRI	1.03	Se: 63.4%	Sp: 66.7%
Beckebaum [74] (2010)	157	TE (LSM)	7.9 kPa (≥ F2)	Se: 73%	Sp: 100%
Lee [48] (2020)	83	TE (LSM)	6.3 kPa (≥ F2)	Se: 60%	Sp: 78%
Sebagh [18] (2012)	26	TE (LSM)	7.9 kPa (≥ F2)	Se: 62.5%	Sp: 66.7%
Meta-analyses					
Bhat [3] (2017)	435	FIB-4	3.23–4.09	AUC: 0.76 OR: 7.08 (95% CI 4.00–12.55)	
	1196	TE (LSM)	4.7–12.3 kPa (≥ F2)	AUC: 0.93 OR: 21.17 (95% CI 14.10–31.77)	
Vo [76] (2020)	184	APRI	0.4–0.99	AUC: 0.53–0.74 (95% CI)	
	206	TE (LSM)	5.6–11.2 kPa (≥ F2)	AUC: 0.71–0.98 (95% CI)	

than in the native liver. Table 3 summarizes non-invasive methods for detecting fibrosis after LT.

Detecting the steatosis in post transplantation, are there non-invasive methods?

Early detection of steatosis in the liver graft is still a matter of debate because of the lack of knowledge about its follow-up and of its outcomes on the graft survival and patient survival[32]. Liver biopsy remains the gold standard for the detection of macro- and micro-vesicular steatosis. Fatty liver index[60], abdominal ultrasound, transient elastography with controlled attenuation parameter (CAP) and magnetic resonance imaging-proton density fat extraction (MRI-PDFF) are different available diagnostic tools.

The sensitivity of abdominal ultrasound is weak when steatosis represents less than 20% of the liver[61]. As stated in the 2023 update AASLD guidelines, CAP may be used to identify steatosis[62]. In a recent large English study, including 450 patients suspected with MAFLD, TE using M and XL probes, showed a good accuracy in detecting the steatosis $\geq$ 5% (AUROCs from 0.76 to 0.87)[63]. However, its ability to grading steatosis $\geq$ 33% and $\geq$ 66% is weak. This weakness was confirmed in a large meta-analysis published in 2021[64]. Evidence is weak and even absent in post LT. Few observational studies used TE with CAP to evaluate the prevalence of steatosis and its risk factors in a post-LT population. The first one was published in 2015, before the commercialization of the XL-probe and showed a prevalence of steatosis (CAP $\geq$ 252 dB/m) in 44% patients and a prevalence of severe steatosis (CAP $\geq$ 300 dB/m) in 24% patients[65]. Another more recent study and with use of the XL probe, showed a prevalence of steatosis (CAP $\geq$ 222 dB/m) in 70% and a prevalence of severe steatosis (CAP $\geq$ 290 dB/m) in 40% patients[66]. In another study comparing CAP and LB (performed at the discretion of the hepatologist), the inclusion of cytokeratin 18 (CK18) to the CAP resulted in enhanced diagnostic accuracy for NASH post-LT, increasing it from 76% to 82%[67]. We found only one study systematically comparing CAP to LB prospectively[68]. The table 4 presents the different cut-offs proposed in the literature.

MRI-PDF is the most accurate method for detecting and grading the steatosis of the liver[33]. MRI-PDFF also showed excellent result in detecting changes of the steatosis of the liver, and could be more sensitive than the liver biopsy[69]. We found no publication about the use of MRI-PDFF in the allograft after LT.

Are there other indications for non-invasive methods in the context of LT?

In a interesting way, LSM was evaluated for the first time in detecting the acute cellular rejection (ACR) by Crespo et al. [70]. With, their small cohort of 27 liver recipient with biopsy proven ACR, they were able to separate mild from moderate/severe (BANFF score $\geq$ 5) ACR with LSM cut-off at 8.5 kPa (AUROC of 0.92). They also showed a good correlation between decreasing in LSM and good evolution of ACR. This study is of course self-limited because of the very small population, and TE will probably play anecdotal position in estimating the grade of ACR because of the need of LB to make the difference with other causes of elevated liver enzymes after LT.

Non-invasives tests could also be incorporated in the management of long-term immunosuppression after LT by stratifying immunological risk of liver damage. Vionnet et al.[71] identified LSM, class II donor-specific antibodies and alanine aminotransferase as non-invasive predictors of alloimmune damage. TE could identify patients who could benefit from tapering of immunosuppression.

Perspectives

Life expectancy of LT patients is rising with new important issues in terms of managing post-transplant and immunosuppressive complications and avoiding graft loss. Fibrosis is one of the main causes of graft injury and emerges much earlier than altered liver blood tests. Previous studies with LT cohort showed high prevalence of fibrosis, highly correlated with presence of IPTH. Like in pediatric population with LAFSc, a precise and validated histologic scoring system is needed for adult population to allow risk assessment, follow-up, and management.

Non-invasive methods, and above all TE, are clearly validated to diagnose fibrosis in native liver. Evidence for steatosis is weaker. Limitations and complications of LB creates a need for alternative tools in the post-transplant setting. TE with LSM was investigated in few studies, showed a high accuracy in a large meta-analysis[3]. The role of LB in the follow-up of the graft is changing with the emerging of non-invasive tests. Histology keeps its role for the differential diagnostic, but TE could find a place in screening, following and eviction of serial biopsies. However, a better understanding of the phenomenon of IPTH and related development of fibrosis on the liver graft is necessary to interpret the results optimally and adjust the treatment appropriately.

The increasing prevalence of metabolic syndrome and its associated risks of developing steatotic liver disease and cardiovascular diseases underscore the need for non-invasive approaches to assess the occurrence of MASLD and NASH in the liver graft. To achieve this, we require a prospective validation of TE with CAP in patients undergoing protocolar liver biopsies. This validation will help confirm the effectiveness of TE with CAP as a valuable tool in monitoring liver transplant patients and grafts. Conducting larger studies could further define ideal cut-off values, aiding clinicians in drawing conclusions and recommending lifestyle and treatment changes. Moreover, research on non-invasive investigations for recurrent and de novo MASLD in post-LT patients is essential.

The utilization and validation of non-invasive approaches could enable clinicians to regularly monitor the patient and perform LB only in specific instances, such as to confirm the clinical suspicions or identify the root cause of fibrosis. This approach could also provide an opportunity to monitor the effect of clinical, medical, or behavioural interventions.

Table 4
CAP cut-offs for detecting steatosis after LT.

Author, year	Number of patients (n)	Method of detection	Cut-off for steatosis	Cut-off for severe steatosis
Karlas[65] (2015)	204	CAP	252 dB/m	230 dB/m
Siddiqui[68] (2022)	99	CAP	270 dB/m	295 dB/m
Chayanupatkul [66] (2020)	150	CAP	222 dB/m	290 dB/m

1. CAP: controlled attenuation parameter; 2. dB/m: decibels per meter.

Conclusion

The role of non-invasive tests in the monitoring of liver transplant recipients is yet to be established. Nonetheless, non-invasive techniques along with specific biomarkers, show promise in assisting clinicians in making decisions regarding lifestyle changes and immunosuppression.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Mokdad AA, Lopez AD, Shahraz S, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. BMC Med 2014;12:145. https://doi.org/10.1186/s12916-014-0145-y.
[2] Fox AN, Brown RS. Is the patient a candidate for liver transplantation? Clin Liver Dis 2012;16(2):435–48. https://doi.org/10.1016/j.cld.2012.03.014.
[3] Bhat M, Tazari M, Sebastiani G. Performance of transient elastography and serum fibrosis biomarkers for non-invasive evaluation of recurrent fibrosis after liver transplantation: a meta-analysis. PLoS ONE 2017;12(9):e0185192. https://doi.org/10.1371/journal.pone.0185192.
[4] Hartleif S, Hodson J, Lloyd C, et al. Long-term Outcome of Asymptomatic Patients With Graft Fibrosis in Protocol Biopsies After Pediatric Liver Transplantation. Transplantation May 5, 2023. https://doi.org/10.1097/TP.0000000000004603. Published online.
[5] Dumortier J, Giostra E, Belbouab S, et al. Non-alcoholic fatty liver disease in liver transplant recipients: another story of "seed and soil. Am J Gastroenterol 2010;105(3):613–20. https://doi.org/10.1038/ajg.2009.717.
[6] Evans HM, Kelly DA, McKiernan PJ, Hübscher S. Progressive histological damage in liver allografts following pediatric liver transplantation. Hepatology 2006;43(5):1109–17. https://doi.org/10.1002/hep.21152.
[7] Venturi C, Sempoux C, Quinones JA, et al. Dynamics of allograft fibrosis in pediatric liver transplantation. Am J Transplant 2014;14(7):1648–56. https://doi.org/10.1111/ajt.12740.
[8] Hübscher SG. What is the long-term outcome of the liver allograft? J Hepatol 2011;55(3):702–17. https://doi.org/10.1016/j.jhep.2011.03.005.
[9] Hübscher S. What does the long-term liver allograft look like for the pediatric recipient? - PubMed. Liver Transplantation 2009;15(2):19–24.
[10] Kelly D, Verkade HJ, Rajanayagam J, McKiernan P, Mazariegos G, Hübscher S. Late graft hepatitis and fibrosis in pediatric liver allograft recipients: current concepts and future developments. Liver Transpl 2016;22(11):1593–602. https://doi.org/10.1002/lt.24616.
[11] Magee JC. Graft fibrosis in stable pediatric liver transplant recipients: what does it mean? Hepatology 2009;49(3):726–8. https://doi.org/10.1002/hep.22864.
[12] Koshiba T, Li Y, Takemura M, et al. Clinical, immunological, and pathological aspects of operational tolerance after pediatric living-donor liver transplantation. Transpl Immunol 2007;17(2):94–7. https://doi.org/10.1016/j.trim.2006.10.004.
[13] Peeters PM, Sieders E, vd Heuvel M, et al. Predictive factors for portal fibrosis in pediatric liver transplant recipients. Transplantation 2000;70(11):1581–7. https://doi.org/10.1097/00007890-200012150-00008.
[14] Qin T, Fu J, Verkade HJ. The role of the gut microbiome in graft fibrosis after pediatric liver transplantation. Hum Genet 2021;140(5):709–24. https://doi.org/10.1007/s00439-020-02221-8.
[15] Barrault C, Roudot-Thoraval F, Tran Van Nhieu J, et al. Non-invasive assessment of liver graft fibrosis by transient elastography after liver transplantation. Clin Res Hepatol Gastroenterol 2013;37(4):347–52. https://doi.org/10.1016/j.clinre.2012.11.003.
[16] Beckebaum S, Iacob S, Klein CG, et al. Assessment of allograft fibrosis by transient elastography and noninvasive biomarker scoring systems in liver transplant patients. Transplantation 2010;89(8):983–93. https://doi.org/10.1097/TP.0b013e3181cc66ca.
[17] Lutz HH, Schroeter B, Kroy DC, Neumann U, Trautwein C, Tischendorf JJW. Doppler Ultrasound and Transient Elastography in Liver Transplant Patients for Noninvasive Evaluation of Liver Fibrosis in Comparison with Histology: a Prospective Observational Study. Dig Dis Sci 2015;60(9):2825–31. https://doi.org/10.1007/s10620-015-3682-0.
[18] Sebagh M, Samuel D, Antonini TM, et al. Twenty-year protocol liver biopsies: invasive but useful for the management of liver recipients. J Hepatol 2012;56(4):840–7. https://doi.org/10.1016/j.jhep.2011.11.016.
[19] Pissaia A, Borderie D, Bernard D, Scatton O, Calmus Y, Conti F. APRI and FIB-4 Scores Are Useful After Liver Transplantation Independently of Etiology. Transplant Proc 2009;41(2):679–81. https://doi.org/10.1016/j.transproceed.2008.12.014.
[20] Kamar N, Garrouste C, Haagsma EB, et al. Factors associated with chronic hepatitis in patients with hepatitis E virus infection who have received solid organ transplants. Gastroenterology 2011;140(5):1481–9. https://doi.org/10.1053/j.gastro.2011.02.050.
[21] Burra P, Masier A, Boldrin C, et al. Torque Teno Virus: any pathological role in liver transplanted patients? Transpl Int 2008;21(10):972–9. https://doi.org/10.1111/j.1432-2277.2008.00714.x.
[22] Perito ER, Vase T, Ramachandran R, et al. Hepatic steatosis after pediatric liver transplant. Liver Transpl 2017;23(7):957–67. https://doi.org/10.1002/lt.24773.
[23] Cortes-Santiago N, Leung DH, Castro E, Finegold M, Wu H, Patel KR. Hepatic Steatosis Is Prevalent Following Orthotopic Liver Transplantation in Children With Cystic Fibrosis. J Pediatr Gastroenterol Nutr 2019;68(1):96–103. https://doi.org/10.1097/MPG.0000000000002154.
[24] Kosola S, Lampela H, Makisalo H, et al. Metabolic syndrome after pediatric liver transplantation. Liver Transpl 2014;20(10):1185–92. https://doi.org/10.1002/lt.23931.
[25] Vallin M, Guillaud O, Boillot O, Hervieu V, Scoazec JY, Dumortier J. Recurrent or de novo nonalcoholic fatty liver disease after liver transplantation: natural history based on liver biopsy analysis. Liver Transpl 2014;20(9):1064–71. https://doi.org/10.1002/lt.23936.
[26] Mikolasevic I, Stojsavljevic S, Blazic F, et al. Noninvasive markers of liver steatosis and fibrosis after liver transplantation - Where do we stand? World J Transplant 2021;11(3):37–53. https://doi.org/10.5500/wjt.v11.i3.37.
[27] Saeed N, Glass L, Sharma P, Shannon C, Sonnenday CJ, Tincopa MA. Incidence and Risks for Nonalcoholic Fatty Liver Disease and Steatohepatitis Post-liver Transplant: systematic Review and Meta-analysis. Transplantation 2019;103(11):e345–54. https://doi.org/10.1097/TP.0000000000002916.
[28] Narayanan P, Mara K, Izzy M, et al. Recurrent or De Novo Allograft Steatosis and Long-term Outcomes After Liver Transplantation. Transplantation 2019;103(1):e14–21. https://doi.org/10.1097/TP.0000000000002317.
[29] Míková I, Neřoldová M, Hubáček JA, et al. Donor PNPLA3 and TM6SF2 Variant Alleles Confer Additive Risks for Graft Steatosis After Liver Transplantation. Transplantation 2020;104(3):526–34. https://doi.org/10.1097/TP.0000000000002876.
[30] Trunečka P, Míková I, Dlouhá D, et al. Donor PNPLA3 rs738409 genotype is a risk factor for graft steatosis. A post-transplant biopsy-based study. Dig Liver Dis 2018;50(5):490–5. https://doi.org/10.1016/j.dld.2017.12.030.
[31] Galvin Z, Rajakumar R, Chen E, et al. Predictors of De Novo Nonalcoholic Fatty Liver Disease After Liver Transplantation and Associated Fibrosis. Liver Transpl 2019;25(1):56–67. https://doi.org/10.1002/lt.25338.
[32] Burra P, Becchetti C, Germani G. NAFLD and liver transplantation: disease burden, current management and future challenges. JHEP Rep 2020;2(6):100192. https://doi.org/10.1016/j.jhepr.2020.100192.
[33] European Association for the Study of the Liver. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol 2021;75(3):659–89. https://doi.org/10.1016/j.jhep.2021.05.025.
[34] Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996;24(2):289–93. https://doi.org/10.1002/hep.510240201.
[35] Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995;22(6):696–9. https://doi.org/10.1016/0168-8278(95)80226-6.
[36] Restellini S, Goossens N, Clément S, et al. Collagen proportionate area correlates to hepatic venous pressure gradient in non-abstinent cirrhotic patients with alcoholic liver disease. World J Hepatol 2018;10(1):73–81. https://doi.org/10.4254/wjh.v10.i1.73.
[37] Angelico R, Spada M, Liccardo D, et al. Allograft Fibrosis After Pediatric Liver Transplantation: incidence, Risk Factors, and Evolution. Liver Transpl 2022;28(2):280–93. https://doi.org/10.1002/lt.26218.
[38] Venturi C, Sempoux C, Bueno J, et al. Novel histologic scoring system for long-term allograft fibrosis after liver transplantation in children. Am J Transplant 2012;12(11):2986–96. https://doi.org/10.1111/j.1600-6143.2012.04210.x.
[39] Lucey MR, Terrault N, Ojo L, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl 2013;19(1):3–26. https://doi.org/10.1002/lt.23566.
[40] Dumortier J, Besch C, Moga L, et al. Non-invasive diagnosis and follow-up in liver transplantation. Clin Res Hepatol Gastroenterol 2022;46(1):101774. https://doi.org/10.1016/j.clinre.2021.101774.
[41] Thiele M, Madsen BS, Hansen JF, Detlefsen S, Antonsen S, Krag A. Accuracy of the Enhanced Liver Fibrosis Test vs FibroTest, Elastography, and Indirect Markers in Detection of Advanced Fibrosis in Patients With Alcoholic Liver Disease. Gastroenterology 2018;154(5):1369–79. https://doi.org/10.1053/j.gastro.2018.01.005.
[42] Xiao G, Zhu S, Xiao X, Yan L, Yang J, Wu G. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: a meta-analysis. Hepatology 2017;66(5):1486–501. https://doi.org/10.1002/hep.29302.
[43] Binet Q, Loumaye A, Preumont V, Thissen JP, Hermans MP, Lanthier N. Non-invasive screening, staging and management of metabolic dysfunction-associated fatty liver disease (MAFLD) in type 2 diabetes mellitus patients: what do we know so far ? Acta Gastroenterol Belg 2022;85(2):346–57. https://doi.org/10.51821/85.2.9775.
[44] Kamphues C, Lotz K, Röcken C, et al. Chances and limitations of non-invasive tests in the assessment of liver fibrosis in liver transplant patients. Clin Transplant 2010;24(5):652–9. https://doi.org/10.1111/j.1399-0012.2009.01152.x.
[45] Delire B, Komuta M, Michaux L, Lanthier N. A rare cause of high liver stiffness. Acta Gastroenterol Belg 2020;83(4):675–6.
[46] Franchis R de, Bosch J, Garcia-Tsao G, et al. Baveno VII – Renewing consensus in portal hypertension. J. Hepatol. 2022;76(4):959–74. https://doi.org/10.1016/j.jhep.2021.12.022.
[47] Vinciguerra T, Brunati A, David E, et al. Transient elastography for non-invasive evaluation of post-transplant liver graft fibrosis in children. Pediatr Transplant 2018;22(2). https://doi.org/10.1111/petr.13125.
[48] Lee CK, Nastasio S, Mitchell PD, et al. Transient elastography assessment of liver allograft fibrosis in pediatric transplant recipients. Pediatr Transplant 2020;24(6):e13736. https://doi.org/10.1111/petr.13736.
[49] Winters AC, Mittal R, Schiano TD. A review of the use of transient elastography in the assessment of fibrosis and steatosis in the post–liver transplant patient. Clin Transplant 2019;33(10). https://doi.org/10.1111/ctr.13700.

[50] Fasullo M, Patel M, Khanna L, Shah T. Post-transplant biliary complications: advances in pathophysiology, diagnosis, and treatment. BMJ Open Gastroenterol 2022;9(1):e000778. https://doi.org/10.1136/bmjgast-2021-000778.
[51] Piardi T, Lhuaire M, Bruno O, et al. Vascular complications following liver transplantation: a literature review of advances in 2015. World J Hepatol 2016;8(1):36–57. https://doi.org/10.4254/wjh.v8.i1.36.
[52] Lanthier N, Stärkel P, Horsmans Y. New imaging assisted methods for liver fibrosis quantification: is it really favorable to classical transient elastography? J. Hepatol. 2015;63(3):765–6. https://doi.org/10.1016/j.jhep.2015.04.027.
[53] Deurdulian C, Grant EG, Tchelepi H, et al. Assessment of Fibrosis in Liver Transplant Recipients: diagnostic Performance of Shear Wave Elastography (SWE) and Correlation of SWE Findings With Biopsy Results. AJR Am J Roentgenol 2019;213(6):W264–71. https://doi.org/10.2214/AJR.19.21160.
[54] Dubois M, Ronot M, Houssel-Debry P, et al. Performance of B-mode ratio and 2D shear wave elastography for the detection and quantification of hepatic steatosis and fibrosis after liver transplantation. Eur J Gastroenterol Hepatol 2020;32(2):222–30. https://doi.org/10.1097/MEG.0000000000001500.
[55] Yoshino K, Taura K, Okuda Y, et al. Efficiency of acoustic radiation force impulse imaging for the staging of graft fibrosis after liver transplantation. Hepatol Res 2019;49(4):394–403. https://doi.org/10.1111/hepr.13289.
[56] Tomita H, Hoshino K, Fuchimoto Y, et al. Acoustic radiation force impulse imaging for assessing graft fibrosis after pediatric living donor liver transplantation: a pilot study. Liver Transpl 2013;19(11):1202–13. https://doi.org/10.1002/lt.23708.
[57] Vo HD, Radio SJ, Granader EJ, Wojkiewicz LE, Turner P, Mauch TJ. Diagnostic performance of 2D-shear wave elastography and serum fibrosis markers for evaluation of hepatic graft fibrosis in pediatric liver-inclusive transplant recipients: a prospective pilot study. Pediatr Transplant 2022;26(4):e14225. https://doi.org/10.1111/petr.14225.
[58] Nielsen J, Kjær MS, Rasmussen A, et al. Noninvasive Prediction of Advanced Fibrosis in Pediatric Liver Disease-Discriminatory Performance of 2D Shear Wave Elastography, Transient Elastography and Magnetic Resonance Elastography in Comparison to Histopathology. Diagnostics (Basel) 2022;12(11):2785. https://doi.org/10.3390/diagnostics12112785.
[59] Singh S, Venkatesh SK, Keaveny A, et al. Diagnostic Accuracy of Magnetic Resonance Elastography in Liver Transplant Recipients: a Pooled Analysis. Ann Hepatol 2016;15(3):363–76. https://doi.org/10.5604/16652681.1198808.
[60] Bedogni G, Bellentani S, Miglioli L, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 2006;6(1):33. https://doi.org/10.1186/1471-230X-6-33.
[61] Dasarathy S, Dasarathy J, Khiyami A, Joseph R, Lopez R, McCullough AJ. Validity of real time ultrasound in the diagnosis of hepatic steatosis: a prospective study. J Hepatol 2009;51(6):1061–7. https://doi.org/10.1016/j.jhep.2009.09.001.
[62] Rinella M.E., Neuschwander-Tetri B.A., Siddiqui M.S., et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology*.:10.1097/HEP.0000000000000323. doi:10.1097/HEP.0000000000000323.
[63] Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2019;156(6):1717–30. https://doi.org/10.1053/j.gastro.2019.01.042.
[64] Petroff D, Blank V, Newsome PN, et al. Assessment of hepatic steatosis by controlled attenuation parameter using the M and XL probes: an individual patient data meta-analysis. Lancet Gastroenterol Hepatol 2021;6(3):185–98. https://doi.org/10.1016/S2468-1253(20)30357-5.
[65] Karlas T, Kollmeier J, Böhm S, et al. Noninvasive characterization of graft steatosis after liver transplantation. Scand J Gastroenterol 2015;50(2):224–32. https://doi.org/10.3109/00365521.2014.983156.
[66] Chayanupatkul M, Dasani DB, Sogaard K, Schiano TD. The Utility of Assessing Liver Allograft Fibrosis and Steatosis Post-Liver Transplantation Using Transient Elastography With Controlled Attenuation Parameter. Transplant Proc 2021;53(1):159–65. https://doi.org/10.1016/j.transproceed.2020.02.160.
[67] Alhinai A, Qayyum-Khan A, Zhang X, et al. Non-alcoholic steatohepatitis in liver transplant recipients diagnosed by serum cytokeratin 18 and transient elastography: a prospective study. World J Hepatol 2021;13(12):2179–91. https://doi.org/10.4254/wjh.v13.i12.2179.
[68] Siddiqui MS, Idowu MO, Stromberg K, et al. Diagnostic Performance of Vibration Controlled Transient Elastography in Liver Transplant Recipients. Clin Gastroenterol Hepatol 2021;19(2):367–74. https://doi.org/10.1016/j.cgh.2020.03.067.
[69] Stine JG, Munaganuru N, Barnard A, et al. Change in MRI-PDFF and Histologic Response in Patients With Nonalcoholic Steatohepatitis: a Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol 2021;19(11):2274–83. https://doi.org/10.1016/j.cgh.2020.08.061. e5.
[70] Crespo G, Castro-Narro G, García-Juárez I, et al. Usefulness of liver stiffness measurement during acute cellular rejection in liver transplantation. Liver Transpl 2016;22(3):298–304. https://doi.org/10.1002/lt.24376.
[71] Vionnet J, Miquel R, Abraldes JG, et al. Non-invasive alloimmune risk stratification of long-term liver transplant recipients. J Hepatol 2021;75(6):1409–19. https://doi.org/10.1016/j.jhep.2021.08.007.
[72] Fouquet V, Alves A, Branchereau S, et al. Long-term outcome of pediatric liver transplantation for biliary atresia: a 10-year follow-up in a single center. Liver Transpl 2005;11(2):152–60. https://doi.org/10.1002/lt.20358.
[73] Perito ER, Persyn E, Bucuvalas J, et al. Graft Fibrosis Over 10 to 15 Years in Pediatric Liver Transplant Recipients: multicenter Study of Paired, Longitudinal Surveillance Biopsies. Liver Transplantation 2022;28(6):1051–62. https://doi.org/10.1002/lt.26409.
[74] Beckebaum S, Iacob S, Klein CG, et al. Assessment of allograft fibrosis by transient elastography and noninvasive biomarker scoring systems in liver transplant patients. Transplantation 2010;89(8):983–93. https://doi.org/10.1097/TP.0b013e3181cc66ca.
[75] Imai H, Kamei H, Onishi Y, et al. Diagnostic Usefulness of APRI and FIB-4 for the Prediction of Liver Fibrosis After Liver Transplantation in Patients Infected with Hepatitis C Virus. Transplant Proc 2018;50(5):1431–6. https://doi.org/10.1016/j.transproceed.2018.03.005.
[76] Vo HD, Harp KA, Mauch TJ. Diagnostic performance of non-invasive tests for evaluation of hepatic graft fibrosis in pediatric liver transplantation: a scoping review. Transplant Rev (Orlando) 2020;34(4):100568. https://doi.org/10.1016/j.trre.2020.100568.