


Nonalcoholic steatohepatitis in posttransplantation liver: Review article

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SUMMARY

Introduction: Nonalcoholic steatohepatitis (NASH) associated or not with cirrhosis is the third leading indication for liver transplantation (LT) around the world. After transplants, NASH has a high prevalence and occurs as both recurrent and de novo manifestations. De novo NASH can also occur in allografts of patients transplanted for non-NASH liver disease.

Objective: To evaluate recurrent or de novo NASH in post-LT patients.

Method: A literature review was performed using search engines of indexed scientific material, including Medline (by PubMed), Scielo and Lilacs, to identify articles published in Portuguese and English until August 2016. Eligible studies included: place and year of publication, prevalence, clinical characteristics, risk factors and survival.

Results: A total of 110 articles were identified and 63 were selected. Most of the studies evaluated recurrence and survival after LT. Survival reached 90-100% in 1 year and 52-100% in 5 years. Recurrence of NAFLD (steatosis) was described in 15-100% and NASH, in 4-71%. NAFLD and de novo NASH were observed in 18-67% and 3-17%, respectively. Metabolic syndrome, diabetes mellitus, dyslipidemia and hypertension were seen in 45-58%, 18-59%, 25-66% and 52-82%, respectively.

Conclusion: After liver transplants, patients present a high prevalence of recurrent and de novo NASH. They also show a high frequency of metabolic disorders. Nevertheless, these alterations seem not to influence patient survival.

Keywords: Nonalcoholic Fatty Liver Disease. Liver Transplantation. Fatty Liver. Metabolic Syndrome. Diabetes Mellitus.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) affects about a third of the Western population, being the largest cause of elevation of aminotransferases in the world.¹ It is a broad spectrum pathological condition that includes steatosis, steatohepatitis (NASH), fibrosis and eventually cirrhosis (Figure 1) and hepatocellular carcinoma (HCC).^{2,3}

Steatosis may have a slow and asymptomatic course, but in 20% to 30% of cases it progresses to steatohepatitis, the stage of disease with the greatest potential for progression to cirrhosis and HCC (Figure 1).

Factors associated with the development of NASH include obesity, diabetes mellitus (DM), dyslipidemia and insulin resistance, which makes this disorder increas-

ingly recognized as the hepatic component of metabolic syndrome (MetS).⁴ Compared to the general population, NASH patients have increased cardiovascular risk and mortality.⁵ The significant increase in morbidity and mortality due to the obesity epidemic caused NAFLD, especially NASH combined with cirrhosis, to become the 3rd largest cause of liver transplantation, with the estimate that it will be the leading cause in 20 years.^{6,7}

After transplantation, some studies have observed up to 100% recurrence of NAFLD after 5 years.⁸⁻¹⁰ The appearance of NAFLD in transplanted patients due to causes other than NASH, i.e. de novo NAFLD, was first described by Poordad et al.¹¹ in patients undergoing transplantation on account of hepatitis C. Due to better results after he-

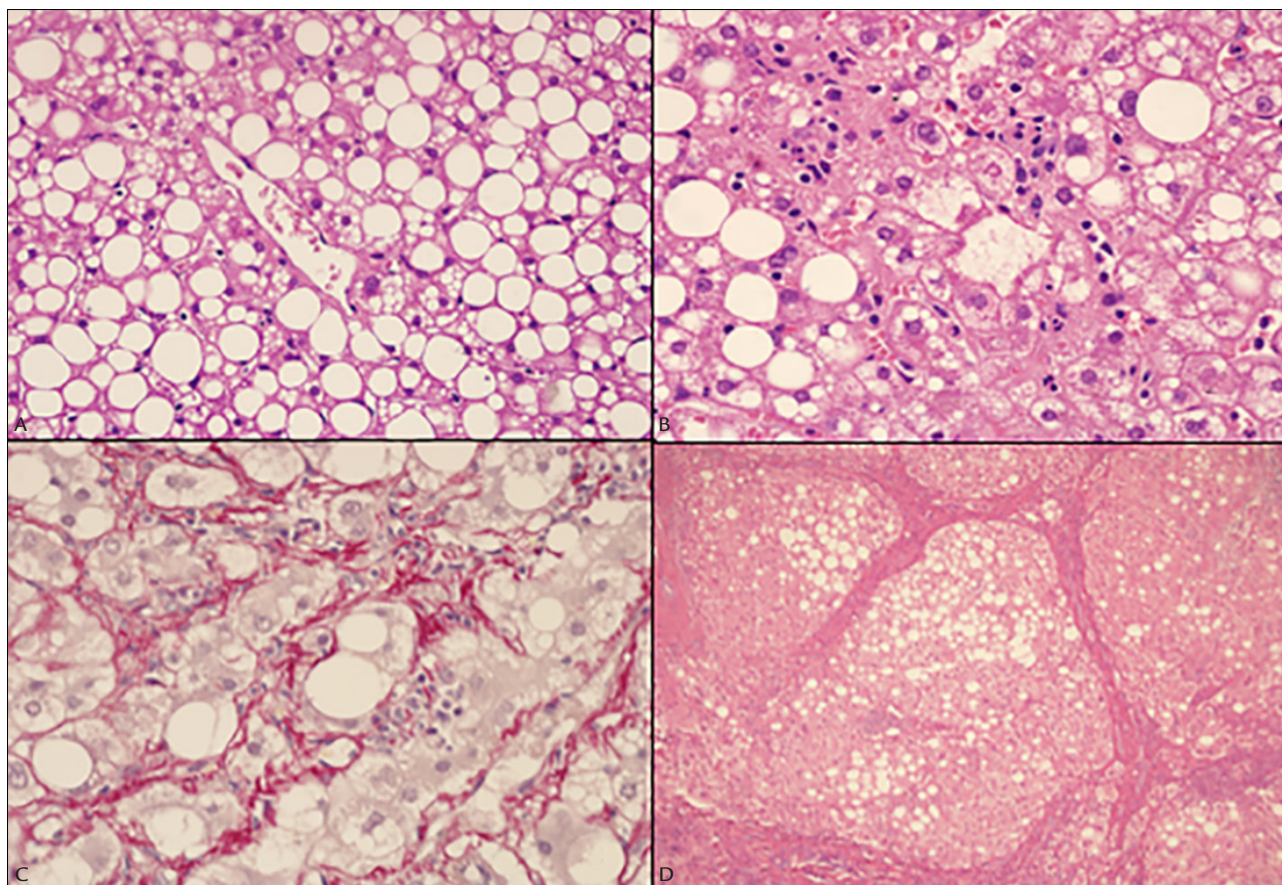


FIGURE 1 A. Steatosis: micro and macrovacuolar. B. Nonalcoholic steatohepatitis (NASH): steatosis, lobular inflammation and hepatocellular ballooning. C. Perisinusoidal fibrosis. D. Cirrhosis.

Courtesy of Professor Luiz Antônio Rodrigues Freitas.

patic transplantation, increased survival in the first year posttransplantation, and better control of chronic rejection,¹² an increased incidence of later changes such as de novo NAFLD and cardiovascular complications was noted.¹³

This review of the literature aimed to evaluate the relevance of recurrence or de novo NASH in liver transplant patients.

METHOD

Scientific articles indexed through PubMed, including Medline, SciELO and Lilacs, published in English and Portuguese, were used as search methods.

Prevalence, incidence, clinical characteristics, risk factors and survival in liver transplant patients were evaluated. The terms used in English were “NAFLD” or “NASH” or “steatosis” or “fatty liver” and “recurrency” and/or “liver transplantation.” In Portuguese, we used as search terms “DHGNA” or “esteato-hepatite” or “esteatose” and/or “de novo”, and/or “recorrência” and/or “transplante hepático.” According to the study design, cross-sectional,

longitudinal or descriptive investigations were included, with patients over 18 years of age, showing site and year of publication, prevalence and/or clinical characteristics of the patients, being published until August 2016.

RESULTS

The initial search yielded 1,285 studies. We removed 423 duplicate articles and 752 after reading titles and abstracts, since they did not address the issue with relevance. Following the proposed theme, 110 articles were identified and 63 were selected. We excluded 47 articles because they were review studies or case reports. The selected studies were conducted in Europe, Asia and North America, and five were Brazilian.¹⁴⁻¹⁷ Samples ranged from 7 to 10,204 patients and, due to the heterogeneity of the subject, the studies were grouped according to the following topics.

Survival

Sixteen (16) articles discussed the survival of patients transplanted by NASH (Table 1) and some of these articles

included in their statistics patients who were transplanted due to cryptogenic cirrhosis. No difference was observed in the mean survival of patients undergoing transplantation because of NASH compared to the survival of patients transplanted due to other etiologies. Only one study by Afzali et al.¹⁸ showed survival at 5 years in NASH transplanted patients as higher than patients with alcoholic disease, hepatitis C (HCV) and hepatocellular carcinoma (HCC). Some studies failed to show differences in survival between patients transplanted due to NASH or other causes.^{21,22,26,31} Malik et al.³¹ found no difference in survival between patients who underwent transplantation due to NASH who relapsed compared to those who did not relapse.

Mortality and cardiovascular events are more common in patients transplanted due to NASH in the first few years after transplantation. We found 11 studies regarding cardiovascular mortality with a number of patients ranging from 21 to 5,653, totaling 7,662 patients evaluated with a follow-up period of 3 to 10 months. Cardiovascular mortality ranged from 7% to 26%.^{18,22-24,26,27,31,33-36} Compared to transplanted patients due to other etiologies, the incidence is 15% higher in the first year³⁷ but does not increase the overall mortality after one year or in the long term compared to the other etiologies.^{36,38}

TABLE 1 Survival of NASH patients undergoing liver transplantation.

Reference	Patients N	Survival 1 year (%)	Survival 3 years (%)	Survival 5 years (%)
Charlton et al. ⁶	1,840	84	78	-
Afzali et al. ¹⁸	1,810+3,843 ^{cc}	87	81	75
El Atrache et al. ^{#19}	83	-	-	52
Dureja et al. ²⁰	11	78	-	-
Agopian et al. ²¹	144	84	75	70
Kennedy et al. ²²	129	90	88	85
Barritt et al. ²³	21	76	76	-
Yalamanchili et al. ²⁴	18+239 ^{cc}	86	-	71
Heuer et al. ²⁵	40	75	-	-
Bhagat et al. ²⁶	71	82	79	75
VanWagner et al. ²⁷	30	81	73	60
Houlihan et al. ²⁸	48	88	82	-
Tanaka et al. ²⁹	7	100	100	100
Singal et al. ³⁰	1,368	86	82	80
Malik et al. ³¹	98	79	74	72
Hejllova et al. ^{*32}	309	-	100	94

[#]Survival in a patient with metabolic syndrome.

^{*}Evaluated the survival of patients with de novo NAFLD. In this study, the 10-year survival rate was 81%.

^{cc}Cryptogenic cirrhosis was evaluated in conjunction with patients transplanted due to NASH in these studies.

Recurrence of NASH and de novo NASH

We selected 11 articles that addressed the recurrence of NASH, as shown in Table 2.

The studies of Contos et al.,⁹ Ong et al.,¹⁰ El Atrache et al.,¹⁹ and Dureja et al.²⁰ found advanced fibrosis, greater than grade 3, in about 4% of the samples. Contos et al.⁹ associate the increased recurrence of NAFLD with the use of corticosteroids. Charlton et al.,³⁹ in an earlier study conducted in 2001, showed 12.5% of cirrhotic patients, a percentage higher than the one found in more recent studies. It is possible that the higher frequency of recurrence in the older series, as well as the greater severity of the cases in that period, is related to the type of immunosuppression used at the time, more strongly based on corticosteroids.

We found eight articles reporting the presence of de novo NASH.

The onset of de novo NASH occurs as of the sixth month posttransplant, only after nutritional recovery from the immediate posttransplant.

As observed in Table 2, the incidence is high, and increases according to the follow-up time.^{30,42} Hejllova et al.³² found an increase from 30% after 1 year to 47% after 10 years. The series studied showed a low incidence of severe forms of the disease, at most 3%, except for Hejllova et al.³² who showed 17% of advanced fibrosis, probably associated to the longer follow-up of the patients. Even so, there was no difference in the survival of patients with F3/F4 fibrosis compared to the others. There is no report of retransplantation or graft dysfunction.

The studies associate as factors related to de novo NASH the use of tacrolimus,¹² DM,¹² dyslipidemia,^{12,30} high blood pressure (HBP),¹² alcoholic cirrhosis,¹² donor with a fatty liver⁴³ and weight gain after transplantation.^{12,30,37}

Risk factors

Risk factors for NASH were found in 29 studies. Of these, eight reported on MetS. The authors observed that patients transplanted due to NASH have an incidence of MetS similar to those transplanted for other reasons, around 50% (Table 3). In the series evaluated by Laish et al.³⁵ and El Atrache et al.,¹⁹ the population evaluated consisted exclusively of patients transplanted due to NASH. In the investigation by Seo et al.,⁴⁰ the population consisted of patients with de novo NASH. Despite the known relation between insulin resistance and metabolic syndrome, there are few articles evaluating posttransplant insulin resistance. The only studies, by Bianchi et al.⁴⁵, Anastácio et al.¹⁴ and Veldt et al.,⁵⁹ showed a value of the HOMA index very close to that considered normal in the several populations and in the index study by Marchesini et al.⁶⁰ that considered 3

TABLE 2 Recurrence of NASH and de novo NASH in patients undergoing liver transplantation.

Reference	Patients N	Follow-up (months)	Recurrence		De novo	
			NAFLD (%)	NASH (%)	NAFLD (%)	NASH (%)
Yalamanchili et al. ²⁴	18	60	45	4		
Tanaka et al. ²⁹	7	120	14	-		
Bhagat et al. ²⁶	71	60	-	33		
Contos et al. ⁹	27	>12	52	11		
Charlton et al. ³⁹	15	>12	60	33		
Dureja et al. ²⁰	88	>12	39	28		
El Atrache et al. ¹⁹	83	45	-	24		
Ong et al. ¹⁰	51	>24	25.5	16		
Vallin et al. ⁸	11	>60	100	71.4		
Malik et al. ³¹	98	60	-	25		
Agopian et al. ²¹	144	60	15	8		
Seo et al. ⁴⁰	68	28			18	9
Sprinzl et al. ⁴¹	129	24			34	5.4
Dumortier et al. ¹²	421	>6			31	5.3
Kim et al. ⁴³	156	>12			27	6.7
Hejlova et al. ³²	546	>120			56.7	10
Lim et al. ³⁷	30	44			40	13
Vallin et al. ⁸	80	>60			67	17.2
Finkenstedt et al. ⁴²	237	>60			32.6	

as cutoff point. Bianchi et al.⁴⁵ found a value of 3.1 in patients with MetS. Anastácio et al.¹⁴ found 2.4 in a Brazilian population and Veldt et al.⁵⁹ 2.2 and 1.2 in diabetic and non-diabetic patients, respectively.

Posttransplant diabetes mellitus

Diabetes is often found in patients after liver transplantation. The population of pretransplant diabetics varies according to the etiology of the transplantation, most often NASH, and the characteristics of this population (obesity, age and ethnicity – more frequent among Westerners). Posttransplant diabetes (NODAT, New Onset Diabetes After Transplantation) is related to obesity, family history, glucose intolerance prior to transplantation, and hepatitis C as the etiology of transplantation, but it is also related to immunosuppressants. There are a number of studies arguing that the pathophysiology of NODAT is immunosuppressive toxicity in pancreatic B cells.^{53,61,62}

As shown in Table 3, which includes 18 studies on diabetes, the longer the population follow-up, the higher the prevalence. Only one study associates NODAT with a lower frequency of sarcopenia and lower mortality in the first year posttransplantation. An explanation for this fact would probably be related to the better nutritional

recovery seen in these patients.⁵⁷ There is no association of NODAT with graft dysfunction and decreased survival.⁶³ Even though studies evaluating patients with post-transplant NAFLD^{8,19,40,45} yield prevalence rates for diabetes similar to those of the general population, there is an investigation by Stepanova et al.⁶⁴ including over 15,000 transplanted patients, some 3,000 of which transplanted due to NASH, which eventually concluded that the latter have a higher risk of developing DM.

Dyslipidemia, hypertension and obesity in liver transplant patients

It is known that transplanted patients have a higher incidence of dyslipidemia and hypertension. Currently, the basis of immunosuppressive treatment is performed with calcineurin inhibitors. Some studies compared patients who used different immunosuppressants. Bianchi et al.,⁴⁵ as well as other authors,^{55,58} compared patients who used cyclosporine and tacrolimus, with an incidence of MetS of 52 vs. 60, HBP of 59 vs. 41, dyslipidemia of 57 vs. 38, and DM of 34 vs. 44, respectively. Although both favor metabolic disorders, cyclosporin is more associated with hypertension and dyslipidemia, whereas tacrolimus is associated with increased DM frequency (Table 3). The

TABLE 3 Frequency of metabolic disorders in patients undergoing liver transplantation.

Reference	Patients N	Follow-up (months)	MetS (%)	DM (%)	NODAT (%)	Dyslipid (%)	HBP (%)
Sprinzel et al. ⁴¹	44	24	48				52
Seo et al. ⁴⁰	68	28		38		25	69
El Atrache et al. ¹⁹	83	45	53	76			71
Hanouneh et al. ⁴⁴	148	60	53	59			60
Bianchi et al. ⁴⁵	296	38	45	38	29.4	50	52.7
Laryea et al. ⁴⁶	118	>60	58			48	62
Laish et al. ³⁵	252	>60	52				
Anastácio et al. ⁴⁷	148	>60	50				60
Yalamanchili et al. ²⁴	257	60		36.8			52
Lv et al. ⁴⁸	438	60		18			
Dumortier et al. ¹²	421	>6		23.5		12	51.8
Marroni et al. ¹⁶	75	>3		38			
Kennedy et al. ²²	129	>60		59			
Ong et al. ¹⁰	13	>60		53			
Agopian et al. ²¹	144	60		57			50
Vallin et al. ⁸	80	>60		37.8			52
Parolin et al. ¹⁷	82	20			18.9		
Mirabella et al. ⁴⁹	830	10			10.8		
Ling et al. ⁵⁰	10,204	30			24.3		
Carey et al. ⁵¹	225	>12			17.3		
Saliba et al. ⁵²	211	24			22.7		
Moon et al. ⁵³	778	57			36.5		
Gisbert et al. ⁵⁴	85	>12				66	
Trotter et al. ^{#55}	57	>6				30	
Dehghani et al.* ⁵⁶	170	>12				70	
Marroni et al. ¹⁵	75	> 3					14**
Darstein et al. ⁵⁷	255	>60					55
Hejlova et al. ³²	309	>120					67
Canzanello et al. ^{¥58}	158	>24					82

#The authors found 30% in patients who used cyclosporine and 6% with tacrolimus.

*The authors found 70% of hypertriglyceridemia and 15% of hypercholesterolemia.

¥The authors found 82% for cyclosporine and 64% for tacrolimus.

**Only new cases of posttransplant hypertension.

MetS: metabolic syndrome; DM: diabetes mellitus; NODAT: New Onset Diabetes After Transplantation; HBP: high blood pressure.

studies by Gisbert et al.⁵⁴ and Dehghani et al.⁵⁶ revealed that hypertriglyceridemia is the most frequent dyslipidemia in posttransplanted patients.

There are several investigations about obesity before transplantation and its influence on transplantation, graft dysfunction and mortality. Nevertheless, there are few studies evaluating posttransplant obesity. Seo et al.⁴⁰ found 10% weight gain in patients after transplantation. The statistics found vary from 20% to 36% of obese individuals in the population investigated.^{38,46,65} Everhart et al.,³⁸ in a study assessing 774 patients, found the following risk factors for obesity: use of corticosteroids, genetic factors

and recent marriage. Kouz et al.,⁶⁵ in turn, observed that obesity is more common in patients undergoing transplantation because of NASH compared to other etiologies. Regarding risk factors, obesity is associated with increased development of NODAT and de novo NASH.¹²

DISCUSSION

The present review of the literature suggests that patients transplanted due to any etiology have a high incidence of NAFLD, mainly steatohepatitis (NASH), which is the phase with the greatest potential for progression of the disease in the posttransplant period. It occurs due to

recurrence of the disease or the onset of de novo NASH in transplanted patients due to other diseases. The frequency of both increases according to the time of follow-up. Higher recurrence is found in the older series, which may be related to the type of immunosuppression used at the time, more strongly based on corticosteroids.^{9,30,39}

In the more detailed evaluations, the association between de novo NASH and use of tacrolimus,¹² DM,¹² dyslipidemia,^{12,30} HBP,¹² alcoholic cirrhosis,¹² donor with a steatotic liver⁴³ and weight gain after transplantation^{12,30,37} were observed. However, no differences were observed in the mean survival of transplant patients due to NASH compared to the survival of patients transplanted on the account of other etiologies even in the first year, when mortality associated with cardiovascular events is higher in patients transplanted due to NASH.

Similar to what is observed with NASH, there is a high prevalence of metabolic disorders in these patients, apparently related to the use of immunosuppressants.

When new cases of diabetes after transplantation (NODAT) are added to those of patients with diabetes prior to transplantation, prevalences of 50% can be found.^{10,19,21,31} NODAT was observed in 10% to 36% of the population and was related to obesity, positive family history, glucose intolerance prior to transplantation and hepatitis C as the etiology of transplantation, in addition to immunosuppressants, especially calcineurin inhibitors.^{53,62}

Numerous studies have demonstrated a higher incidence of dyslipidemia and hypertension in posttransplant patients. Some of them compared patients using different immunosuppressants. Among calcineurin inhibitors, currently the basis of treatment, cyclosporine has been shown to be more associated with hypertension and dyslipidemia, while tacrolimus is associated with increased DM frequency as previously mentioned.^{45,55,58}

Although poorly studied in posttransplant patients, obesity was more commonly found in transplanted individuals due to NASH⁶⁵ compared to other etiologies, as well as association with NODAT and de novo NASH.¹² MetS was found in approximately 50% of patients after transplantation with no difference being found between patients transplanted due to NASH or other etiologies. A possible explanation for this fact should be the interference of immunosuppressants in the factors (DM, HBP, dyslipidemia and obesity) associated with MetS. In patients with non-transplanted NASH there is a strong correlation between MetS and insulin resistance; however, few studies have evaluated insulin resistance in this population. The few studies^{14,45,59} evaluating insulin resistance based on the calculation of the HOMA index showed values

very close to those considered normal. This aspect should be further evaluated in the future.

Our study has limitations, particularly its descriptive character, which does not allow conclusions based on strong scientific evidence. The heterogeneity of the studies regarding the topic addressed, the varied designs and the characteristics of the different populations hindered the performance of systematic analyses. Most of the studies evaluated were cross-sectional. Due to temporal differences related to the immunosuppressive regimen, many of these studies were not comparable, leading to biases in evaluation and clinical outcome.

CONCLUSION

Our review suggests that liver transplant patients have a high prevalence of steatosis and NASH, as well as post-transplant metabolic disorders. NAFLD/NASH after liver transplantation is usually not a serious disease and mortality is similar to that found in individuals who do not develop the disease.

Immunosuppressants appear to play an important role in the prevalence of NASH and its associated factors, as well as in the behavior of the disease. Further studies are still needed to better understand NAFLD/NASH after liver transplantation, especially its pathophysiology, treatment and prevention.

RESUMO

Esteato-hepatite não alcoólica no pós-transplante de fígado: artigo de revisão

Introdução: A doença hepática gordurosa não alcoólica (DHGNA) é a terceira causa de transplante hepático no mundo. Tem elevada prevalência após transplante hepático (TH) e é representada pela recorrência da esteato-hepatite (NASH), ou por NASH *de novo*, que ocorre em pacientes transplantados por outra etiologia.

Objetivo: Realizar uma revisão da literatura para avaliar a relevância da recorrência ou do NASH *de novo* em pacientes transplantados de fígado.

Método: Realizada revisão da literatura através de artigos indexados no Medline, Scielo e Lilacs até 2016 publicados em inglês e português. Foram considerados elegíveis estudos que incluíram local e ano de publicação, prevalência e características clínicas dos pacientes.

Resultados: Foram identificados 110 artigos e selecionados 63, que avaliaram a recorrência de NASH, NASH *de novo* e sobrevida após o TH. A sobrevida foi de 90% a 100% em um ano e de 52-100% em 5 anos. A recorrência de

esteatose variou de 15-100% e a de NASH de 4-71%, enquanto esteatose e NASH *de novo* variaram de 18-67% e 3-17%, respectivamente. A frequência de síndrome metabólica, diabetes, dislipidemia e hipertensão variaram de 45-58%, 18-59%, 25-66% e 52-82%, respectivamente.

Conclusão: No pós-transplante de fígado, os pacientes apresentam elevada prevalência de recorrência, de NASH *de novo* e de distúrbios metabólicos. Entretanto, essas alterações parecem não influenciar a sobrevida dos pacientes.

Palavras-chave: Hepatopatia Gordurosa Não Alcoólica. Transplante de Fígado. Fígado Gorduroso. Síndrome Metabólica. Diabetes Mellitus.

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