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Retrospective Study

Transarterial embolization is an acceptable bridging therapy to hepatocellular carcinoma prior to liver transplantation

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is an aggressive malignant neoplasm that requires liver transplantation (LT). Despite patients with HCC being prioritized by most organ allocation systems worldwide, they still have to wait for long periods. Locoregional therapies (LRTs) are employed as bridging therapies in patients with HCC awaiting LT. Although largely used in the past, transarterial embolization (TAE) has been replaced by transarterial chemoembolization (TACE). However, the superiority of TACE over TAE has not been consistently shown in the literature.

AIM

To compare the outcomes of TACE and TAE in patients with HCC awaiting LT.

METHODS

All consecutive patients with HCC awaiting LT between 2011 and 2020 at a single center were included. All patients underwent LRT with either TACE or TAE. Some patients also underwent percutaneous ethanol injection (PEI), concomitantly or in different treatment sessions. The choice of LRT for each HCC nodule

was determined by a multidisciplinary consensus. The primary outcome was waitlist dropout due to tumor progression, and the secondary outcome was the occurrence of adverse events. In the subset of patients who underwent LT, complete pathological response and post-transplant recurrence-free survival were also assessed.

RESULTS

Twelve (18.5%) patients in the TACE group (only TACE and TACE + PEI; n = 65) and 3 (7.9%) patients in the TAE group (only TAE and TAE + PEI; n = 38) dropped out of the waitlist due to tumor progression (P log-rank test = 0.29). Adverse events occurred in 8 (12.3%) and 2 (5.3%) patients in the TACE and TAE groups, respectively (P = 0.316). Forty-eight (73.8%) of the 65 patients in the TACE group and 29 (76.3%) of the 38 patients in the TAE group underwent LT (P = 0.818). Among these patients, complete pathological response was detected in 7 (14.6%) and 9 (31%) patients in the TACE and TAE groups, respectively (P = 0.145). Post-LT, HCC recurred in 9 (18.8%) and 4 (13.8%) patients in the TACE and TAE groups, respectively (P = 0.756). Posttransplant recurrence-free survival was similar between the groups (P log-rank test = 0.71).

CONCLUSION

Dropout rates and posttransplant recurrence-free survival of TAE were similar to those of TACE in patients with HCC. Our study reinforces the hypothesis that TACE is not superior to TAE as a bridging therapy to LT in patients with HCC.

Key Words: Hepatocellular carcinoma; Transarterial embolization; Transarterial chemoembolization; Liver transplantation; Locoregional therapy; Bridging

Core Tip: Hepatocellular carcinoma (HCC) is an aggressive malignant neoplasm, and the treatment of choice is liver transplantation (LT). Because the waiting time is often unpredictable, locoregional therapy is used to halt HCC progression until an organ is available. Although largely replaced by transarterial chemoembolization (TACE), transarterial embolization (TAE) or bland embolization is an alternative with a lower cost and safer adverse event profile. Our findings, in conjunction with those of previous studies, provide evidence of non-superiority of TACE over TAE, thereby encouraging a more liberal use of TAE for bridging HCC to LT.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is an aggressive malignant neoplasm that arises in the presence of cirrhosis. Unless appropriate treatment is administered, HCC may progress, rupture, or metastasize[1-3]. In the presence of cirrhosis and portal hypertension, liver transplantation (LT) is the treatment of choice for HCC[4,5].

The Milan criteria is widely used to identify patients likely to benefit from LT[6,7]. Although some organ allocation systems may prioritize patients with HCC for LT[8], most of these patients face a long waiting period. Thus, locoregional therapy (LRT) is indicated for this patient population to halt tumor progression beyond the acceptable limits of the Milan criteria (bridging therapy)[9].

Although the main LRT options are transarterial chemoembolization (TACE) and radiofrequency ablation (RFA), other modalities such as transarterial radioembolization, percutaneous ethanol injection (PEI), microwave ablation, and transarterial embolization (TAE) are also employed worldwide. Recently, our group demonstrated that PEI is an acceptable bridging therapy to LT in patients with HCC[10,11]. The choice of LRT is influenced by tumor size, number, and location, liver function, and individual center experience[10-12].

Although widely used in the past, TAE has been replaced by TACE. The potential advantage of TACE over TAE may be the addition of a chemotherapeutic agent. However, because HCC expresses a *multidrug resistance* gene, it is resistant to most chemotherapeutic agents available[13]. Furthermore, the advantages of TACE over TAE have not been confirmed in clinical practice. A recent systematic review and meta-analysis comparing randomized control trial (RCT) data on TAE and TACE use among patients with unresectable HCC detected no superiority of TACE over TAE in terms of disease-free survival[14].

Only one study till date has compared the outcomes of TAE *vs* TACE in terms of dropout rates of patients with HCC on the transplant list[15]. Thus, the aim of this study was to analyze the outcomes of TAE and TACE as an LRT for

patients with HCC awaiting LT. The dropout rates and post-transplant outcomes of both techniques have been compared.

MATERIALS AND METHODS

This study was a retrospective analysis of a prospectively filled dataset from the Hospital de Clínicas de Porto Alegre (HCPA) Liver Transplant Program. All adults (aged > 18 years) with cirrhosis and HCC who were enlisted for orthotopic liver transplantation (OLT) between 2011 and 2020 at the authors' institution and had undergone TACE or TAE for bridging or downstaging were included. Patients with HCC who met the Milan criteria were included in this analysis. Patients who did not meet the Milan criteria were included only after downstaging HCC using LRT to meet the Milan criteria.

The choice of LRT for each HCC nodule was determined by a consensus among LT surgeons, hepatologists, and interventional radiologists. Because RFA is not available in the Brazilian public health system, PEI was preferred for lesions ≤ 3 cm in size and accessible *via* percutaneous ultrasound-guided liver puncture. For tumors > 3 cm in size, TACE or TAE were preferred. Until 2013, TAE was the only modality of embolization available in the Brazilian public health system[16]. Since then, TACE is preferred over TAE. However, even after 2013, some patients underwent TAE because of contraindications to doxorubicin or unavailability of the drug. For some patients with more than one tumor, PEI was performed in addition to TACE or TAE, either in the same treatment session or in different sessions. Patients who underwent PEI only or RFA were not included in this study.

TACE and TAE were performed by one of the two experienced interventional radiologists (Scaffaro LA and Farenzena M) *via* the femoral route under sedation. A 5-F Cobra or Mikaelson catheter was used to achieve selective catheterization and perform an arteriogram of the celiac trunk and superior mesenteric artery. The tumor feeding artery was selectively catheterized using a 2.8-F microcatheter (Progreat; Terumo). For each TACE session, doxorubicin-lipiodol emulsion followed by polyvinyl alcohol (PVA) or microspheres with particle size 100 μm–300 μm were infused. For TAE, only PVA or microspheres with particle size 100 μm–300 μm were infused without the addition of a chemotherapeutic agent. PEI was also performed by one of the same two experienced interventional radiologists under computed tomography (CT) or ultrasound guidance. The tumor was punctured percutaneously using a 20-gauge needle under sedation.

Follow-up imaging [contrast-enhanced CT or magnetic resonance imaging (MRI)] was performed 6 wk–8 wk after each procedure. The need for subsequent therapy was decided on the basis of residual contrast enhancement in the lesion region, which indicated the presence of residual tumor. The imaging follow-up protocol remained the same throughout the study period.

Contrast-enhanced CT or MRI was used to characterize preprocedural disease extent, including the size and number of lesions. Because 74% of LIRADS 4 lesions and 94% of LIRADS 5 lesions are HCCs[17], both were considered as HCC tumors. Biopsy of the lesions was not routinely performed. Based on the tumor size and number of lesions, tumor burden was classified according to the Barcelona Liver Clinic staging system[5]. The Model for End-Stage Liver Disease (MELD) score was calculated as described in the study by Malinchoc *et al*[18]. Preprocedural alpha-fetoprotein (AFP) level was defined as the AFP level immediately before the first LRT. The following patient demographic data were collected: Age, sex, cirrhosis etiology, calculated MELD score, preprocedural AFP level, number of lesions, diameter of the largest tumor, and number of procedures.

According to the LRT chosen, the study patients were divided into four groups: Only TAE, only TACE, TAE + PEI and TACE + PEI. The primary study outcome was waitlist dropout due to tumor progression beyond the limits of the Milan criteria. The secondary outcomes were as follows: (1) Pathological response; (2) side effects of LRT, as graded by the Clavien–Dindo classification[19]; and (3) post-transplant HCC recurrence, as evaluated by post-transplant recurrence-free survival. Patients were followed until their death, waitlist dropout, or the end of the study on June 30, 2023.

For the main outcome measure (waitlist dropout), the date of the first LRT session of each patient enlisted for LT was defined as day zero of the follow-up. Dropout due to tumor progression was considered an event. Time to dropout due to tumor progression was defined as the number of days between the first LRT and the dropout date. The dropout rate was analyzed using the Kaplan–Meier method in a time-to-event manner. Patients who underwent LT or dropped out due to any cause other than tumor progression (*e.g.*, clinical or psychosocial dropout) were excluded on the transplant or dropout day, respectively.

For the evaluation of post-transplant recurrence-free survival in a subset of the cohort's patients who underwent LT, the transplant day was defined as day zero of the follow-up. The analysis of post-transplant recurrence-free survival included HCC recurrence or death due to any cause as the events. Patients lost to follow-up were censored.

The pathological response and vascular invasion by the tumor were assessed by a dedicated liver pathologist. Complete or near-complete pathological response was defined as 90% tumor necrosis on histopathological examination of the explanted liver of patients who underwent OLT.

Categorical variables were compared using the Fisher's exact test. The normality of the continuous variables was estimated using the Shapiro–Wilk test. Continuous variables were analyzed using the Mann–Whitney test or Student's t-test as appropriate. Time-to-event data (time to dropout due to tumor progression and recurrence-free survival) were estimated using the Kaplan–Meier method and compared using the log-rank test. For all the analyses pertaining to waitlist dropout, follow-up day zero in patients whose HCC was downstaged to meet the Milan criteria was set to when they were enlisted. All comparisons were two-sided with a level of significance of 0.05. All analyses were performed using R for microwave-assisted, continuous-flow organic synthesis (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria)[20]. The statistical methods used in the study were reviewed by a biomedical statistician from HCPA.

RESULTS

From 2011 to 2021, 183 patients with HCC were placed on the LT waiting list. Of these, 80 patients were excluded for the following reasons: No LRT was performed (n = 17), RFA was performed (n = 6), and PEI alone was performed (n = 57). One hundred and three patients with HCC who were enlisted for LT underwent LRT with TAE or TACE. Of these, 65 (63.1%) patients underwent TACE and 38 (36.9%) underwent TAE. There was no statistically significant difference between the groups in terms of patient, tumor, and treatment characteristics (Table 1).

Dropout due to tumor progression

Dropout due to tumor progression occurred in 7 (17.5%), 5 (20%), 2 (9.5%), and 1 (5.9%) patients who underwent only TACE (n = 40), TACE + PEI (n = 20), only TAE (n = 21), and TAE + PEI (n = 17), respectively (Table 2). The difference among the four treatment groups was not statistically significant (P = 0.565). The overall dropout due to tumor progression was 12 (18.5%) and 3 (7.9%) in the TACE (only TACE and TACE + PEI, n = 65) and TAE (only TAE and TAE + PEI, n = 38) groups, respectively (P = 0.162). In a time-to-event analysis using the Kaplan–Meier method (Figure 1A), no significant difference in dropout rates was detected between the TACE and TAE groups (P log-rank test = 0.29).

Adverse events

Of the 65 patients who underwent TACE, adverse events occurred in 8 (12.3%) patients, of which 7 were classified as Clavien–Dindo Grade 2 or lower. The remaining patient died following a combined TACE + PEI procedure due to hemorrhage. Of the 38 patients who underwent TAE, adverse events occurred in 2 (5.3%) patients. Both events were classified as Clavien–Dindo Grade 1. The difference between adverse events in the TACE and TAE groups was not statistically significant (P = 0.316).

Post-transplant outcomes

The demographic and treatment characteristics of patients who underwent OLT are listed in Table 3. In total, 77 (74.8%) of the 103 included patients underwent LT. Forty-eight (73.8%) of the 65 patients in the TACE group and 29 (76.3%) of the 38 patients in the TAE group underwent LT (P = 0.818). No statistically significant difference in the study variables was detected between the groups.

After transplantation, HCC recurred in 9 (18.8%) of the 48 patients in the TACE group and 4 (13.8%) of the 29 patients in the TAE group (P = 0.756). The recurrence-free survival curves are shown in Figure 1B. No statistical difference was detected in the recurrence-free survival between TACE and TAE (P log-rank test = 0.71).

DISCUSSION

The present study evaluated the outcomes of TACE and TAE in patients with HCC on the LT waitlist. Neither the proportion of patients who underwent LT nor the dropout rate due to tumor progression beyond the limits of the Milan criteria differed between the groups. Moreover, in patients who later underwent LT, recurrence-free survival was similar regardless of the bridging therapy employed. Adverse events were not statistically different between the TAE and TACE groups. However, a higher incidence of adverse events was observed in the TACE group (12.3%) than in the TAE group (5.3%).

Whether the addition of a chemotherapeutic agent to TAE has a significant clinical effect has been the subject of several studies. The first RCT on this issue suggested that TACE was superior to TAE in patients with unresectable HCC, a patient group that is different to the one analyzed in the present study[21]. However, that trial was discontinued because preliminary results demonstrated the benefit of TACE over no treatment, precluding a more precise comparison between TACE and TAE. Since then, three RCTs have failed to demonstrate improved overall or progression-free survival of TACE over TAE in patients with HCC who are unsuitable for curative treatment[22-24]. Additionally, two recent meta-analyses of RCTs suggested that there were no benefits of TACE over TAE in patients with unresectable HCC[14,25].

Only one case-control study by Kluger *et al*[15] directly compared TACE with TAE in patients with HCC on the LT waitlist. Similar to our findings that study also demonstrated no difference in dropout rates, complete pathological response, and recurrence-free survival between TAE and TACE as a bridging therapy to LT. Tsochatzis *et al*[26] demonstrated that either TACE or TAE improved post-transplant outcomes in comparison to no pre-transplant treatment. Most patients in the study by Tsochatzis *et al*[26] underwent TAE instead of TACE. Although a direct comparison between TACE and TAE regarding clinical outcomes was not performed, there was no difference in terms of histological response in the explanted livers. Another study found a higher rate of histological necrosis in patients who underwent TACE than in patients who underwent TAE[27]. However, that study did not report the dropout rate. Furthermore, its small sample size (n = 16) precludes a conclusion regarding post-transplant outcomes.

In our study, the rate of complete or near-complete tumor necrosis was relatively low in both groups (TACE 14.6% *vs* TAE 31%). This may be attributed to the fact that our pathology report only considered complete tumor necrosis when no viable tumor was observed in the entire liver explant. The rate of complete or near-complete tumor necrosis was similar between the TACE and TAE groups, with a trend toward a higher rate in the TAE group. A similar trend in complete pathological response was observed in the study by Kluger *et al*[15] (TAE 36% *vs* TAE 26%). Conversely, Nicolini *et al*[27] found more tumor necrosis in patients who underwent TACE than in those who underwent TAE (77% *vs* 27.2%). Given the conflicting results, it remains controversial whether there is a difference between TACE and TAE in terms of complete tumor necrosis.

Table 1 Patient, tumor, and treatment characteristics, *n* (%)

Variables	TACE	TAE	*P* value
Number	65	38	
Age (yr), median (IQR)	60 (55, 65)	61.5 (55, 64)	0.962
Male sex	40 (61.5)	23 (60.5)	> 0.99
Diagnosis			0.889
HCV	51 (78.5)	32 (84.2)	
HBV	4 (6.2)	2 (5.3)	
Alcohol	4 (6.2)	3 (7.9)	
NASH	4 (6.2)	1 (2.6)	
Other	2 (3.1)	0	
Calculated MELD score, median (IQR)	9 (8, 12)	11 (9, 12)	0.122
Preprocedural AFP level, median (IQR)	22.5 (5.6, 68.3)	15.75 (6.8, 94.5)	0.992
Number of lesions			0.652
1	37 (56.9)	22 (57.9)	
2	18 (27.7)	11 (28.9)	
3	10 (15.4)	4 (10.5)	
≥ 4	0	1 (2.6)	
Largest tumor diameter, median (IQR)	3 (2.4, 3.8)	3.3 (2.4, 3.9)	0.634
Milan-out	10 (15.4)	8 (21.1)	0.591
Use of PEI	25 (38.5)	17 (44.7)	0.541
Number of procedures, median (IQR)	2 (1, 3)	2 (1, 2.75)	0.914

Milan-out refers to patients beyond the limits of the Milan criteria. TACE: Transarterial chemoembolization; TAE: Transarterial embolization; HCV: Hepatitis-C virus; HBV: Hepatitis-B virus; MELD: Model for End-Stage Liver Disease; AFP: Alpha-feto protein; PEI: Percutaneous ethanol injection; IQR: Interquartile range; NASH: Non-alcoholic steatohepatitis.

Table 2 Dropout due to tumor progression in the treatment groups, *n* (%)

	Dropout due to tumor progression		
		No	Yes
TACE	TACE only	33 (82.5)	7 (17.5)
	TACE + PEI	20 (80)	5 (20)
	Overall TACE	53 (81.5)	12 (18.5)
TAE	TAE only	19 (90.5)	2 (9.5)
	TAE + PEI	16 (94.1)	1 (5.9)
	Overall TAE	35 (92.1)	3 (7.9)

Fisher's exact test for comparison of the four groups [transarterial chemoembolization (TACE) only, TACE + percutaneous ethanol injection (PEI), transarterial embolization (TAE) only, and TAE + PEI]: $P = 0.565$. Fisher's exact test for comparison of the two groups (Overall TACE *vs* overall TAE): $P = 0.162$. TACE: Transarterial chemoembolization; TAE: Transarterial embolization; PEI: Percutaneous ethanol injection.

In this study, the rate of adverse events, which included one death, was higher in the TACE group than in the TAE group (prevalence, 12.3% *vs* 5.3%). This difference was not statistically significant, which may be attributable to the small sample size (type II error). Two meta-analyses found increased toxicity after TACE than after TAE[14,27]. In a study evaluating the use of TAE in patients on the LT waitlist, the incidence of major complications (Clavien–Dindo Grade 3 or higher) was considerably low (2.6%)[28]. In our study, the two adverse events (5.3%) in the TAE group were minor (Clavien–Dindo Grade 1).

Table 3 Patient, tumor, and treatment characteristics of patients who underwent liver transplantation, *n* (%)

Variables	TACE	TAE	*P* value
Number	48	29	
Age (yr), median (IQR)	60.5 (55.75, 65.25)	62 (53, 63)	0.458
Male sex	30 (62.5)	19 (65.5)	0.812
Diagnosis			0.385
HCV	37 (77.1)	25 (86.2)	
HBV	4 (8.3)	1 (3.4)	
Alcohol	3 (6.2)	3 (10.3)	
NASH	4 (8.3)	0	
Other	0	0	
Calculated MELD score, median (IQR)	9 (8, 11.25)	11 (9, 12)	0.109
Pretransplant AFP, median (IQR)	11.7 (4.77, 46)	9.1 (4.4, 31.95)	0.668
Number of lesions			0.704
1	29 (60.4)	16 (55.2)	
2	12 (25)	8 (27.6)	
3	7 (14.6)	4 (13.8)	
≥ 4	0	1 (3.4)	
Largest tumor diameter, median (IQR)	2.8 (2.3, 3.8)	3.3 (2.5, 3.6)	0.333
Milan-out	5 (10.4)	8 (27.6)	0.064
Use of PEI	19 (39.6)	15 (51.7)	0.348
Complete pathological response	7 (14.6)	9 (31)	0.145
Vascular invasion	8 (16.7)	4 (13.8)	> 0.99

Milan-out refers to patients beyond the limits of the Milan criteria. TACE: Transarterial chemoembolization; TAE: Transarterial embolization; HCV: Hepatitis-C virus; HBV: Hepatitis-B virus; MELD: Model for End-Stage Liver Disease; PEI: Percutaneous ethanol injection; IQR: Interquartile range; NASH: Non-alcoholic steatohepatitis.

The ultimate goals of HCC bridging therapies are to prevent dropout due to tumor progression beyond the limits of the Milan criteria and to ensure long-term recurrence-free survival after LT. As there seems to be no superiority of TACE over TAE regarding those clinical outcomes, evidence of TACE's superiority over TAE in this group of patients is lacking. Given the tendency of increased toxicity and the indisputable higher cost of TACE when compared with TAE, we believe that our study findings, in conjunction with those of the study by Kluger *et al*[15], should encourage a more liberal use of TAE for bridging therapy to LT in patients with HCC.

Our study has some limitations. It was a retrospective study. However, the data were extracted from a prospectively filled database. In addition, most patients underwent PEI in addition to TACE or TAE, which might have confounded the interpretation of the study results. Nevertheless, the proportion of patients who underwent PEI was similar between the groups. Several patients with HCC on the LT waitlist have more than one tumor with different features that render them suitable for different types of LRTs. Thus, we believe that the addition of patients who underwent an ablation procedure makes our sample more similar to "real-life" patients, thereby improving the external validity of the study.

CONCLUSION

In conclusion, the use of TAE in patients with HCC who are on the LT waitlist produced similar outcomes as the use TACE in terms of dropout rate, transplant rate, pathological necrosis, and post-transplant recurrence-free survival. Our study further reinforces that TACE is not superior to TAE for the treatment of HCC. Thus, TAE may be employed in scenarios in which the use of chemotherapeutic agents is contraindicated, such as intolerance to antineoplastic drugs, and in frail patients in whom its concomitant use with PEI or RFA is required.

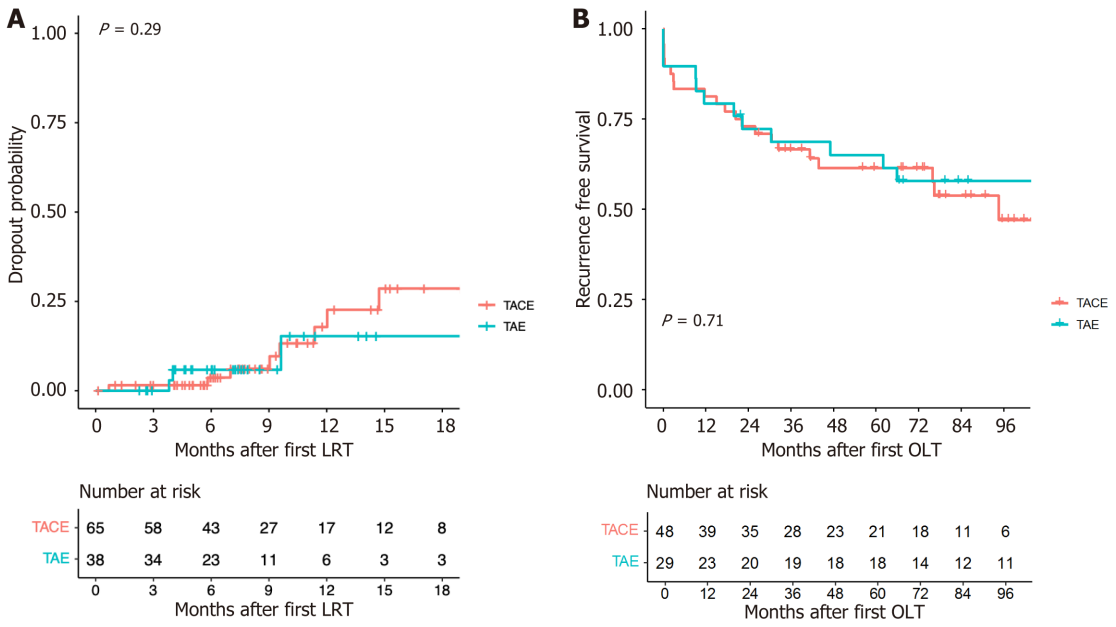

Figure 1 Kaplan–Meier analysis. A: Waitlist dropout due to tumor progression according to locoregional therapy performed. Log-rank test for the comparison between the two groups: *P* = 0.29; B: Post-transplant recurrence-free survival according to locoregional therapy performed. Log-rank test for the comparison between the two groups: *P* log-rank test = 0.71. TACE: Transarterial chemoembolization; TAE: Transarterial embolization; LRT: Locoregional therapy; OLT: Orthotopic liver transplantation.

FOOTNOTES

Author contributions: Lazzarotto-da-Silva G and Chedid MF participated in the research design, data collection, data analysis, and writing of the manuscript; Scaffaro LA, Farenzena M, Feier FH, Grezzana-Filho TJM, Rodrigues PD, de Araujo A, Alvares-da-Silva MR, Marchiori RC, and Kruel CRP participated in the research design and revision of the final version of the manuscript; Prediger L and Silva RK participated in data collection and writing of the manuscript.

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