Non-cancerous prognostic factors of hepatocellular carcinoma after liver transplantation[1]

Fatores prognósticos não oncológicos no carcinoma hepatocelular tratado com transplante hepático

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ABSTRACT

PURPOSE: To explore non-cancerous factors that may be related with medium-term survival (24 months) after liver transplantation (LT) in this data from northeast Brazil.

METHODS: A cross-sectional study was carried out in patients who underwent deceased-donor orthotopic LT because hepatocellular carcinoma (HCC) at the University of Pernambuco, Brazil. Non-cancerous factors (i.e.: donor-, receptor-, surgery- and center-related variables) were explored as prognostic factors of medium-term survival using univariate and multivariate approachs.

RESULTS: Sixty-one patients were included for analysis. Their three, six, 12 and 24-month overall cumulative survivals were 88.5%, 80.3%, 73.8% and 65.6%, respectively. Our univariate analysis identified red blood cell transfusion (Exp[b]=1.26; p<0.01) and hepato-venous reconstruction technique (84.6% vs. 51.4%, p<0.01; respectively for piggyback and conventional approaches) as significantly related to post-LT survival. The multivariate analysis confirmed the hepato-venous reconstruction technique was an independent prognostic factor.

CONCLUSION: The piggyback technique was related to improved medium-term survival of hepatocellular carcinoma patients after liver transplantation in this northeast Brazilian sample.

Key words: Organ Transplantation. Liver Neoplasms. Carcinoma, Hepatocellular. Survival Analysis. Prognosis.

RESUMO

OBJETIVO: Explorar fatores prognósticos não oncológicos para a sobrevivência de médio prazo (24 meses) de portadores de carcinoma hepatocelular tratados com transplante hepático.

MÉTODOS: Estudo de corte incluindo pacientes submetidos a transplante ortotópico de fígado (doador-cadáver) pelo Serviço de Cirurgia Geral e Transplante Hepático da Universidade de Pernambuco, UPE. Exploraram-se variáveis relacionadas ao doador, receptor, procedimento cirúrgico e serviço transplantador, como potenciais fatores prognósticos para a sobrevivência de médio prazo dos transplantados, aplicando-se análise uni e multivariada.

RESULTADOS: Sessenta e um pacientes foram incluídos para análise. A sobrevivência cumulativa de três, seis, 12 e 24 meses observada foi de 88,5%, 80,3%, 73,8% e 65,6%, respectivamente. Por análise univariada, identificou-se a transfusão de hemácias (Exp[b]=1,26; p<0,01) e técnica cirúrgica empregada (84,6% vs. 51,4%, p<0,01; respectivamente, piggyback vs. convencional) como estatisticamente relacionadas à sobrevivência dos pacientes estudados. Por análise multivariada, confirmou-se a técnica empregada como fator prognóstico independente.

CONCLUSÃO: A técnica cirúrgica piggyback se relacionou a melhor sobrevivência de médio prazo de pacientes com carcinoma hepatocelular após transplante de fígado nesta casuística do nordeste Brasileiro.

Descritores: Transplante de Órgãos. Neoplasias Hepáticas. Carcinoma Hepatocelular. Análise de Sobrevivência. Prognóstico.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common neoplasm worldwide and the third most common cause of cancer mortality, accounting for 9.2% of all cancer deaths[1]. Overall, its incidence has been estimated at 10.8 per 100.000 person-years; however, almost 85% of the cases occur in developing countries[2]. In 2008, about 750.000 new HCC cases were reported worldwide, with 13.300 HCC cases in North America and 57.900 in Europe[1]. All these rates increased from the previous global cancer statistics[3]. In Brazil, its clinical and epidemiological aspects widely vary amongst different regions[4], where is considered a neoplasm of low prevalence in general[5].

Liver transplantation (LT) represents the most promising product of modern surgery for treatment of patients suffering from chronic end-stage liver disease and remains a cornerstone in the management of patients with HCC[6]. On the other hand, recurrence of hepatocellular carcinoma after LT is common as 13.4%, which leads to an unfavorable prognosis with mortality rate about 56.3%[7]. Thus, as factors related to cancer alone are not enough to predict prognosis of patients with HCC undergoing surgical treatments[8], to identify non-cancerous prognostic factors it may serve to improve outcomes, selecting appropriated approaches.

The aim of this study was to explore non-cancerous prognostic factors that may be related with medium-term survival among patients undergoing LT due to HCC at the University of Pernambuco, Brazil

Methods

A cross-sectional study was carried out including adults and adolescent patients (> 16 years) undergoing deceased-donor orthotopic LT at the Department of Surgery and Liver Transplantation of the Oswaldo Cruz University Hospital, University of Pernambuco, Brazil; between July 15, 2003 and July 14, 2009. Recipients of split-liver or sequential (domino) transplants were not eligible for this study as well as those patients with incomplete data in their medical records or transplanted because of fulminant hepatic failure. Finally, only patients suffering HCC were considered to this analysis. All of them were followed up to June 15, 2011. Descriptive statistics include non-cancerous donor-, receptor-, surgery- and center-related variables. MELD score was calculated using laboratory tests collected immediately prior to the LT with no adjustments to prioritize these patients on the waiting list. For descriptive analyses, we summarized the continuous variables using medians (interquartile range) and categorical variables as proportions. These variables were also compared between groups using Mann-Witney U test or chi-square tests. The survival probabilities were constructed using the Kaplan–Meier method.

Serum markers were used to confirm the diagnosis of viral hepatitis and the pre-operative diagnosis of HCC was based on Barcelona-2000 conference diagnostic criteria[9] and confirmed by explants pathology. Decision about LT was discussed in a multidisciplinary meeting considering the Milan criteria[10] and clinical parameters.

All procedures were performed by the same surgical team. Recipients of LT underwent hepatectomy with inferior vena cava preservation (*piggy-back* fashion) or conventional technique, both without veno-venous bypass. The use of conventional or *piggy-back* technique was the surgeon's choice based on anatomical and clinical findings. The pedicle elements were anastomosed using standard techniques. After LT, tacrolimus, mycophenolate (sodium or mofetil) and prednisone were used as immunosuppressive treatment, with no major changes in the protocols applied between 2003 and 2009. We weaned the patients off corticosteroids as soon as possible, based on clinical and laboratory evaluations

Non-cancerous variables were explored as medium-term (24 months) prognostic factors of patient survival using univariate and multivariate approachs. The association of each variable with post-LT survival was first tested using univariate Cox's model (continuous data) or log-rank test (categorical data). Then, factors whose association with survival showed a p-value < 0.20 were used in a multivariate Cox's proportional-hazards

model in order to identify the independent prognostic factor. We additionally adjusted this multivariate analysis for transplantation era (quartiles) and allocation criteria (chronologic vs. MELD). Median follow-up of alive patients was 44.6 months (Q_{25}=34.7–Q_{75}=51.6) and all of them was followed for at least 24-month in order to determine the primary endpoint (death).

The statistical analyses were performed using the STATISTICA Data Analysis Software System, Version 8.0 (Statsoft, Inc., Tulsa, OK, USA) and all analysis considered a two-tailed p-value of 0.01 as statistically significant. This study was registered in the Brazilian National System of Human Research – SISNEP (CAAE - 0003.0.106.000/10) and approved by the HUOC Ethics Research Committee (protocol number 12/2010). All procedures complied with the standards of Declaration of Helsinki and current ethical guidelines.

Results

From 15 July 2003 to 14 July 2009, 298 LT were performed in 288 patients at our Department. Two hundred-eight patients were initially selected, but only 61 received LT because a HCC diagnosis. Their baseline characteristics and descriptive statistics are summarized in Table 1.

Patient 3-, 6-, 12-, and 24-month overall cumulative survivals were 88.5%, 80.3%, 73.8%, and 65.6%, respectively (Figure 1A). Over the 94.5 months follow-up period, 26 liver allograft recipients died (42.6%) and none underwent re-transplantation. The main causes of death were infection, malignancy recurrent and liver failure/transplant rejection.

Our univariate analysis identified red blood cell transfusion (Exp[b]=1.26; p<0.01) and hepato-venous reconstruction method (84.6% vs. 51.4%; p<0.01) (figure 1, B) as significantly related to 24-month post-LT survival. The multivariate analysis demonstrated that hepato-venous reconstruction technique was an independent prognostic factor of medium-term post-LT survival after adjusted for transplantation era (Exp[b]=5.92; p<0.01) and allocation criterion (Exp[b]=5.45; p<0.01). We found a borderline statistical significance (Exp[b]=4.17; p=0.01) for this variable in the unadjusted multivariate analysis (Table 2).

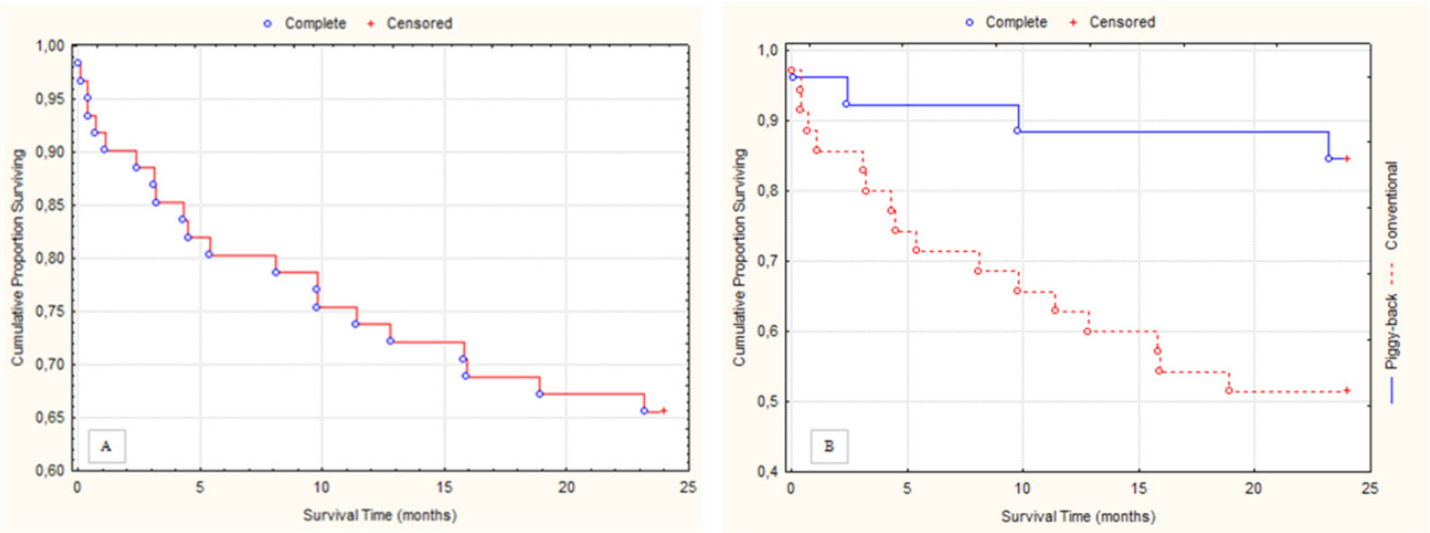

FIGURE 1 - Kaplan–Meier survival analysis (24 months) after liver transplantation to treatment of hepatocellular carcinoma. **A.** The 3-, 6-, 12- and 24-month overall cumulative survival were 88.5%, 80.3%, 73.8% and 65.6%, respectively. **B.** Analysis of patients stratified according to hepato-venous reconstruction technique showed higher cumulative survival amongst patient in which the *piggy-back* technique was applied (84.6% vs. 51.4%. p<0.01, by the log-rank test).

TABLE 1 - Baseline characteristics and descriptive statistics.

Variables	**Overall** (n=61)	**Hepato-venous reconstruction technique** median (interquartile range) or n (%)		**p-value**[1]
		Piggy-back (n=26)	Conventional (n=35)	
Recipient Variables				
Recipient Age (years)	58 (53-64)	59 (55-66)	58 (52-62)	0.14
MELD Score	13 (10-15)	12 (9-15)	13 (10-15)	0.11
Gender				
Male	54 (88.5)	22 (84.6)	32 (91,4)	0.44[2]
Female	7 (11.5)	4 (15.4)	3 (8.6)	
ABO Blood Group				
A	26 (42.6)	10 (38.5)	16 (45.7)	
B	5 (8.2)	3 (11.5)	2 (5.7)	0.99
AB	2 (3.3)	1 (3.8)	1 (2.9)	
O	28 (45.9)	12 (46.2)	16 (45.7)	
Child-Pugh Class				
A	28 (45.9)	13 (50)	15 (42.9)	0.83
B	24 (39.3)	11 (42.3)	13 (37.1)	
C	9 (14.8)	2 (7.7)	7 (20)	
Diagnosis				
Hepatitis C virus	32 (52.5)	17 (65.4)	15 (42.9)	0.13[4]
Others[3]	22 (47.5)	9 (34.6)	20 (57.1)	
Donor and Center Variables				
Monthly Transplants Rate	6 (5-8)	6 (5-8)	5 (4-8)	0.77
Donor Age (years)	40 (27-50)	42.5 (28-52)	38 (26-44)	0.20
Cold Ischemia (hours)	6.1 (5.3-8.4)	5.8 (5.2-8.1)	6.4 (5.6-9.4)	0.10
Warm Ischemia (minutes)	45 (39-50)	40 (35-45)	48 (43-51)	<0.01*
Red Blood Cells Transfusion (units)	6 (1-4)	2 (0-3)	2 (1-5)	0.25
Platelets Transfusion (units)	0 (0-10)	0 (0-10)	0 (0-10)	0.59
Temporal Variables				
Liver Allocation Criterion				
Chronologic (7/15/2003 – 7/14/2006)	10 (16.4)	2 (7.7)	8 (22.8)	0.16[2]
Pos-MELD (7/15/2006 – 7/14/2009)	51 (83.6)	24 (92.3)	27 (77.2)	
Transplantation Era (quartiles)[5]				
First Era (7/15/2003 – 9/22/2005)	6 (9.8)	1 (3.8)	5 (14.3)	
Second Era (9/23/2005 – 8/22/2007)	19 (31.2)	9 (34.6)	10 (28.6)	0.80
Third Era (8/23/2007 – 8/21/2008)	25 (41)	13 (50)	12 (34.3)	
Forth Era (8/22/2008 – 7/14/2009)	11 (18)	3 (11.6)	8 (22.8)	

TABLE 2 - Non-cancerous prognostic factors (24-months survival) of hepatocellular carcinoma after liver transplantation.

Variables	Univariate [6]	Multivariate [7]
		Unadjusted Allocation Criterion Transplantation Era
Diagnostic Categories[8]	0.88	– – –
ABO Blood Group	0.51	– – –
Receptor Gender	0.14	0.05 0.05 0.03
Receptor Age	0.32	– – –
MELD Score	0.35	– – –
Child-Pugh Class	0.02	0.45 0.42 0.37
Donor Age	0.91	– – –
Cold Ischemia Time	0.07	0.17 0.59 0.44
Warm Ischemia Time	0.39	– – –
Red Blood Cells Tranfusion	<0.01	0.02 0.07 0.14
Platelets Transfusion	0.02	0.15 0.06 0.06
Monthly Transplant Rate	0.46	– – –
Hepato-venous Reconstruction	<0.01	0.01 <0.01 <0.01

Discussion

Standard surgical management of patients with HCC includes locoregional ablation, surgical resection or liver transplantation, depending on the status of the liver[2]. However, LT has been considered the treatment of choice for patients suffering of HCC, mainly due to its increasing rates of survival, lower rate of recurrence and preventing the emergence of new tumors (second primary tumors) by removing the cirrhotic liver[6,11,12].

Exploring prognostic factor offers the opportunity to predict outcomes and may serve to improve the treatment for HCC patients who received ortothopic LT. By far, their main determinants of outcome have repeatedly been found to be lymphovascular invasion and poor differentiation, which reflects the biological aggressiveness of tumor[2,13-17]. Similarly, pre-transplantation treatments have been also described as prognostic factors of survival for this malignancy[15,18]. However, there is a lack of evidence if non-cancerous factors, beyond those described above, influence survival outcomes of HCC patient after LT.

The prognosis for HCC patients is usually very poor, unless patients can be identified at an early stage with preserved liver functions[19,20]. On the other hand, based in the MELD score, we did not confirm the critical role of cirrhosis severity for post-LT survival of HCC patients. This finding probably occurred because a large proportion of these patients do not have severe liver disease at the time of LT[21-23], when the effect of their hepatic dysfunction may not be clinically relevant to translate into a survival outcome[24,25]. Accordingly, because HCC patients exhibit better liver function than non-HCC at the time of LT[18,21,22,25,26], this preserved liver function may also attenuate the negative impact of transfusion-related immunomodulation (TRIM syndrome)[27] on survival of patients with HCC and may explain our divergent results previously published, where red blood transfusion was found as a independent prognostic factor of survival into a sample including HCC and non-HCC patients[21].

If survival of HCC patients is influenced by the etiology of the liver disease or patient sex remains controversial. According to our data, concurrent hepatitis C virus diagnosis and patient sex, do not appear significantly influencing survival of HCC patients after LT, in agreement with some previous data[23,29]. On the contrary, female patients and some liver disease may provide better prognosis to patients with HCC, but this is possibly more because of higher compliance with surveillance than to real biological differences[28,29]. Moreover, some of others donor-, receptor-, surgery- and center-related factors (i.e.: donor age, cold ischemia time, MELD score and hemocomponents transfusion)

commonly linked to post-LT survival in general[30-35], were not confirmed as significant prognostic factors of survival for HCC patients in this study.

Surprisingly, the *piggy-back* hepato-venous reconstruction technique appeared independent and positively influencing the medium-term survival in this study. This approach has been suggested as an alternative to the conventional method of LT and has become the preferred approach in many transplantation centers[36]. In a recent systematic review from Cochrane Database, the authors did not find significant difference in post-operative mortality, primary graft non-function, vascular complications, renal failure, transfusion requirements, intensive therapy unit or hospital stay between the conventional vs. *piggy-back* hepato-venous anastomosis. Nevertheless, this alternative technique was related to shorter warm ischaemic time and higher proportion of patients who developed chest complications. Nowadays, there is currently no clear evidence to recommend or refute the use of *piggy-back* method[37].

In randomized Brazilian reports, the *piggy-back* approach was related to higher rate of pulmonary infiltrates[38], but not to bacterial translocation[39] or stimuli for the production of inflammatory molecules[40], when compared to the conventional method. However, until publication of this study, there were no trials comparing *piggy-back* with conventional method without veno-venous bypass[37]. In our Department, our learning curve evolved initially with this last, which is performed with recognized swiftness and has been preferred whenever technical difficulty arose during performance of the hepatectomy[41]. Thus, also because same regional socio-economic limitations (i.e.: IDH=0.7), we have accumulated considerable experience with the management of marginal grafts[42,43] and use of conventional technique without veno-venous bypass[21,41,44]. On the other hand, the *piggy-back* approach has been increasingly used at our Department because lower surgical and warm ischemia times, red blood cells and plasma transfusions, as well as lower 30-day mortality and better 1-year cumulative survival[41].

The *piggy-back* technique has been suggested to be avoided in patients with HCC because an theoretical increased risk of a positive vena cava margin and the potential for metastatic spread of tumor in the native vena cava or through the hepatic veins, as well as because an increased operative manipulation of the diseased organ in this approach[45]. However, it remains controversial if the *piggy-back* technique violates the surgical cancer principles or if it matter in an organ transplantation settings[46]. Comparing survival outcomes in recipients with HCC who underwent liver transplantation using the *piggy-back* or conventional approachs, Mangus and colleagues[45] found statistically similar survival for both techniques, suggesting the presence of HCC in liver transplant patients should not preclude the use of *piggy-back* approach. However, only 19 patients in that study underwent a *piggy-back* approach vs. 119 who were transplanted by the conventional technique. Moreover, as resection for HCC seems to follow the surgical cancer principles, further studies comparing techniques of liver transplantation for patients with HCC must be conducted in order to elucidate this important issue[46].

In this sample, despite some differences in variables, only warm ischemia time was statistically significantly different between *piggy-back* vs. conventional techniques; however, this potential confounding factor did not significantly correlated with survival amongst HCC patients. Thus, how *piggy-back* technique may influence survival in HCC patients after LT or if this influence may supplant the cancer-related factors in a long-term follow-up remains unclear. Based in these findings, we are now planning a prospective trial (including cancer-related variables) in order to determine the best surgical approach for HCC patients.

Herein we have reviewed our experience with HCC patients underwent deceased donor orthotopic LT to explore if some non-cancerous factors (i.e.: donor-, receptor-, surgery- and center-related factors) impact on their survival. Notably, our sample has some special characteristics: first, the same surgical team performed all procedures using standard techniques without veno-venous bypass; second, our own database has been prospectively maintained and continuously updated. Lastly, our sample presented a better balanced proportion between *piggy-back* vs. conventional groups than previously reported[45].

In line with recent recommendations and practice in observational research[47], all analysis of this study considered a p-value of 0.01 to denote statistical significance. Furthermore, instead of categorising continuous variables, we prefer to keep them continuous in order to minimize some loss in the statistical power of our analysis and the occurrence of residual confounding factors[48,49]. Similarly, because a significant increase in the number of patients transplanted to treat HCC in our Department as result of MELD allocation policy and because better survival outcomes observed in the most recent periods of our transplantation activities, probably due to governmental efforts to encourage organ transplantation[21]; we also adjusted our multivariate analysis for the allocation criteria (chronologic vs. MELD) and transplantation eras (quartiles). In this approach, separate regression models were first fit to each group and the log-likelihoods for those models were summed up. This log-likelihood was then compared to that of the overall model (collapsed across groups).

We also point that analysis of additional donor-related variables may provide additional information, especially because a large proportion of extended-criteria donors were used at our Department[21,34,42,43]. However, despite our relative small sample size, the main scientific merit of this report was to add some evidence to determine if the surgical approach influence survival outcomes of HCC patients after LT. Our data suggests further studies are necessary to determine whether piggyback hepato-venous anastomosis should be preferred for patients candidate to LT because HCC.

Conclusion

The *piggyback* hepato-venous reconstruction technique was related to improved medium-term survival of hepatocellular carcinoma patients after liver transplantation in this northeast Brazilian sample.

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(Footnotes)
1. Comparisons between *piggy-back* vs. conventional techniques using the *Mann-Witney U* test for continuous variables or chi-square tests for categorical variables.
2. Fischer's exact test.
3. Categories were not mutually exclusive, so multiple diagnoses were possible.
4. Yates's correction.
5. Each era included 52 consecutive LT, but only those performed to treat HCC patient were counted.
* Statistically significant ($p<0.01$).
6. Univariate analysis using the log rank test (categorical data) or the Cox-proportional hazards model (continuous data).
7. Multivariate analysis using the Cox-proportional hazards model. This analysis was also adjusted to allocation criterion (Chronologic vs. MELD) and transplantation era (quartiles).
8. HCV vs. Non-HCV patients.