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CLINICAL RESEARCH

Prognostic value of ^{13}C-phenylalanine breath test on predicting survival in patients with chronic liver failure

I Gallardo-Wong, S Morán, G Rodríguez-Leal, B Castañeda-Romero, R Mera, J Poo, M Uribe, M Dehesa

I Gallardo-Wong, S Morán, G Rodríguez-Leal, Laboratory of Gastrohepatology Research, CMN Siglo XXI, Mexican Institute of Social Security, Mexico
B Castañeda-Romero, M Dehesa, Gastroenterology Departament, CMN Siglo XXI, Mexican Institute of Social Security, Mexico
R Mera, Department of Pathology, Louisiana State University Health Sciences Center, New Orleans, Louisiana, United States
J Poo, M Uribe, Hospital Médica Sur, Mexico
Supported by CONACYT and FOFOI-IMSS, Mexico
Correspondence to: Segundo Moran, MD, Laboratory of Gastrohepatology Research, Hospital de Pediatría, CMN, Siglo XXI, IMSS. Av Cuauhtémoc 330, Colonia Doctores, Delegación Cuauhtémoc, CP 06720, Mexico. segundomoran@hotmail.com
Telephone: +52-55-56276900 Fax: +52-55-57610952
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Abstract

AIM: To evaluate the prognostic value of percentage of ^{13}C-phenylalanine oxidation (^{13}C-PheOx) obtained by ^{13}C-phenylalanine breath test (^{13}C-PheBT) on the survival of patients with chronic liver failure.

METHODS: The hepatic function was determined by standard liver blood tests and the percentage of ^{13}C-PheOx in 118 chronic liver failure patients. The follow-up period was of 64 mo. Survival analysis was performed by the Kaplan-Meier method and variables that were significant ($P < 0.10$) in univariate analysis and subsequently introduced in a multivariate analysis according to the hazard model proposed by Cox.

RESULTS: Forty-one patients died due to progressive liver failure during the follow-up period. The probability of survival at 12, 24, 36, 48 and 64 mo was 0.88, 0.78, 0.66, 0.57 and 0.19, respectively. Multivariate analysis demonstrated that Child-Pugh classes, age, creatinine and the percentage of ^{13}C-PheOx (HR 0.338, 95% CI: 0.150-0.762, $P = 0.009$) were independent predictors of survival. When Child-Pugh classes were replaced by all the parameters of the score, only albumin, bilirubin, creatinine, age and the percentage of ^{13}C-PheOx (HR 0.449, 95% CI: 0.206-0.979, $P = 0.034$) were found to be independent predictors of survival.

CONCLUSION: Percentage of ^{13}C-PheOx obtained by ^{13}C-PheBT is a strong predictor of survival in patients with chronic liver disease.

Key words: ^{13}C-phenylalanine breath test; Liver cirrhosis; Chronic liver failure; Survival

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INTRODUCTION

The identification of patients with poor prognosis is of crucial importance, especially since liver transplantation has emerged as an important therapy for patients with advanced cirrhosis[1]. The exact prediction of survival for an individual patient with cirrhosis is not easy. This may be one of the reasons to explain why so many studies have investigated factors which predict survival of these patients[2-4].

In recent years, growing interest has been devoted to the quantitative liver function tests, as they are expected to increase the accuracy of estimating the severity of liver disease; however, several studies on their prognostic value have shown contradictory results[5-8].

C-phenylalanine oxidation (^{13}C-PheOx) is a valuable indicator of liver function. It represents the cytosolic enzyme activity, is a non-invasive test, easy to perform and distinguishes patients with various degrees of liver disease from otherwise healthy persons. Some studies have shown that the severity of liver cirrhosis correlates with the suppression of $^{13}CO_2$ recovery after a dose of phenylalanine; other studies have reported that as liver function worsens, as defined by the Child-Pugh (CP) score, so does the phenylalanine metabolism[9-14]. Nowadays, the CP score is still the most widely used tool to estimate the severity of liver disease in patients with cirrhosis and to predict survival.

The prognostic value of ^{13}C-phenylalnine breath test (^{13}C-PheBT) for survival in patients with chronic liver disease is yet to be established. Therefore, the aim of this study was to evaluate the prognostic value of percentage of ^{13}C-PheOx obtained by ^{13}C-PheBT for the survival of patients with chronic liver failure.

MATERIALS AND METHODS

Patients

Consecutive patients with chronic liver failure were studied at the Laboratory of Gastro-Hepatology of Centro Médico Nacional Siglo XXI. The study was approved by the Ethical Committee of the hospital. Patients were included according to the following criteria: age above 18 years, both genders; diagnosis of chronic liver failure based on history, clinical and biochemical findings combined with ultrasonographic results, plus liver biopsy when possible; and written informed consent of patients when entering the study. Exclusion criteria were pulmonary alterations, neurologic diseases different to encephalopathy; participation in other studies during the preceding thirty days of this study; and presence of other diseases conditioning a short prognosis by themselves (e.g. carcinoma). According to these criteria, 121 patients were selected from a group of 136 patients with chronic liver disease after having excluded 9 patients with hepatocellular carcinoma, 5 patients because of their unwillingness to participate and one patient with a percentage of ^{13}C-PheOx > 17.

The etiology was defined on the basis of the history obtained from patients and their relatives and serological tests for viruses. The cause of liver disease was chronic alcohol consumption (≥ 30 g/d for 2 years or more) in 23 (19.5%) patients, chronic type-C hepatitis/HVC in 56 (47.5%), mixed (viral + alcohol) in 8 (6.8%) and other causes (cryptogenic, autoimmune, Budd Chiari syndrome, primary biliary cirrhosis, chronic type-B hepatitis/HBV-related cirrhosis and idiopathic) in 31 (26.3%). No patients had hemochromatosis or Wilson's disease.

Methods

All patients were studied following the same protocol with data collected by the laboratory staff and were followed up either as outpatients or inpatients when necessary, according to general medical practice. Survival time was accounted until March 2005. The hepatic function was evaluated by ^{13}C-PheBT and standard liver blood tests. All patients were classified by the CP score as class A (5-6 points), class B (7-9 points) or class C (10-15 points)[15]. This classification comprises albumin, total bilirubin (TB), prothrombin time (PT), ascites and encephalopathy. Ascites was classified as "absent" or "present" according to clinical examination and ultrasonographic findings. The clinical diagnosis and degree of encephalopathy were determined according to the West-Haven criteria[16]. Other tests were alanin transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (AP), creatinine and glucose. Biochemical data were evaluated by standard clinical chemical methods (Dimension, ARXL-Max DADE®, Boehringer, Germany).

^{13}C-PheBT was measured following an overnight fast without control of prior dietary intake. A 100-mg oral dose of L-[1-^{13}C] phenylalanine-isotopic purity 99% ^{13}C (Isotec® Inc, Ohio, USA)-dissolved in 50 mL water was administered. Alveolar breath samples were collected while in resting position and following a normal exhalation. At each sample time, patients were asked to blow directly into a 10-mL exetainer tube (Labco Limited®, Buckinghamshire, U.K.) through a straw. Duplicate breath samples were taken before administration of the ^{13}C-phenylalanine dose (basal), and every 10 min thereafter until completion of 1 h. Enrichment of $^{13}CO_2$ was determined by isotope ratio mass spectrometry (BreathMat-plus® Finnigan Bremen, Germany). The rate of hepatic ^{13}C-phenylalanine oxidation at each time point was calculated from the appearance of $^{13}CO_2$ on exhaled air, assuming a CO_2 production rate of 300 mmol/m^{-2} body surface area per hour, as described by Shneider *et al*[17]. The analytical data were expressed as percentages of the ^{13}C-phenylalanine dose metabolized per hour (percentage of ^{13}C-phenylalanine oxidation/^{13}C-PheOx)[10-12]. The day when patients first presented for the registration of clinical and laboratory data and the measurement of ^{13}C-PheBT was considered as "zero time" for the follow-up period of observation.

Statistical analysis

Results were expressed as percentages and mean ± SD. Receiving operating characteristic (ROC) analysis was used to define the optimal percentage of ^{13}C-phenylalanine oxidation cut-off point with the highest sensitivity and specificity among thresholds. The analysis was carried out in two steps. To identify independent prognostic variables, a univariate analysis was performed with the Kaplan-Meier statistics. The curves were compared using the log-rank test. During the first stage, covariates analyzed for inclusion in the model were age, sex, etiology, pharmacologic treatment, previous hemorrhage, creatinine, glucose, ^{13}C-phenylalanine oxidation, CP score and complications. Variables that were significant ($P < 0.10$) in the univariate analysis were subsequently introduced in a multivariate analysis. Then each chosen covariate was reconsidered and eliminated if $P > 0.05$. The procedure was performed stepwise until no further covariates could be added or removed according to the afore-mentioned criteria.

In a second step, the same Cox model analysis was performed substituting the CP score with the five variables (albumin, bilirubin, prothrombin time, ascites and encephalopathy) that define the score.

To check the proportionality of the hazard in time for the different functional classes, log of the cumulative hazard was plotted against time, demonstrating a parallel behavior in patients with low and high values for the selected predicting covariates when inspected. The goodness of fit of the model was investigated by a partial likelihood function and the Akaike's information criterion (AIC). The decision to include or to exclude the respective regressor variables was based on a χ^2 test[18-20]. Statistical analysis was carried out by using the STATA V 8.0 statistical package (StataCorp LP, College Station, Tex).

RESULTS

One hundred and twenty-one consecutive patients with chronic liver failure were included. Cirrhosis was confirmed by liver biopsy in 35 (28.9%) cases, and the constellation of typical physical signs, such as ascites, oesophageal varices, upper gastrointestinal bleeding, and

Table 1 Characteristics of 118 patients with chronic liver failure (n = 118, mean ± SD)

Variables	Surviving n = 77	Non-surviving n = 41	P value
Age (yr)	51.8 ± 10.6	55.8 ± 9.6	0.043
Sex (F/M)	49/28	22/19	0.292
Etiology			
Alcoholic/others	15/62	8/33	0.997
Alcohol consumption	38	18	0.573
Pharmacological treatment	71	41	0.067
History of upper GI hemorrhage	53/24	28/13	0.952
Ascites	26	24	0.010
Encephalopathy	7	6	0.360
Albumin (g/L)	34 ± 6.0	29 ± 46	0.000
Total bilirubin (mmol/L)	27.4 ± 17.1	58.1 ± 99.2	0.059
Prothrombin time (%)	76.2 ± 18.9	67.6 ± 25.1	0.058
ALT (nkat/L)	1.2 ± 1.14	0.99 ± 0.81	0.247
AST (nkat/L)	1.3 ± 0.99	1.63 ± 0.81	0.370
AP (nkat/L)	4.18 ± 3.38	4.50 ± 3.41	0.623
Creatinine (mmol/L)	13.7 ± 3.4	22.2 ± 30.8	0.100
Glucose (mmol/L)	6.3 ± 2.4	5.8 ± 1.2	0.216
Child Pugh class			
Class A	45	6	
Class B	23	26	0.000
Class C	9	9	
Child-Pugh score (points)	6.7 ± 1.9	8.3 ± 2.1	0.000
^{13}C-phenylalanine oxidation (%)	4.9 ± 2.9	3.8 ± 2.2	0.027

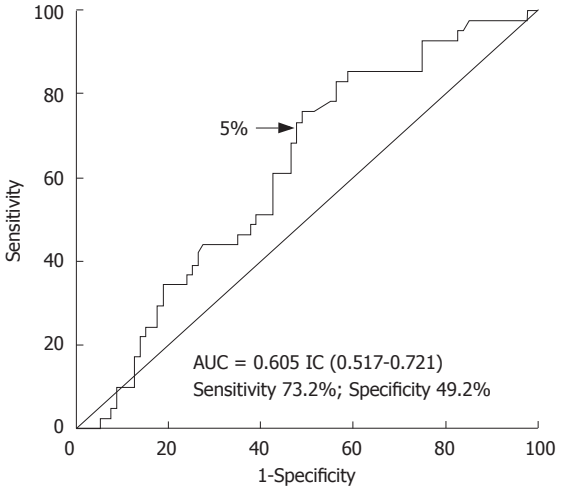

Figure 1 (ROC) curve for percentage of ^{13}C-phenylalanine oxidation in predicting mortality (The optimal cut off point with the highest sensitivity and specificity for survival in 118 patients with chronic liver failure was 5.0%).

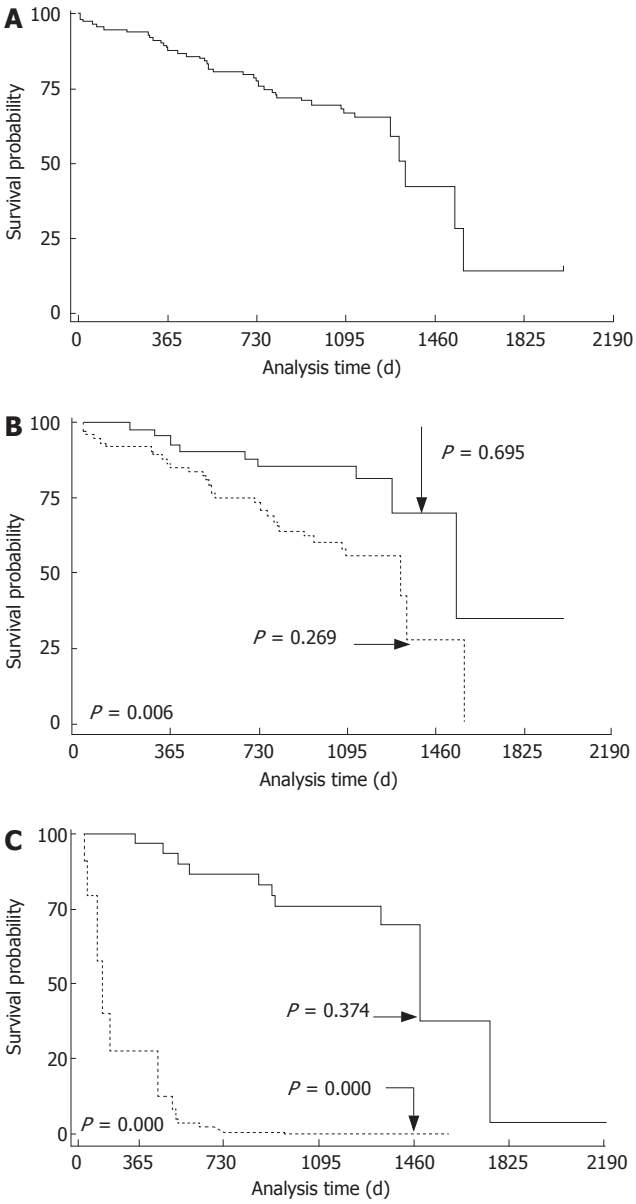

Figure 2 Kaplan-Meier statistics for survival probability. **A:** All patients; **B**: Percentage of ^{13}C-phenylanine oxidation; **C:** Percentage of ^{13}C-phenylanine oxidation adjusted for covariables (age < 60 years and ⩾ 60 years, albumin, total bilirubin and creatinine). *P* values are given by nonparametric log-rank test.

typical laboratory findings, was accepted as evidence of chronic liver failure in the other 86 (71.0%) patients. During the follow-up period, 44 (20 males, 24 females) patients died. Causes of death were liver failure in 9 (7.6%) patients, upper gastrointestinal bleeding in 10 (8.5%), ascites in 6 (5.1%) and encephalopathy in 8 (6.8%) associated to liver failure, hepatorenal syndrome in 4 (3.4%) and hepatocellullar carcinoma in 4 (3.4%), whereas 3 patients died of other causes (accident, transplant surgery and gastric cancer). These three patients were excluded from the further analysis.

Table 1 depicts the demographic and clinical data, biochemical features and liver function tests of patients. The ROC curves showed that the optimal percentage of ^{13}C-PheOx cut-off value for predicting survival in liver disease patients was 5.0% (sensitivity 73.2%; specificity 49.3%) (Figure 1). Serum albumin, total bilirubin and PT were clustered on the basis of the CP score. Ascites and encephalopathy were clustered as "absent" or "present". The median probability of survival after entering the study in all the included patients was 1316 d (Figure 2A). The correlation between the percentage of C-PheOx (< 5.0% and ⩾ 5.0%) and survival was highly significant ($P < 0.006$; Figure 2B). Likewise, the results of this study confirmed that percentage of ^{13}C-PheOx was correlated with the CP score ($r = -0.255$, $P = 0.005$).

Eleven of the twenty investigated variables showed an independent association to poor prognosis in the univariate analysis. The variables: albumin ($P < 0.000$), total bilirubin ($P < 0.000$), prothrombin time (%) (PT) ($P < 0.000$), creatinine ($P < 0.000$), ascites at follow-up ($P < 0.000$),

Table 2 Variables with an independent prognostic value, as indicated by two Cox's models in patients with chronic liver failure (n = 118)

Variables	Coefficient	Hazard ratio[1]	SE	95% CI	P value
1					
Albumin (g/L)	-1.254	0.285	0.085	0.158-0.512	0.000
Total bilirubin (mmol/L)	0.149	1.161	0.051	1.065-1.265	0.001
Creatinine (mmol/L)	0.510	1.666	0.263	1.222-2.270	0.001
Age					
≤ 60 yr	1.000[2]				
> 60 yr	0.765	2.150	0.779	1.056-4.377	0.035
^{13}C cumulative dose					
< 5.0%	1.000[2]				
≥ 5.0%	-0.798	0.449	0.178	0.206-0.979	0.044
2					
Child Pugh class					
A	1.000[2]				
B	1.629	5.099	2.382	2.040-12.743	0.000
C	2.078	7.993	4.627	2.570-24.859	0.000
Creatinine (mmol/L)	0.417	1.518	0.200	1.173-1.966	0.002
Age,					
≤ 60 yr	1.000[2]				
> 60 yr	1.029	2.799	1.044	1.347-5.816	0.006
^{13}C cumulative dose					
< 5.0%	1.000[2]				
≥ 5.0%	-1.081	0.338	0.140	0.150-0.762	0.009

[1]Hazard ratio of Cox's proportional hazard regression; [2]Reference category.

complications at follow-up (P < 0.000), encephalopathy at follow-up (P = 0.012), upper gastrointestinal bleeding at follow-up (P = 0.015), age (P = 0.034) AST (P = 0.081) and ascites when entering the study (P = 0.042). The variables with no independent association to prognosis: ALT (P = 0.135), patients' entry to the hospital at follow-up (P = 0.146), AP (P = 0.198), treatment of portal hypertension (P = 0.213), history of encephalopathy (P = 0.424), gender (P = 0.437), history of upper gastrointestinal bleeding (P = 0.464), etiology (P = 0.478) and alcohol consumption (P = 0.804).

The multivariate analyses demonstrated that the Child-Pugh classes, age (< 60 years and ≥ 60 years), creatinine and the percentage of ^{13}C-PheOx were independent predictors of survival. When the Child-Pugh classes were replaced by all the parameters of the score, only albumin, bilirubin, creatinine, age < 60 years and ≥ 60 years, and the percentage of ^{13}C-PheOx were found to be independent predictors of survival. Etiology of liver disease, gender, history of gastrointestinal bleeding, ascites, encephalopathy and prothrombin time were not significant predictors of survival after adjusting for the other explanatory variables on the model. Statistical parameters for the variables included in the final Cox model are depicted in Table 2. The first Cox's model included significant variables contained in Child-Pugh score and the second model included Child-Pugh classes.

A prognostic index (PI) predicting death was derived from the best model as: PI = exp (-0.798 × ^{13}C-PheOx) + (0.765 × age) + (-1.25 × albumin) + (0.149 × bilirubin) + (0.510 × creatinine). We attributed a value of 0 for ^{13}C-PheOx < 5% and 1 for ^{13}C-PheOx ≥ 5%, 0 for male sex and 1 for female sex, 0 for age < 60 years and 1 for age ≥ 60 years. The relationship between PI due to the best adjusted model and risk of death were compared with a PI for percentage of ^{13}C-PheOx (Figure 2C). The ROC curve for PI of adjusted model for predicting death from liver failure always depicted a better performance than that obtained from percentage of ^{13}C-PheOx alone (Figure 3). Areas under the curve were also significantly larger (AUC = 0.822, 95% CI: 0.748-0.896 *vs* AUC = 0.605; 95% CI: 0.501- 0.708, P = 0.000).

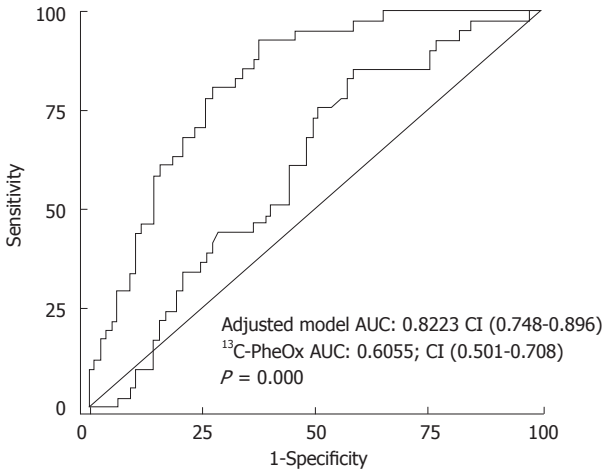

Figure 3 (ROC) curve for percentage of ^{13}C-phenylalanine oxidation and percentage of ^{13}C-phenylalanine oxidation adjusted for age (age < 60 years and ≥ 60 years), albumin, total bilirubin and creatinine in predicting mortality (n = 118).

DISCUSSION

This study shows that the percentage of ^{13}C-PheOx is an important prognostic factor of long-term survival in patients with chronic liver failure. In fact, values lower than 5.0% for the percentage of ^{13}C-PheOx were associated with an elevated probability of dying and values over 5.0% were associated with a better outcome (probability 0.26 *vs* 0.69 at 48 mo and 0.00 *vs* 0.37 at 64 mo). In addition, predictive value was conserved even after adjusting for covariates (Figure 2B-C). Furthermore, percentage of ^{13}C-PheOx added new prognostic information to that obtained by CP classification or the common clinical and biochemical data included in the CP score. The results of this study additionally confirm that percentage of ^{13}C-PheOx correlates inversely with the CP score (r = -0.2550, P = 0.0053). These data are consistent with other studies showing that ^{13}C-PheBT correlates with parameters reflecting the severity of hepatic diseases, including albumin, total bilirubin, PT and CP score[12,21-24].

Additionally, some studies have documented that percentage of ^{13}C-PheOx values are significantly lower in patients with liver cirrhosis than in healthy adults[12,14,23]. It has also been suggested that the decreased ability of decompensated livers to oxidize phenylalanine may be the result of progressive liver damage, individual cellular function; low activities of phenylalanine hydroxylase (PAH) and p-hydroxyphenylpiruvate hydroxylase; the severity or the course of liver disease that produced a decrease

in the total number of cells and the functioning liver cell mass with a consequent reduction in phenylalanine metabolism[10,12,14,23]. Likewise, the percentage of ^{13}C-PheOx in patients with cirrhosis was estimated to be 20% of the normal value, suggesting that reduced enzyme levels account for a decreased metabolism in phenylalanine[13]. Hehir *et al*[9] described that the fractional clearance rates of aromatic amino acids in plasma of patients with acute fulminant liver disease are 2 to 10 times lower than those in normal subjects.

Other authors have demonstrated that ^{13}C-PheBT is used to monitor the clinical course of patients with chronic liver failure[13,25], as a clinical predictor to assess postoperative early complications in patients undergoing hepatectomy[26] or to evaluate the restoration of the plasmatic phenylalanine clearance to normal during the postoperative period that is attributed to the ability of the new liver to catabolize this amino acid[9]. In an experimental model, ^{13}C-PheBT was used to monitor the hepatic dysfunction associated with obstructive jaundice[27]. However, there is scarce information on the prognostic value of ^{13}C-PheBT with regard to the survival of patients with cirrhosis. Our study suggests that the percentage of ^{13}C-PheOx adds new prognostic information to that obtained by the CP score or the common clinical and biochemical data included in the CP score. Nevertheless, discrepant results were recently obtained by Koeda *et al*[24] who could not demonstrate a correlation of ^{13}C-PheBT with mortality. They examined 23 patients with liver cirrhosis, 6 of them died of hepatic dysfunction in a follow-up period of 816 d. The lack of significance of ^{13}C-PheBT in their study may have probably related, at least in part, to the fact that less end-points were analyzed. It has been clearly established that the number of end-points heavily influences the ability to detect significant effects[24,2].

In contrast to previous reports, ^{13}C-PheOx constituted an important prognostic index in our series. In fact, mortality due to liver-related causes was best predicted by a prognostic index containing albumin, bilirubin, creatinine, age, and ^{13}C-PheBT than by a prognostic index containing the CP score, creatinine, age and ^{13}C-PheBT, as assessed by a partial likelihood function and the Akaike's information criterion (AIC). However, there are no more data available on the prognostic value of ^{13}C-PheOx.

A limitation in our study could be that it was not possible to calculate a model for end-stage liver disease (MELD)[28] because we did not perform the international normalized ratio of prothrombin time (INR) in all patients. MELD score is superior to CP score as a predictor of intermediate mortality is unclear[29].

Even when the use of ^{13}C-breath tests with various substrates is not a novelty in hepatology, the clinical usefulness of these tests that explore the hepatocellular subfunctions (microsomal, cytosolic or mithocondrial) as well as the superiority of some quantitative prognostic liver function tests compared with the CP score are still unclear[30,31].

Amynopyrine breath test (ABT) has been used to predict short-term prognosis and mortality in patients with alcoholic hepatitis. There are contradictory results of ABT for predicting survival in patients with cirrhosis. Some studies showed that ABT is better than the Child-Turcotte score, whilst others demonstrate that ABT is not better. However, some other studies seem to provide additional prognostic information to the CP score[31-34].

Galactose elimination capacity (GEC), a valuable indicator of liver function, is dependent on hepatic blood supply and inhibited by alcohol consumption. It has been demonstrated that GEC adds some more prognostic information when the CP score is not included; whereas, other studies reported that, GEC is unable to improve the prognostic ability of GEC[8,35-37].

The caffeine breath test (CBT) represents a valid indicator of plasma caffeine clearance (CC) and correlates with the varying degrees of liver dysfunction. However, both tests do not appear to add prognostic information beyond that provided by the CP classification. CBT and CC may decrease with increasing age, cigarette smoking and disease state[38-40].

Indocyanine green elimination (IGC) provides some prognostic information related to survival of patients with cirrhosis, but does not improve the predictive ability of clinical information considered for the CP score. It is also sensible to hepatic blood flow, and adversely affected by cardiovascular drugs (calcium channel blockers) and is significantly reduced after portosystemic shunting[6,8,41,42].

On the other hand, the interest in search for accurate prognostic tests for patients with chronic liver disease is still of utmost importance since the emergence of liver transplantation is an important therapy for patients with advanced cirrhosis[1].

In conclusion, ^{13}C-PheBT is a strong predictor of survival in patients with chronic liver failure that adds information which may not be available from the common clinical and biochemical data included in the CP score for the assessment of the risk of death due to liver disease. Should these data be confirmed in other studies and different settings, the ^{13}C-PheBT could prove to be a useful clinical tool to routinely evaluate the prognosis of patients with chronic liver disease in addition to the common clinical and biochemical data, because of its non-invasiveness and safety.

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COMMENTS

Background

In recent years, there has been a growing interest in quantitative liver function tests, including breath tests, since they are expected to increase the accuracy of estimating the severity of liver disease. L-[1-^{13}C] phenylalanine breath test ^{13}C-PheBT distinguishes patients with various degrees of liver disease from healthy persons. However, the prognostic value of ^{13}C-PheBT for survival of patients with chronic liver disease is yet to be established.

Research frontiers

Even when the use of ^{13}C-breath tests with various substrates is not a novelty in hepatology, the clinical usefulness of these tests that explore the hepatocellular subfunctions (microsomal, cytosolic or mithocondrial) and measure of hepatocyte

functional capacity in liver diseases as well as the prognostic value of ^{13}C-breath tests compared with the Child-Pugh (CP) or model for end-stage liver disease (MELD) are still unclear.

Innovations and breakthroughs

The current study provides evidence that ^{13}C-PheBT is a strong predictor of survival in patients with chronic liver failure and adds information which may not be available from the common clinical and biochemical data included in the CP score for the assessment of the risk of death due to liver disease.

Applications

^{13}C-PheBT could prove to be a useful clinical tool to routinely evaluate the prognosis of patients with chronic liver disease in addition to the common clinical and biochemical data, because of its non-invasiveness and safety.

Terminology

L-[1-^{13}C] phenylalanine breath test measures hepatocyte functional capacity by estimating the oxidation of L-[1-^{13}C] phenylalanine and represents the hepatic cytosolic enzyme activity.

Peer review

This manuscript describes the prospective evaluation of ^{13}C-phenylalanine breath test in the evaluation of prognosis in cirrhotic patients.

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