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# Waiting list for liver transplantation: clinical and economic burden

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**ABSTRACT – Background** – Burden of disease is an indicator that relates to health status. United States and European epidemiological data have shown that the burden of chronic liver disease has increased significantly in recent decades. There are no studies evaluating the impact of complications of chronic liver disease on the waiting list for deceased donor liver transplantation (LTx). **Objective –** To determine the clinical and economic burden of complications of liver disease in wait-listed patients from the perspective of a transplant center. **Methods** – The study retrospectively analyzed medical records of 104 patients wait-listed for deceased donor LTx from October 2012 to May 2016 and whose treatment was fully provided at the study transplant center. Clinical data were obtained from electronic medical records, while economic data were collected from a hospital management software. To allocate all direct medical costs, two methods were used: full absorption costing and micro-costing. **Results –** The most common complication was refractory ascites (20.2%), followed by portosystemic encephalopathy (12.5%). The mean number of admissions per patient was 1.37±3.42. Variceal hemorrhage was the complication with longest median length of stay (18 days), followed by hepatorenal syndrome (13.5 days). Hepatorenal syndrome was the costliest complication (mean cost of $3,565), followed by portosystemic encephalopathy ($2,576) and variceal hemorrhage ($1,530). **Conclusion –** The burden of chronic liver disease includes a great cost for health systems. In addition, it is likely to be even greater as a result of the insidious course of the disease.

**Keywords** – Liver cirrhosis; costs and cost analysis; hepatic encephalopathy; hepatorenal syndrome; waiting lists; cost of illness.

## INTRODUCTION

Burden of disease is an indicator that relates to health status. There are two ways of measuring it: a) epidemiologically as prevalence or incidence of a given condition and its effects (fatal or not); and b) economically as financial impact on public or private health care systems[1].

United States (US)[2] and European[3] epidemiological data have shown that the burden of chronic liver disease has increased significantly in recent decades. Its leading causes are hepatitis B virus (HBV), hepatitis C virus (HCV), nonalcoholic fatty liver disease (NAFLD), and alcoholic cirrhosis[2,3]. A Mexican study[4] has estimated that by 2050 the health care systems in that country will report approximately 2 million cases of chronic liver disease per year. The authors also stressed that alcoholic liver disease will remain the leading cause, followed by NAFLD[4].

An analysis of 2001-2010 Brazilian Unified Health System data revealed that chronic liver diseases ranked eighth among the leading causes of death, with a hospital admission rate of 0.72% and a mortality rate of 3.34%. Among liver diseases, cirrhosis was the leading cause of hospitalization and mortality in southern and southeastern Brazil, respectively[5].

To the best of our knowledge, there are no studies evaluating the impact of complications of chronic liver disease on the waiting list for deceased donor liver transplantation (LTx). Therefore, the aim of this paper was to determine the clinical and economic burden of complications of liver disease in wait-listed patients from the perspective of a transplant center. This will hopefully contribute to fill a knowledge gap in the management of LTx waiting lists.

## METHODS

### Cohort selection

A retrospective cohort, cost-of-illness study was conducted. To be eligible, patients should be aged >18 years, male or female, evaluated for LTx from October 2012 to May 2016, and included in the adult LTx group at *Complexo Hospitalar Irmandade Santa Casa de Misericórdia de* Porto Alegre (ISCMPA), a tertiary care center in Southern Brazil. Patients who were included on the waiting list because of severe acute liver failure or need of re-LTx were excluded from analysis. Also excluded were those under evaluation or wait-listed for LTx but regularly treated at other hospitals, where they underwent tests or were admitted, according to clinical outcomes. Patients were monitored until December 31, 2016, to potentially complete a follow-up of at least 7 months.

The natural history of cirrhosis is initially characterized by a

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compensated phase, which is then followed by a decompensated phase. The latter consists of the appearance of complications triggered by the development of portal hypertension, by changes in the synthetic function of the liver, or by both. Spontaneous bacterial peritonitis (SBP), portosystemic encephalopathy (PSE), ascites, variceal hemorrhage (VH), hepatorenal syndrome (HRS), and hepatocellular carcinoma (HCC) are the most common[6]. The transition from a compensated to a decompensated phase occurs at a rate of 5–7% per year[7] and, as the patient develops any of those complications, cirrhosis becomes a systemic disease affecting multiple organs[8].

To be analyzed, admissions (to the ward, intensive care unit, or emergency department) should be caused by chronic liver disease, occurring from the day of the first appointment with the LTx group (registration date) until one of the following outcomes: transplantation, death while waiting, or exclusion from the waiting list. Demographic and clinical data, Model for End-stage Liver Disease (MELD) score, dates of admission and discharge, number and type of medications prescribed, and number of laboratory and imaging tests performed were obtained directly from the electronic medical record of each patient.

### Economic data

This cost-of-illness study was based on the perspective of the transplant center. Only direct medical costs – those directly used for a given procedure or treatment – were analyzed, so that the sum of the incurred costs would represent an objective measure of resource use[9-11]. To allocate all incurred direct medical costs, the hospital accounting department adopts the following methods: a) absorption costing associated with RKW (Reichskuratorium für Wirtschaftlichkeit), or full absorption costing; and b) micro-costing[12,13].

In the full absorption costing method, each hospital unit is considered a cost center, consisting of an autonomous production unit with specific coverage areas and incurred costs. Brazilian legislation provides for this method, which is the most widely used in hospitals[14]. Each cost center records costs of overheads, medical and nonmedical staff, and materials and medications using distribution criteria defined by the hospital. Because LTx is a sequential process, costs of treatments and procedures are allocated to each cost center – micro-costing – based on each patient's flow through different hospital units. The breakdown of all incurred costs in a given cost center, either divided by service unit or by consumption unit in the case of materials and medications, results in unit costs, whose sum corresponds to the total amount of resources used to treat patients. The information on costs of hospital procedures represents the combination of incurred costs in the functional structure and how they are used in patient care.

### Data analysis

The hospital bill was obtained using a hospital management software (Phillips Tasy®; Phillips Clinical Informatics, Blumenau, SC, Brazil). All costs were converted from Brazilian reais (R$) to US dollars ($) using the Central Bank of Brazil currency converter (available at: http://www4.bcb.gov.br/pec/conversao/conversao.asp Accessed on: April 8, 2018). Because of little variation in quotations in 2017, an exchange rate of $1 = R$3.307, as of December 31, 2017, was used. To compare economic data from 2012 to 2016, values were standardized using the Brazil Consumer Price Index for the period (available at: http://pt.global-rates.com/estatisticas-economicas/inflacao/indice-de-precos-ao-consumidor/ipc/brasil.aspx. Accessed on: April 8, 2018)[9,15].

### Ethical considerations

This study follows guidelines for reporting observational studies[16] and was approved by the Research Ethics Committee of Santa Casa de Misericordia of Porto Alegre (protocol no. 1.386.991). Informed consent was waived because of the noninterventional and retrospective design of the study. All researchers signed a data use agreement to ensure data safety and ethical use.

### Statistical analysis

IBM SPSS software package, version 22.0 for Windows (IBM, Armonk, NY, US), was used for statistical analysis. Quantitative data were described as mean and standard deviation. If the assumptions of normality were violated, median and interquartile range were used. Categorical data were reported as count and percentage. Student's *t*-test or Mann-Whitney U test was used to compare means in case of skewed distribution. Categorical data were compared using chi-square test or Fisher's exact test. $P<0.05$ were considered statistically significant.

## RESULTS

### Characteristics of the sample

From October 1, 2012 to May 31, 2016, a total of 172 patients were evaluated and subsequently included on the waiting list for deceased donor LTx. Of those, 30 patients were excluded because they had acute liver failure or required re-LTx and 38 were excluded because they were treated at other hospitals. The final sample consisted of 104 patients who were followed until one of these outcomes: a) transplantation; b) death or exclusion; and c) remaining on the list at the end of follow-up.

The patients were divided into two groups according to the occurrence of admission because of underlying liver disease from registration date to outcome date, resulting in 47 patients with admission and 57 patients without admission. Demographic data and characteristics of each group are shown in TABLE 1. In both groups, median age was 57 years and most patients were men. The leading cause of chronic liver disease in both groups was HCV, followed by alcohol. The most common comorbidity in patients requiring admission was type 2 diabetes (39.1% vs 14.0%, $P=0.029$).

When clinical outcomes – transplantation, death while waiting, exclusion, and remaining on the waiting list at censorship – were compared to the presence or absence of complications of liver disease, no statistically significant differences were found between the groups (TABLE 1).

### Clinical and economic burden

In the study period, the mean number of admissions per patient was 1.37±3.42. The most frequent complication was refractory ascites (90 admissions, prevalence of 20.2%), followed by PSE (15 admissions, 12.5%) and HRS (seven admissions, 6,7%) (TABLE 2). The complication with longest median length of stay was VH (18 days), followed by HRS (13.5 days) and PSE (11 days) (TABLE 2).

In terms of economic burden, the costliest complication was HRS (mean cost per admission, $3,565), followed by PSE ($2,576) (TABLE 2). The total cost of staying on the waiting list was $308,997, of which decompensation of liver disease represents 39%, more than a third of the amount (TABLE 3).

**TABLE 1**. Demographic and clinical data of 104 patients on the LTx waiting list stratified by occurrence or not of admission.

| | Sample n=104 | With admission n=47 | Without admission n=57 | *P* |
|---|---|---|---|---|
| Patients' characteristics | | | | |
| Age at evaluation, years ± SD | 57.3±8.9 | 57.0±9.8 | 57.5±8.2 | 0.815 |
| Gender, male, n (%) | 70 (67.3) | 32 (68.1) | 38 (66.7) | 0.878 |
| BMI, n (%) | 28.10±4.32 | 27.3±4.7 | 28.0±7.4 | 0.585 |
| Etiology of liver disease, n (%) | | | | 0.511 |
| Hepatitis B | 7 (6.7) | 4 (8.5) | 3 (5.3) | |
| Hepatitis C | 58 (55.8) | 26 (55.3) | 32 (56.1) | |
| Alcohol | 13 (12.5) | 4 (8.5) | 9 (15.8) | |
| NAFLD | 9 (8.7) | 6 (12.8) | 3 (5.3) | |
| Other | 17 (16.3) | 7 (14.9) | 10 (17.5) | |
| Comorbidities, n (%) | | | | |
| Hypertension | 29 (27.9) | 13 (27.7) | 16 (28.1) | 0.963 |
| Diabetes | 23 (22.1) | 15 (31.9) | 8 (14.0) | 0.029 |
| MELD score at inclusion, ±SD* | 14.0±4.5 | 14.7±5.5 | 13.3±4.3 | 0.146 |
| Medications, n (%) | | | | |
| Beta-blocker | 51 (49.0) | 23 (48.9) | 28 (49.1) | 0.985 |
| Loop diuretics | 54 (51.9) | 24 (51.1) | 30 (52.6) | 0.873 |
| Potassium-sparing diuretics | 64 (61.5) | 29 (61.7) | 35 (61.4) | 0.975 |
| Proton Pump Inhibitor | 43 (41.3) | 18 (38.3) | 25 (43.9) | 0.566 |
| Lactulose | 30 (28.8) | 12 (25.5) | 18 (31.6) | 0.498 |

BMI: body mass index; LTx: liver transplantation; MELD: Model for End-stage Liver Disease; NAFLD: nonalcoholic fatty liver disease; SD: standard deviation; LTx: liver transplantation.

* Data available for 100 participants; Data expressed as mean ± SD.

**TABLE 2.** Most common diagnoses in admissions due to complications of liver disease in 47 patients on the LTx waiting list (October 2012 to December 2016).

| Diagnosis | n | n of admissions | Median length of stay (days) | Cost/admission ($)* | Total cost ($±SD) |
|---|---|---|---|---|---|
| Refractory ascites | 21 | 90 | 0.0 (0.0–5.0) | 246.51 | 22,433±1,639 |
| PSE | 13 | 15 | 11.0 (5.0–43.0) | 2,576 | 38,641±4,506 |
| HRS | 7 | 8 | 13.5 (5.3–71.0) | 3,565 | 28,516±3,552 |
| VH | 7 | 5 | 18.0 (5.5–45.5) | 1,530 | 12,236±1,840 |
| SBP | 6 | 8 | 6.5 (5.3–8.8) | 895.63 | 7,165±831 |

HRS: hepatorenal syndrome; LTx: liver transplantation; PSE: portosystemic encephalopathy; SBP: spontaneous bacterial peritonitis; VH: variceal hemorrhage; $ US: dollars (exchange rate on 12/31/2017). *Mean cost. Data expressed as median (interquartile range).

**TABLE 3**. Direct medical costs of the LTx waiting list categorized by cost center (n = 104).

| Cost center | n** | Cost/ patient ($)* | Total cost ($) | % |
|---|---|---|---|---|
| Outpatient Services | | | | |
| LTx Office | 212 | 23.32 | 4,944.08 | 1.6 |
| Specialties Office | 374 | 11.86 | 4,435.82 | 1.4 |
| Social Work | 70 | 3.18 | 222.72 | 0.1 |
| Inpatient Services | | | | 0.0 |
| Emergency Department | 158 | 447.92 | 70,770.79 | 22.9 |
| Inpatient Unit | 331 | 207.71 | 68,752.69 | 22.3 |
| Intensive Care Unit | 55 | 730.43 | 40,173.63 | 13.0 |
| Surgical Unit | 16 | 314.82 | 5,037.13 | 1.6 |
| Physical Therapy | 144 | 9.35 | 1,346.23 | 0.4 |
| Nutrition | 160 | 6.10 | 976.31 | 0.3 |
| Neuroradiology | 34 | 1,775.05 | 60,351.62 | 19.5 |
| Chemotherapy | 13 | 35.21 | 457.7 | 0.1 |
| Hemotherapy | 44 | 80.79 | 3,554.78 | 1.2 |
| Dialysis | 22 | 82.90 | 1,823.85 | 0.6 |
| Imaging Tests | | | | 0.0 |
| Computed Tomography | 36 | 160.90 | 5,792.57 | 1.9 |
| MRI | 35 | 268.96 | 9,413.69 | 3.0 |
| Echocardiography | 23 | 67.78 | 1,558.97 | 0.5 |
| Ultrasound | 65 | 40.98 | 2,663.63 | 0.9 |
| Electrocardiogram | 1 | 15.77 | 15.77 | 0.0 |
| Electroencephalogram | 3 | 28.88 | 86.64 | 0.0 |
| Mammography | 5 | 29.21 | 146.03 | 0.0 |
| Radiology | 50 | 23.08 | 1,153.75 | 0.4 |
| Laboratory Tests | | | | 0.0 |
| Clinical Analyses | 610 | 27.08 | 16,517.36 | 5.3 |
| Other units | | | | 0.0 |
| Urodynamics | 1 | 14.90 | 14.9 | 0.0 |
| Densitometry | 1 | | 12.28 | 0.0 |
| Endoscopy | 43 | 117.31 | 5,044.39 | 1.6 |
| Ergometry | 1 | 43.84 | 43.84 | 0.0 |
| Day Hospital | 24 | 147.54 | 3,540.92 | 1.1 |
| Pulmonary Function Tests | 6 | 24.31 | 145.83 | 0.0 |
| Total | | 4,739.17 | 308,997.92 | 100.0 |

MRI: magnetic resonance imaging; LTx: liver transplantation; US $: US dollars (exchange rate on 12/31/2017). *Median cost; **Total number of consultations.

## DISCUSSION

US, European, and Brazilian epidemiological studies have demonstrated a high prevalence of chronic liver diseases and their impact on quality of life and productivity resulting from associated morbidity and mortality[1-3,5]. A systematic analysis for the Global Burden of Disease Study regarding the period of 1990–2013 showed that mortality rates for cirrhosis increased by 45% (cirrhosis due to HCV, 673%; cirrhosis due to HBV, 35.6%; alcoholic cirrhosis, 31.2%), while deaths due to HCC, an increasingly common complication of cirrhosis, increased by 60.3%[17]. In 2013, the US National Center for Health Statistics ranked cirrhosis as the 12th leading cause of death, accounting for 1.4% of all deaths (mortality rate, 11.5/100,000 population)[18].

A European population-based study[3] using data from the World Health Organization and 260 epidemiological studies reported relevant findings: cirrhosis accounts for approximately 170,000 deaths per year in Europe, with significant variation between countries depending on risk factors. HBV, HCV, and alcohol remain the leading causes[3]. With regard to HCC, approximately 500,000 new cases are diagnosed each year in Europe, with 47,000 deaths per year[3,19,20].

Regarding admissions due to chronic liver disease, a US population-based study[2] reported that, from 2007 to 2012, cirrhosis accounted for 243,170 admissions, with median length of stay of 5.7 days, mortality rate of 5.8% (1,990 deaths), and cost of $3 billion. This study also reported on complications of chronic liver disease and found that ascites or SBP accounted for 15,675 admissions, median length of stay of 5.2 days, mortality rate of 3.5%, and cost of $173,052[2]. PSE caused 52,840 admissions, with median length of stay of 5.4 days and cost of $559,258. The authors stressed that increases in spending were statistically significant regardless of inflation in the study period ($P<0.0001$)[2].

HRS is probably the most severe complication of chronic liver disease, both because its prognosis and its lethality if not treated (median survival is 2 weeks)[21]. A recent economic evaluation concluded that treatment options for HRS (terlipressin and norepinephrine) are equally efficacious; however, terlipressin therapy had lower costs both from the perspective of the Brazilian Unified Health System ($7,437.04 vs $8,406.41, respectively) and from the perspective of the private health insurance system ($13,484.57 vs $15,061.01, respectively)[22]. According to data from the US National Institutes of Health[23], $802 million were intended for research on liver diseases and $324 million for chronic liver disease and cirrhosis in 2018, while the estimated budget for 2019 was $841 million and for $335 million respectively[23].

This Brazilian single-center study showed that complications of chronic liver disease in patients waiting for LTx are costly. To the best of our knowledge, there are no studies evaluating the clinical and economic burden of complications of chronic liver disease in this clinical setting. Patients with refractory ascites had a median length of stay of 0.0 day because the procedure in such cases – abdominal paracentesis – does not require admission and is usually performed at the emergency department.

Clearly, the burden of chronic liver disease is not restricted to an epidemiological issue, as it also means significant costs for health care systems (both public and private), patients, and families. Detailed information on the impact of chronic liver diseases in dif-

ferent settings is relevant for health care management, especially in terms of decision-making, priority setting, resource allocation, and creation of policies for prevention and early treatment of complications. These measures could contribute to ensure that wait-listed patients undergo LTx in best possible conditions, preventing them from leaving the waiting list because of death or poor clinical status.

The limitations of this study include those inherent to single-center, retrospective investigations. In 2012, our hospital implemented a computerized system for resource and patient care management (Tasy). Recent system updates have been performed, but cost allocation has not changed and is still based on full absorption costing and micro-costing.

Because of the nature of this study, determining the prevalence of acute-on-chronic liver failure (ACLF) was challenging. On the one hand, few patients were admitted to the intensive care unit for acute decompensation of chronic liver disease, which is a requirement for the development of ACLF[24-26]. On the other hand, if we tried to characterize patients under one of the three possible definitions (Chronic Liver Failure Consortium [CLIF-C][24], Asian Pacific Association for the Study of the Liver - ACLF Research Consortium [AARC][25], and North American Consortium for the Study of End-Stage Liver Disease [NACSELD][26]), we would have extremely small samples with statistical influence on our results. To avoid possible biases, we decided not to include the ACLF category, as we believe that the best method to study this complication is using prospective studies.

## CONCLUSION

The present results show that chronic liver disease involves significant epidemiological and economic burden to health care systems. The disease probably has an even greater impact because of its insidious course and increasing incidence.

Our data will hopefully contribute to the creation of comprehensive health care policies based on solid, robust, and consistent evidence (from all-level service providers), focusing on prevention, early treatment, and reduced economic burden for transplant centers and society. This could improve allocation and efficiency in the LTx system.

### Authors' contribution

Rodríguez S: conceptualized and designed the data, collected the data, analyzed and interpreted the data, drafted the article, and critically revised the article. Motta F: analyzed and interpreted the data. Balbinotto Neto G and Brandão A: conceptualized and designed the data, analyzed and interpreted the data, drafted the article, and critically revised the article. All authors have read and approved of the final version of the article.

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**RESUMO – Contexto** – O impacto da doença é um indicador relacionado ao estado de saúde. Dados epidemiológicos norte-americanos e europeus mostraram que, nas últimas décadas, o impacto da doença hepática crônica tem aumentado significativamente. Não há estudos que avaliem o impacto das descompensações da doença hepática crônica na lista de espera para transplante hepático (TxH) com doador falecido. **Objetivo –** Determinar o impacto clínico e econômico das descompensações da doença hepática nos pacientes em lista de espera sob a perspectiva do centro transplantador. **Métodos** – Foram analisados, retrospectivamente, os prontuários de 104 pacientes incluídos em lista de espera para TxH com doador falecido entre outubro de 2012 e maio de 2016 e acompanhados integralmente no centro transplantador. Dados clínicos foram obtidos do prontuário eletrônico, enquanto dados econômicos foram coletados através de *software* de gestão hospitalar. A apropriação dos custos médicos diretos foi realizada sob duas metodologias: custeio por absorção pleno e microcusteio. **Resultados –** A descompensação com maior incidência foi a ascite refratária (20,2%) seguida de encefalopatia portossistêmica (12,5%). A média de internações por paciente foi de 1,37±3,42. A hemorragia digestiva alta varicosa foi a descompensação com maior tempo mediano de internação (18 dias), seguida da síndrome hepatorrenal (13,5 dias). A descompensação mais onerosa foi a síndrome hepatorrenal (custo médio de US$ 3.565), seguida encefalopatia portossistêmica (US$ 2.576) e a hemorragia digestiva alta varicosa (US$ 1.530). **Conclusão** – O impacto da doença hepática crônica inclui um custo importante para os sistemas de saúde. Além disso, é provável que seja ainda maior em decorrência do curso insidioso da doença.

**Palavras-chave –** Cirrose hepática; custos e análise de custo; encefalopatia hepática; síndrome hepatorrenal; listas de espera; custo da doença.

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