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Emergency department frequentation and unscheduled readmissions within the first year after liver transplantation, and their impact on survival

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ABSTRACT

The goal of this research was to assess emergency room frequentation and visit causes, and unscheduled readmissions within the first year after liver transplantation discharge from hospital, as well as their impact on graft and patient survival. This was a retrospective study of the medical records of 98 patients (mean age, 55.6 ± 8.59 years, 77.6 % males) who were consecutively discharged from hospital after receiving a first liver transplant in our institution during the period 2012-2015. All visits to the emergency room during the first year after transplantation were analyzed, and survival at two years after transplantation was calculated. Fifty-six of all 98 patients (57.15 %) visited the emergency room on 117 occasions within the first year post-transplantation. Fever ($n = 34$; 29.05 %) and digestive symptoms ($n = 32$; 27.35 %)

were the most common causes of consultation, and resulted in over half of visits. Thirty-five of these 56 patients (62.5 %) required urgent readmission during 50 of all 117 (42.7 %) visits, primarily because of infectious complications (44 %) diverse causes (bacterial pneumonia, cholangitis, *Clostridium difficile* colitis), and biliary tract-related issues. The likelihood of readmission increased from 11.22 % at 30 days after discharge to 22.4 % at 90 days after discharge. Patient survival at 1 and 2 years after transplantation was lower for patients who were readmitted (88.4 % and 80.7 %, respectively) when compared to those who were not (95.56 % and 91.17 %, respectively, $p = 0.002$).

ABBREVIATIONS LIST

ER: emergency room; SD: standard deviation; SPSS: Statistical Package for the Social Sciences; PCR: polymerase chain reaction.

KEYWORDS

Liver transplantation, readmission to hospital, emergency department, biliary complications, post-transplant follow-up.

INTRODUCTION

Patients having undergone liver transplantation make up an increasingly large population with specific complications related to surgical technique, graft function, and immunosuppressive therapy. Pre-existent comorbidities and other health conditions involving the general population add to the above. As a result, liver transplant patients may usually visit emergency rooms (ERs) for a wide variety of symptoms and diagnoses that may lead to an unscheduled hospital readmission. The information available in the literature on this subject is sparse, and restricted to North American series. The goal of our research was to assess the frequentation, causes, and destinations of ER visits and unscheduled readmissions within the first year after discharge from initial hospitalization for liver transplantation, and their impact on both graft and patient survival.

PATIENTS AND METHODS

Design

This was a retrospective study of the medical records of all adult patients who consecutively received a first liver transplant in our site over the period from 2012 to 2015. Patients undergoing liver retransplantation or combined organ transplantation, as well as those who passed away perioperatively were excluded from the study.

The study protocol was approved by the hospital's Ethics Committee, and exempted from informed consent because of its retrospective nature. Patient data were anonymized in accordance with international data protection guidelines and the Spanish law in force when the study was carried out. Information was collected from electronic medical records. All ER visits and unscheduled readmissions within the first year after transplantation surgery were analyzed. Demographic variables and variables related to both transplantation and ER visits were studied, as were the reasons for consultation and final patient destination. A primary reason was allotted to every ER visit, and reasons were categorized as laboratory changes or symptoms by organ systems.

Initial immunosuppression ensued with basiliximab (20 mg on days 0 and 4), tacrolimus (0.05 mg PO every 12 hours, target trough level: 5-8 ng/mL), and mycophenolate mofetil (1 g every 12 hours). In cases where the recipient was IgG-negative and the donor IgG-positive for cytomegalovirus (CMV) serology primo-infection was prevented with valganciclovir 450 mg/12 hrs for six months. In all other situations preemptive management was used (CMV PCR tests weekly for the first month, then monthly for the first year).

Transplant recipients undergo clinical and laboratory follow-up fortnightly during the first month after discharge, then monthly till the sixth month, then at nine months and one year after transplantation.

Statistical analysis

Qualitative variables are expressed as number and percentage, and quantitative variables as mean and standard deviation (SD). Student's t-test was used to compare quantitative variables. As regards categorical variables, Pearson's Chi-squared test was used for 2x3 contingency tables, and Yates' continuity correction or Fischer's exact test for 2x2 tables. For the actuarial survival analysis the Kaplan-Meier method was used, and curves were compared using the log-rank test. Data were analyzed with the SPSS, version 15.0 (Chicago, IL), software program, and significance was established at $p < 0.05$

RESULTS

Study population

During the study period 106 patients underwent liver transplantation. Four patients were excluded for dying ($n = 2$) or needing retransplantation during their initial transplantation hospital stay ($n = 2$), and four additional patients for receiving a combined transplant including another organ besides the liver. The remaining 98 patients were discharged from hospital after transplantation, and made up the study population. Mean age was 55.57 years (SD, 8.59 years) and gender distribution was 77.6 % ($n = 76$) men and 22.4 % ($n = 22$) women. Conditions that led to transplantation included hepatitis C virus cirrhosis ($n = 53$; 54.1%; 28 with hepatocellular carcinoma), alcoholic cirrhosis ($n = 29$; 29.6 %; 13 with hepatocellular carcinoma), and other causes ($n = 16$; 32 %; four with primary biliary cholangitis, three with primary sclerosing cholangitis, three with autoimmune cirrhosis, two with fulminant hepatitis, two with hemochromatosis, one with Caroli's disease, and one with hemangioendothelioma). Hepatitis C viral load was undetectable by PCR before transplantation in 48 of 53 transplant recipients for C virus cirrhosis. Transplant grafts were collected from brain-dead donors in 92.9 % ($n = 91$) of cases, and from asystolic donors in 7.1 % ($n = 7$). Biliary anastomosis was performed in a termino-terminal, choledocho-choledochal manner without Kehr tubes in 95 procedures, and using hepaticojejunostomy in the remaining three cases. Rejection (histologically confirmed or clinically suspected) was managed with methylprednisolone boluses, 500 mL daily for three days. Thirty-eight patients (38.8 %) developed some sort of complication during their transplantation

hospital stay, primarily acute renal dysfunction (21 %) and acute cellular rejection (15 patients had it histologically confirmed and 5 clinically suspected), which required intensifying immunosuppressive therapy (n = 20, 20.4 %). Immunosuppression at discharge was based on extended-release tacrolimus and mycophenolate mofetil.

Visits to the emergency room

Fifty-six of 98 patients (57.1 %) visited the emergency room on 117 occasions within the first year after transplantation: 29 patients did so once; 12 patients twice; 6 patients 3 times; 4 patients 4 times; 2 patients 5 times; one patient 6 times, and 2 patients 7 times. The mean number of ER visits within the first year was 2.1.

In all, 15.4% (n = 18) of visits took place during the first month after liver transplantation discharge from hospital, 17.9 % (n = 21) during the second and third months, 26.5 % (n = 31) in the period from month four to month six, 22.2 % (n = 26) in the period from month seven to month nine, and 17.9 % (n = 21) somewhere between month ten and one year after transplantation discharge. The cumulative incidence of ER consultations at 30 days and 90 days after hospital discharge was 15.4 % (18/117) and 33.3% (39/117), respectively.

Of 117 ER visits, 77.8 % occurred on the patient's own initiative. The reasons for consulting the ER are listed in table 1. Fever (n = 34; 29.0 %) and digestive symptoms (n = 32; 27.4 %) were the commonest reasons for consulting, and gave rise to over one half of consultations.

Unscheduled readmission

Following assessment readmission was indicated for 50 of 117 (42.7 %) events, corresponding to 35 of 56 patients (62.5 %) who visited the ER: 25 patients had one readmission, seven had two readmissions, one had three readmissions, and two had four readmissions.

The indication for readmission and the temporal distribution over the study period are summarized in table 2. The likelihood of unscheduled readmission increased from 10.2 % (10/98) at 30 days to 22.4 % (22/98) at 90 days. Readmission was indicated for all fever and jaundice cases, and for most cases of laboratory changes, abdominal pain,

or diarrhea. Overall, infection (50 %) was the most common cause of readmission over the year the study lasted. During the first 90 days after discharge the most common infectious complication was bacterial pneumonia, and in later periods it was cholangitis. Interestingly, no patients were readmitted for suspected rejection.

Survival

Overall in the study population patient survival at 1 and 2 years after transplantation was 92.9 % and 88.8 %, respectively. During unscheduled readmission 5 (14.3 %) of 35 patients died, all of them from infection. Patient survival at 1 and 2 years after transplantation was lower among patients who required hospital readmission (88.4 % and 80.7 %, respectively) when compared to those who did not (95.6 % and 91.2 %, respectively, $p = 0.002$) (Figure 1).

Risk factors

None of the variables analyzed represented risk factors for unscheduled readmission. Patients who were readmitted and those who were not were comparable in age (55.7 ± 9.7 years vs 55.5 ± 8 years, $p = 0.914$), gender (68.6 % male vs. 82.5 % male; $p = 0.182$), etiology of the condition for which a transplant was indicated ($p = 0.288$), transplantation with urgency status 0 (2.9 % vs 0 %, $p = 0.402$), donor type (5.7 % vs 9.5 % cardiac death, $p = 0.719$), days of hospital stay during the transplantation admission (43.9 ± 36.3 vs 33.4 ± 23 ; $p = 0.135$), and type and frequency of complications during the transplantation admission (Table 3).

DISCUSSION

In the present study over half (57.15 %) of patients consulted the ER during their first year after liver transplantation. Moreover, this was the case despite the fact that all transplant recipients in our hospital are subjected to scheduled clinical follow-up visits at the transplant outpatient clinic at least for one year after the procedure. Furthermore, should any incident occur, patients have direct phone access to an on-call transplant specialist around the clock, seven days a week—appointments are

advanced, and unforeseen emergencies attended to. Despite this 78 % of patients visited the ER on their own initiative, a rate similar to the 80 % of patients in the general population who visit ERs in Spain (1), which may lead to reassess the frequency of outpatient follow-up in the relevant protocols. The ER frequentation rate within the first year after liver transplantation in our series is similar to that described in the literature, which oscillates between 44.4 % and 67.3 % (2-6).

As in other series (2-4,7), fever and digestive symptoms represented the most common causes of consultation to the ER. Fever was the commonest motive, and its development in an immunosuppressed patient having undergone complex surgery warrants an urgent evaluation to rule out any potentially serious infectious complication. In our study more than half of consultations led to unscheduled hospital readmission. This proportion is much higher than the 12-13 % hospitalization rate our hospital's ER has for the general adult population, which suggests that the high rate of ER visits by liver transplant patients is justifiable from a medical standpoint. As a matter of fact, the unscheduled readmission rate in our series is similar to that in the literature for the first year after liver transplantation, which ranges from 49 % to 74 % (2-6), albeit the clinical expertise of liver transplant teams and readmission criteria vary from one hospital to the next.

Awareness of readmission causes and timing may help establish whether readmissions may be prevented. In our series, infection was the most common indication for readmission, and the cause of death for all five patients who passed on during their readmission stay. The frequent indication of readmission for cholangitis over the study period is to be highlighted among infectious conditions. Biliary infection and complications were also the most common causes of readmission in the series by Russo (7) and by Paterno (8). In our series, the absence of readmissions for immune disorders or opportunistic infection also deserves highlighting.

Among the non-transplanted general population, readmission within 30 days after hospital discharge is common, oscillating between 10.1 % in patients discharged after admission for diverse causes (9), and 14.3 % in patients discharged after major surgery (10). Our readmission rate at 30 days after discharge is lower than reported in the literature for liver transplant recipients, which ranges from 16 % to 50 % (1,5,11-13).

This different readmission rate at 30 days after discharge may result from differing patient characteristics, variations in clinical practice and outpatient follow-up, and distinct readmission criteria between hospitals.

In order to assess the impact of readmission on long-term survival we looked at patient survival at 1 and 2 years after transplantation, and found that patients with at least one readmission had lower survival than those who were not readmitted. Similar results were found by several studies, showing that readmission is associated with lower long-term patient survival (2,3,6,8,11-13). Emergency room visits may be an indicator of higher risk after liver transplantation. Whether these patients may benefit from closer postoperative follow-up, such as with a higher frequency of scheduled visits, should be investigated.

We are aware that our study has limitations, including its single-center, retrospective nature in a small number of subjects, which precluded identification of readmission risk factors. Other transplant centers may experience different complications and different readmission rates. However, we believe our information may be relevant given the shortage of publications available on this subject.

To conclude, our work shows that the demand for emergency care within the first year after transplantation discharge from hospital is really high, since over half of patients may return to the ER after discharge for a variety of reasons, primarily non-opportunistic infections and complications secondary to biliary tract strictures. Our readmission rate was fairly high, with six of every ten consulting patients requiring hospital readmission, primarily for infectious and biliary complications. Unscheduled readmissions have a high mortality rate and significantly reduce patient survival. We found no modifiable predictors for readmission, most likely because of the limited number of study patients. Therefore, further studies are needed with a larger sample of patients to assess potential readmission risk factors and prevention strategies.

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Paula Molina: Conception and design, data collection, analysis of results, manuscript writing, final approval.

María Jesús Citores: Analysis of results, final approval.

Esther Montero: Analysis of results, final approval.

Ana Arias: Analysis of results, final approval.

Laura Benítez: Analysis of results, final approval.

Valentín Cuervas-Mons: Conception and design, analysis of results, manuscript writing, final approval.

CONFLICTS OF INTEREST

The authors of the present manuscript declare no conflicts of interest in relation to this paper, according to REED guidelines.

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Table 1. Reasons for consultation at the emergency room within the first year after liver transplantation discharge from hospital.

| | |
|-----------------------|--|
| | Visits to the emergency room N = 98 (%) |
| No. of patients | 56 (57.15) |
| No. of events | 117 |
| No. of events/patient | 2.09 |
| Reasons | N (%) |
| Fever | 34 (29.05) |
| Fever alone | 19 |
| + cough | 6 |
| + abdominal pain | 6 |

| | |
|---------------------|------------|
| + diarrhea | 2 |
| + vomiting | 1 |
| Digestive system | 32 (27.35) |
| Abdominal pain | 18 |
| Diarrhea | 8 |
| Vomiting | 3 |
| Jaundice/Choluria | 3 |
| Musculoskeletal | 17 (14.53) |
| Low back pain | 8 |
| Dorsal trauma | 3 |
| Sprain | 3 |
| Arthritis | 2 |
| Fibula fracture | 1 |
| Laboratory changes | 8 (6.83) |
| Neutropenia | 4 |
| Hypertransaminemia | 2 |
| Elevated creatinine | 2 |
| Skin and mucosas | 5 (4.27) |
| Herpes zoster | 2 |
| Hives | 1 |
| Stomatitis | 1 |
| Aphthous stomatitis | 1 |
| Dyspnea + cough | 5 (4.27) |
| Miscellany | 16 (12.82) |
| Dizziness | 2 |
| Syncope | 2 |
| Metrorrhagia | 2 |
| Renoureteral colic | 2 |
| Dysuria | 2 |
| General malaise | 5 |
| Dog bite | 1 |

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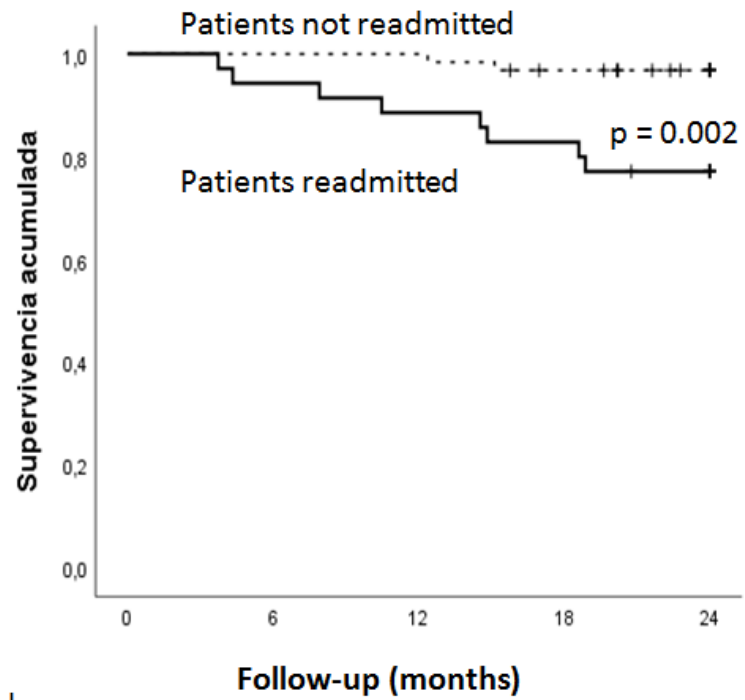
Table 2. Reasons for unscheduled readmission at the emergency room, and their temporal distribution, within the first year after liver transplantation discharge from hospital.

| Readmission indication | Month post-liver transplantation | | | | | |
|--------------------------------------|----------------------------------|--------------|--------------|--------------|----------------|----------------|
| | 1 N (%) | 2-3 N (%) | 4-6 N (%) | 7-9 N (%) | 10-12 N (%) | Total N (%) |
| 1.- Infectious disorder | 6 | 8 | 8 | 6 | 7 | 35 (50) |
| Other than cholangitis | 5 | 7 | 3 | 4 | 3 | 22 (44%) |
| Bacterial pneumonia | 3 | 2 | - | - | 1 | 6 |
| Gram-negative sepsis | 1 | - | - | - | - | 1 |
| Pneumonia by <i>Aspergillus</i> sp | 1 | - | - | - | - | 1 |
| Febrile syndrome: cytomegalovirus | - | - | 1 | 2 | - | 3 |
| <i>Clostridium difficile</i> | - | 3 | 2 | - | 1 | 6 |
| Viral hepatitis (C virus relapse) | - | - | - | 2 | - | 2 |
| Acute pyelonephritis | - | 1 | - | - | 1 | 2 |
| Leishmaniasis | - | 1 | - | - | - | 1 |
| Cholangitis | 1 | 1 | 5 | 2 | 4 | 13 |
| 2.-Laboratory changes | 2 | 0 | 2 | - | 1 | 5 (10%) |
| Drug-induced neutropenia | 2 | - | 2 | - | - | 4 |
| Acute kidney failure | - | - | - | - | 1 | 1 |
| 3.-Surgical issues | 2 | 1 | 4 | 0 | 0 | 7 (8%) |
| Inguinal hernia | - | - | 1 | - | - | 1 |
| Gut obstruction | 1 | - | 2 | - | - | 3 |
| Obstructive jaundice, cholelithiasis | 1 | 1 | 1 | - | - | 3 |
| 4.-Medical issues | 0 | 2 | 1 | 0 | 0 | 3 (6%) |
| Metrorrhagia | - | 1 | 1 | - | - | 2 |
| Syncope | - | 1 | - | - | - | 1 |
| TOTAL | 10 (20%) | 11 (22%) | 15 (30%) | 6 (12%) | 8 (16%) | 50 (100%) |

Table 3. Comparison of patients who required an unscheduled readmission within the first year after hospital discharge versus those who did not.

| | Readmission N = 35 | No readmission N = 63 | P |
|---|-------------------------------|--------------------------------------|----------|
| Recipient age (years) (mean ± SD) | 55.7 ± 9.7 | 55.5 ± 8 | 0.914 |
| Male (%) | 24 (68.6) | 52 (82.5) | 0.182 |
| Transplantation indication/etiology | | | |
| Hepatitis C virus cirrhosis | 22 | 31 | |
| Alcoholic cirrhosis | 7 | 22 | 0.288 |
| Other | 6 | 10 | |
| Donor after cardiac death (%) | 2 (5.7) | 6 (9.5) | 0.709 |
| Complications during initial admission for liver transplantation (%) | | | |
| Biliary tract stricture | 9 (25.7) | 11 (17.5) | 0.331 |
| Rejection | 6 (17.14) | 14 (22.2) | 0.740 |
| Renal dysfunction | 11 (31.4) | 27 (42.8) | 0.370 |
| Infection with cytomegalovirus | 7 (20) | 5 (7.9) | 0.109 |
| Pneumonia or other infectious complications * | 16 (45.7) | 18 (25.4) | 0.137 |

*Herpetic stomatitis, candidal stomatitis, urinary tract infection.



| Patients at risk | | Follow-up (months) | | | | |
|------------------|----|--------------------|----|----|----|--|
| | 0 | 6 | 12 | 18 | 24 | |
| No reingresaron | 63 | 63 | 60 | 58 | 58 | |
| Reingresaron | 35 | 33 | 31 | 29 | 28 | |

Figure 1. Patient survival at two years after transplantation according to whether they had an unscheduled readmission after initial liver transplantation discharge from hospital.