REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

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

Authors:
Paula Molina Ávila, María Jesús Citores Sánchez, Ana Arias Milla, Laura Benítez, Esther Montero Herández, Valentín Cuervas Mons

DOI: 10.17235/reed.2021.7666/2020
Link: PubMed (Epub ahead of print)

Please cite this article as:
Molina Ávila Paula , Citores Sánchez María Jesús, Arias Milla Ana, Benítez Laura , Montero Herández Esther, Cuervas Mons Valentín. Emergency department frequentation and unscheduled readmissions within the first year after liver transplantation, and their impact on survival . Rev Esp Enferm Dig 2021. doi: 10.17235/reed.2021.7666/2020.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

OR 7666

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

Paula Molina Ávila[1], María Jesús Citores Sánchez[2], Ana Arias Milla[3,4], Laura Benítez Gutiérrez[3,4], Esther Montero Hernández[3], Valentín Cuervas Mons[3,4,5]

[1]Emergency Department, [2]Instituto de Investigación Puerta de Hierro-Segovia de Arana (IDIPHISA), [3]Department of Internal Medicine, and [4]Liver Transplantation Unit. Hospital Universitario Puerta de Hierro-Majadahonda. Majadahonda, Madrid. Spain. [5]Department of Medicine. Universidad Autónoma de Madrid. Madrid, Spain

Received: 27/11/2020

Accepted: 28/12/2020

Correspondence: Dr. Paula Molina Ávila. Servicio de Urgencias. Hospital Universitario de Torrejón. C/ Mateo Inurria, s/n. 28850 Torrejón de Ardoz, Madrid. Spain

e-mail: paulamolinavila@yahoo.es.

Authorship: 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.

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

Funding: no funding was received from public or private sources, research institutions or foundations.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

ABSTRACT

The aim of this study was to assess emergency room frequentation, visit causes, and unscheduled readmissions within the first year after discharge from hospital following liver transplantation. Their impact on graft and patient survival was also assessed. 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 undergoing a first liver transplant in our institution during 2012-2015. All visits to the emergency room during the first years after transplantation were analyzed, and survival at two years after transplantation was calculated. Fifty-six of the 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 an urgent readmission during 50 of the 117 (42.7 %) visits. This was primarily due to infectious complications (44 %) of 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 readmitted (95.56 % and 91.17 %, respectively, p = 0.002).

Keywords: Liver transplantation. Readmission to hospital. Emergency department. Biliary complications. Post-transplant follow-up.

INTRODUCTION

Patients who have undergone liver transplantation make up an increasingly large population with specific complications related to surgical technique, graft function,

and immunosuppresive therapy. Pre-extant 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) due to 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 study was to assess the frequentation, causes and destinations of ER visits, and unscheduled readmissions within the first year after hospital discharge following liver transplantation, and their impact on 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 center, 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 was exempt 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 performed. 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 the 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 hours for six months.

Preemptive management was used in all other situations (CMV PCR tests weekly for the first month, then monthly for the first year).

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

Statistical analysis

Qualitative variables are expressed as numbers and percentages, and quantitative variables as the mean and standard deviation (SD). Student's t-test was used to compare quantitative variables. With regard to categorical variables, Pearson's Chi-squared test was used for 2 x 3 contingency tables, and Yates' continuity correction or Fisher's exact test for 2 x 2 tables. The Kaplan-Meier method was used for the actuarial survival analysis, and curves were compared using the log-rank test. Data were analyzed with the SPSS, version 15.0 (Chicago, IL), software program, and statistical significance was established at $p < 0.05$

RESULTS

Study population

During the study period, 106 patients underwent liver transplantation. Four patients were excluded as they died (n = 2) or needed retransplantation during their initial transplantation hospital stay (n = 2), and four more patients were excluded as they received 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. The mean age was 55.57 years (SD, 8.59 years) and the gender distribution was 77.6 % (n = 76) males and 22.4 % (n = 22) females. 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 due to 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 intensification of 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 visited 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.

Overall, 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) 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 due to the patient's own initiative. The reasons for consulting the ER are shown in table 1. Fever (n = 34; 29.0 %) and digestive symptoms (n = 32; 27.4 %) were the common reasons for consulting, and accounted for over 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. A total of 25 patients had one readmission, 7 two readmissions, 1 three readmissions, and 2 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 study period. During the first 90 days after discharge, the most common infectious complication was bacterial pneumonia, and cholangitis during later periods. Interestingly, no patients were readmitted due to suspected rejection.

Survival

The overall survival rates in the study population at 1 and 2 years after transplantation were 92.9 % and 88.8 %, respectively. During unscheduled readmission, 5 (14.3 %) of 35 patients died, all 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 not readmitted (95.6 % and 91.2 %, respectively, p = 0.002) (Fig. 1).

Risk factors

None of the variables analyzed represented risk factors for unscheduled readmission. Readmitted and non-readmitted patients 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 the transplant was indicated (p = 0.288), transplantation with urgency status (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 the 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 for at least 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; their appointments are brought forward and unforeseen emergencies are attended to. Despite this, 78 % of patients visited the ER on their own initiative, which is similar to the 80 % rate of patients in the general population who visit ERs in Spain (1). This may lead to a reassessment of 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 most common 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 of our ER 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). However, the clinical expertise of liver transplant teams and their readmission criteria vary from one hospital to the next.

Awareness of readmission causes and timing may help to 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 away during their readmission stay. The frequent indication of readmission for cholangitis

over the study period should be highlighted among infectious conditions. Biliary infection and complications were also the most common causes of readmission in the series by Russo (7) and Paterno (8). In our series, the absence of readmissions for immune disorders or opportunistic infection should also be highlighted.

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 that reported in the literature for liver transplant recipients, which ranges from 16 % to 50 % (1,5,11-13). These different readmission rates 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, patient survival at 1 and 2 years after transplantation was studied, and patients with at least one readmission had a 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 a higher frequency of scheduled visits, should be investigated.

Our study has some limitations, including its single-center, retrospective nature in a small number of subjects, which precluded the 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 study shows that the demand for emergency care within the first year after transplantation discharge from hospital is very high, since over half of patients may return to the ER after discharge for a variety of reasons, mainly 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. There were no modifiable predictors identified for readmission, most likely because of the limited size of the patient cohort. Therefore, further studies are needed with a larger cohort to assess potential readmission risk factors and prevention strategies.

REFERENCES

1. Unidad de urgencias hospitalaria. Estándares y recomendaciones. Informes, estudios e investigación 2010. Ministerio de Sanidad y Política Social.
2. Oh SY, Lee JM, Lee H, et al. Emergency department visits and unanticipated readmissions after liver transplantation: A retrospective observational study. Sci Rep 2018;8:4084-92. DOI: 10.1038/s41598-018-22404-8
3. McElroy LM, Schmidt KA, Richards CT, et al. Early Postoperative Emergency Department Care of Abdominal Transplant Recipients. Transplantation 2015;99:1652-7. DOI: 10.1097/TP.0000000000000781
4. Unterman S, Zimmerman M, Tyo C, et al. A descriptive analysis of 1251 solid organ transplant visits to the emergency department. E West J Emerg Med 2009;10:48-54.
5. Savitsky EA, Votey SR, Mebust DP, et al. A descriptive analysis of 290 liver transplant visits to an emergency department. Acad Emerg Med 2000;7:898-905. DOI: 10.1111/j.1553-2712.2000.tb02068.x
6. Wilson GC, Hoehn RS, Ertel AE, et al. Variation by center and economic burden of readmissions after liver transplantation. Liver Transpl 2015;21:953-60. DOI: 10.1002/lt.24112
7. Russo MW, Levi DM, Pierce R, et al. A prospective study of a protocol that reduces readmission after liver transplantation. Liver Transpl 2016;22:765-72. DOI: 10.1002/lt.24424

8. Paterno F, Wilson GC, Wima K, et al. Hospital utilization and consequences of readmissions after liver transplantation. Surgery 2014;156:871-8. DOI: 10.1016/j.surg.2014.06.018
9. Brennan JJ, Chan TC, Killeen JP, et al. Inpatient Readmissions and Emergency Department Visits within 30 Days of a Hospital Admission. West J Emerg Med 2015;16:1025-9. DOI: 10.5811/westjem.2015.8.26157
10. Tsai TC, Joynt KE, Orav EJ, et al. Variation in Surgical-Readmission Rates and Quality of Hospital Care. N Engl J Med 2013;369:1134-42. DOI: 10.1056/NEJMsa1303118
11. Pereira AA, Bhattacharya R, Carithers R, et al. Clinical factors predicting readmission after orthotopic liver transplantation. Liver Transpl 2012;18:1037-45. DOI: 10.1002/lt.23475
12. Yataco M, Cowell A, David W, et al. Predictors and impacts of hospital readmissions following liver transplantation. Ann Hepatol 2016;15:356-62. DOI: 10.5604/16652681.1198805
13. Li AH, Lam NN, Naylor KL, et al. Early Hospital Readmissions After Transplantation: Burden, Causes, and Consequences. Transplantation 2016;100:713-8. DOI: 10.1097/TP.0000000000000917

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 mucosa	5 (4.27)
Herpes zoster	2
Hives	1
Stomatitis	1
Aphthous stomatitis	1
Dyspnea + cough	5 (4.27)
Miscellany	16 (12.82)
Dizziness	2

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

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 *Aspergillus* sp	1	-	-	-	-	1
Febrile syndrome: cytomegalovirus		-	1	2	-	3
Clostridium difficile	-	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, choledocholithiasis	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 %)

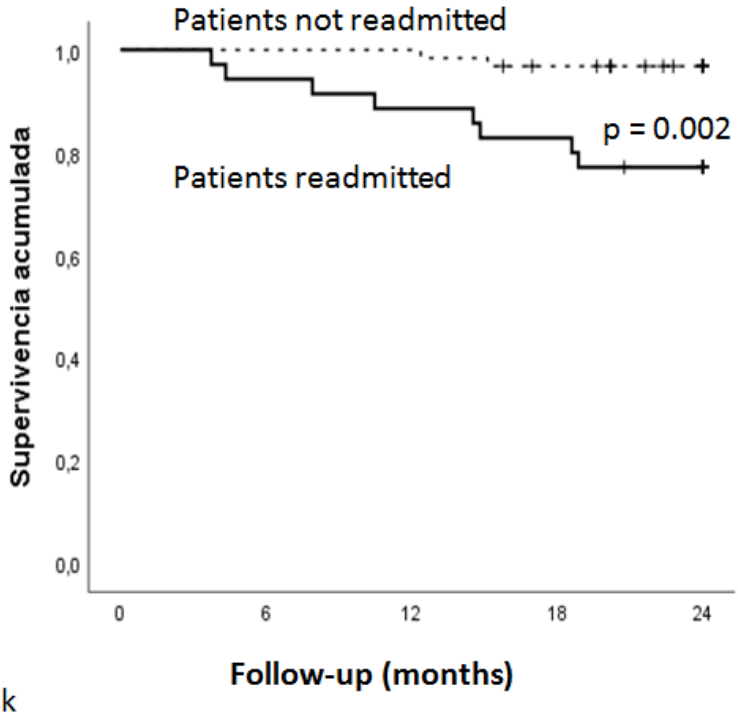
REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

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

	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, candida stomatitis, urinary tract infection.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology



Patients at risk

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 the initial liver transplantation discharge from hospital.