Analysis of the Trend Over Time of High-Urgency Liver Transplantation Requests in Italy in the 4-Year Period 2014-2017

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ABSTRACT

Background. The national protocol for the handling of high-urgency (HU) liver organ procurement for transplant is administered by the Italian National Transplant Center. In recent years, we have witnessed a change in requests to access the program. We have therefore evaluated their temporal trend, the need to change the access criteria, the percentage of transplants performed, the time of request satisfaction, and the follow-up.

Methods. We analyzed all the liver requests for the HU program received during the 4-year period of 2014 to 2017 for adult recipients (≥18 years of age): all the variables linked to the recipient or to the donor and the organ transplants are registered in the Informative Transplant System as established by the law 91/99. In addition, intention to treat (ITT) survival rates were compared among 4 different groups: (1) patients on standard waiting lists vs (2) patients on urgency waiting lists, and (3) patients with a history of transplant in urgency vs (4) patients with a history of transplant not in urgency.

Results. Out of the 370 requests included in the study, 291 (78.7%) were satisfied with liver transplantation. Seventy-nine requests (21.3%) have not been processed, but if we consider only the real failures, this percentage falls to 13.1% and the percentage of satisfied requests rises to 86.9%. The average waiting period for liver transplantation (LT) is 1.7 days and most requests (74%) are met in less than 24 hours, if we consider the hours between the registration of the request and the donor reporting . The percentage of late retransplantations is 2.1%. The clinical indication for HU-LT that appears to improve over time is hepatic artery thrombosis (82.5%). The overall 1-year patient survival is 68.3%. The overall 1-year graft survival, performed on all the patients, is 89% and all the indications for HU-LT appear to go well over time with an average survival rate greater than 85%.

Conclusions. The indications for HU-LT are changing according to the changes in the hepatologic field in recent years. The centralized management of requests has proven to be successful in optimizing responses. Urgent LT is confirmed to be lifesaving in its timeliness.

THE only curative treatment option for patients with advanced liver disease is liver transplantation (LT). The success of LT over the past years has been considerable, with more than 5000 being performed annually in Europe, adding up to more than 140,000 LTs in total [1]. Such a successful outcome is a consequence of the absence of alternative therapies and the good post-transplant survival rate of approximately 90% and 80% at 1 and 5 years, respectively. The success of organ transplantation has led to a significant increase in the number of patients admitted to the waiting list. However, organ donor rates have remained unchanged or have increased only slightly [1].

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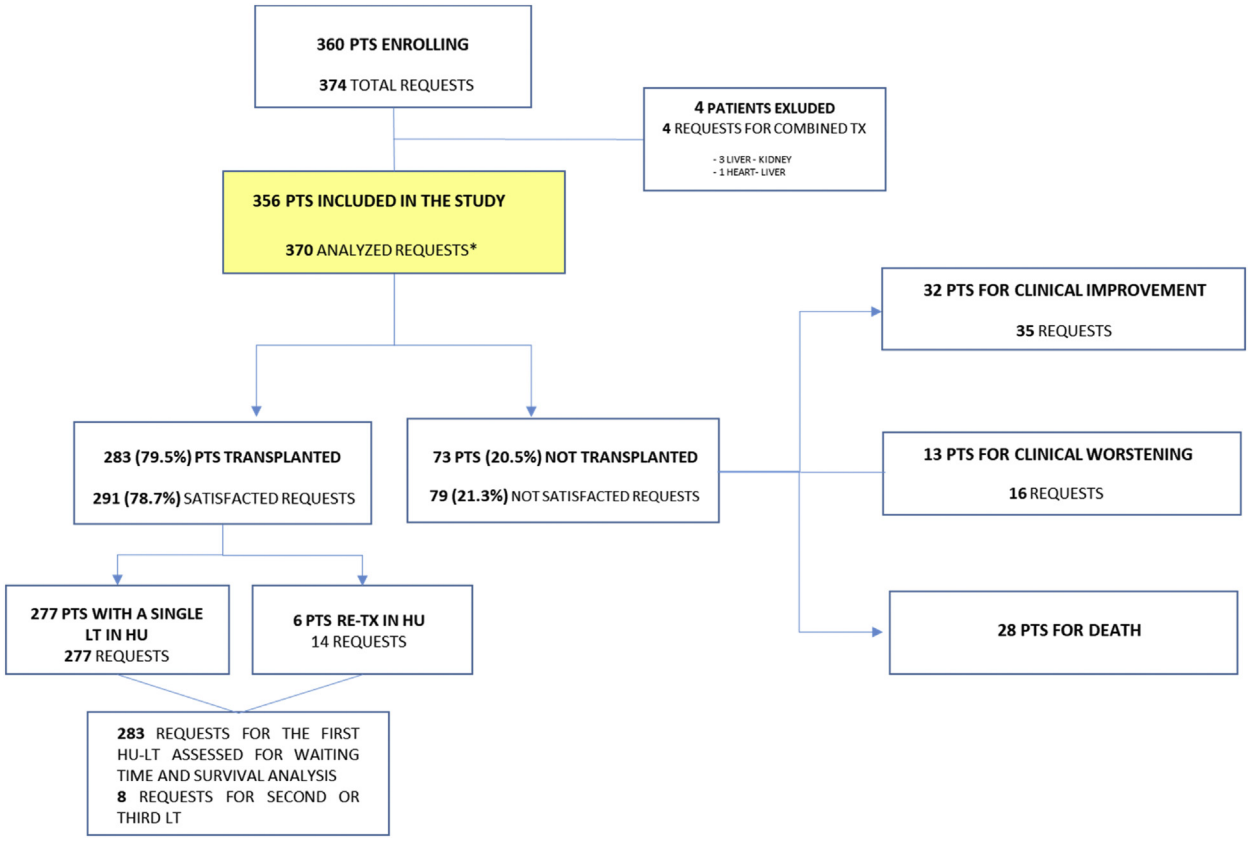

Fig 1. Flow chart of the study (2014-2017). HU, high urgency; LT, liver transplantation; WL, waiting list. *The difference between the number of the patients and the requests is due to double or triple movements in and out of the HU-LT-WL, not always followed by an LT.

On the other hand, with an estimated annual incidence of 2000 cases in the United States [2], acute liver failure is a relatively rare condition, but carries a short-term (3-week) mortality in excess of 40% [3]. In a recent prospective study, short-term survival of patients listed for LT was 84% if transplantation was possible in a timely manner (average within 3.5 days of listing), but only 35% if not [3].

Table 1. Satisfied Requests of HU-LT: Donor-Recipient Match for the First LT (N = 283)

	Recipients			Donors		
	Re-Tx	Single Tx	Total	Re-Tx	Single Tx	Total
Blood Group						
O	3	117	120	4	190	194
A	1	111	112	1	74	75
AB		15	15			0
B	2	34	36	1	13	14
Total	6	277	283	6	277	283
Mean age ± SD (y)	29.7 ± 5.3	48.1 ± 12.1	47.7 ± 12.1	66.7 ± 14.7	53.7 ± 18.6	54.0 ± 18.6
M/F	3/3	185/92	188/95	2/4	140/137	142/141

Abbreviations: F, female; HU, high urgency; LT, liver transplantation M, male; re-tx, retreatment; tx, treatment.

Therefore, the waiting period for transplantation can vary from a few days in the case of patients with acute liver failure to more than 1 year for patients with cirrhosis of intermediate severity or those with hepatocellular carcinoma.

Those with acute liver failure are included, in most countries, in a super-emergency waiting list, granting them absolute priority over all other recipients to receive a transplant within hours or days.

LIVER ALLOCATION

Since 2013 in Italy, the national allocation system has been managed by the National Transplant Center, which also has the task of ensuring a balanced and fair allocation program. Italian score for organ allocation is arranged on 3 levels. In 2015, a consensus redefined the Italian criteria for LT candidate stratification not only based on urgency, but also on the principles of utility and transplant benefit. The current liver allocation system is based on the Model for End-Stage Liver Disease (MELD)/Italian Score for Organ Allocation (ISO), which is defined by biochemical MELD and exceptions [4]. At present, liver grafts are shared according to the following principles: (1) nationwide, for (a) UNOS status 1 patients; (b) pediatric candidates according

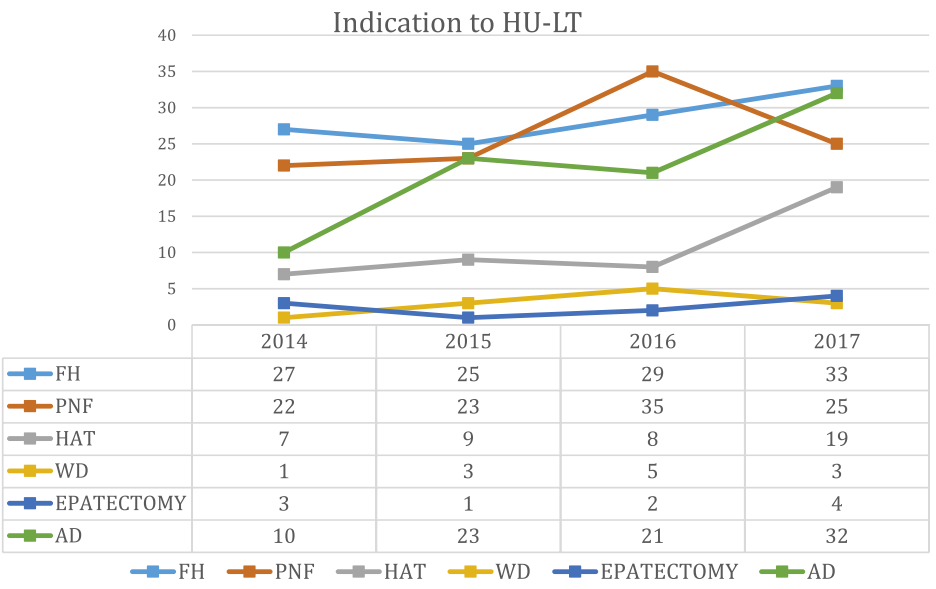

Fig 2. Trend of indication to HU-LT over the time (n = 370). HU, high urgency; LT, liver transplantation.

to the pediatric LT allocation system [10]; (2) macro-areas for adult LT candidates with MELD ≥30; and (3) regionally for adult patients with MELD <30. [4,11]. The first is the national level for high urgency (HU), for example, the United Network for Organ Sharing status 1 both adult and pediatric patients, the pediatric recipients who can benefit from a liver from pediatric donors or a split-liver from adult donors and the liver "payback" program. Whenever a liver is given by a region to a national patient in HU need of a liver, a "refund" is generated. In fact, the first liver available at the region's transplant center is offered as a "payback" to the region that procured the liver for the recipient in urgent need of a liver. The second level is the multiregional level. Italy is divided into 2 areas: one is the northern area and the other is the southern area of the country in which patients with a Model for End-Stage Liver Disease score over 30 are prioritized. The third level is the regional level, where the recipient's priority criterion is based on the transplant benefit, according to the "Italian Score for Organ Allocation in LT" [4].

The Italian procurement or allocation system network follows the rules adopted in Spain. As reported by Miranda et al [5] in Spain, currently, patients in urgent need of a liver have national priority on the waiting list. Liver urgency is defined as a primary graft failure within the first 7 days after the transplant or a fulminant liver failure of any origin with a healthy liver before the event. In the absence of liver urgencies, livers are offered first locally, then regionally, then to the zone and, if no available recipient can be found, to the rest of the country.

Looking at the European situation, a particular experience is represented by the Eurotransplant International Foundation, which is a nonprofit organization that facilitates patient-oriented allocation and cross-border exchange of deceased donor organs for a population of about 135 million in 8 member states of the European Union.

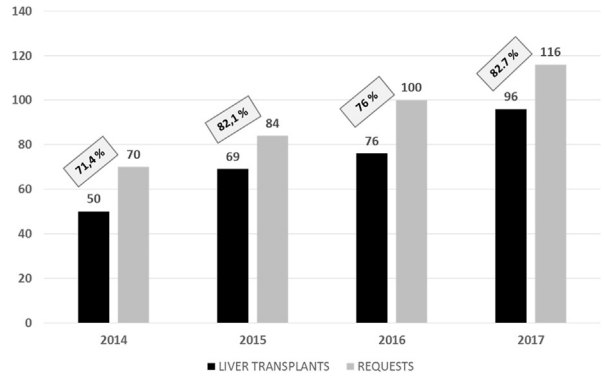

Fig 3. Liver transplants for HU performed and percentage of evasion of requests. HU, high urgency; LT, liver transplantation.

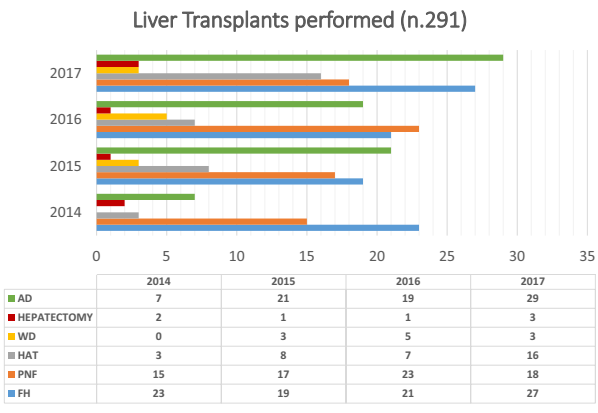

Fig 4. Requests for HU-LT fulfilled with a transplant 2014-2017. HU, high urgency; LT, liver transplantation.

Table 2. Movements of the List After the First LT: Patients Retransplanted

No.	Indication for HU-LT
#1	FH
	AD = delayed graft nonfunction
#2	FH
	PNF
#3	FH
	PNF
#4	FH
	PNF
	PNF
#5	FH
	AD = delayed HAT
	PNF
#6	HAT
	AD = PVT and digestive bleeding

Abbreviations: AD, agreed derogation; HAT, hepatic artery thrombosis; FH, fulminant hepatitis; HU, high urgency; LT, liver transplantation; PNF, primary nonfunction; PVT, portal vein thrombosis.

Eurotransplant offers deceased donor livers sequentially to 3 categories of patients based on urgency: (1) "HU" status, (2) "approved-combined organ" status, and (3) "elective transplants". ABO-incompatible LT is not allowed as long as there are suitable compatible recipients. When a liver is allocated to a recipient outside the donor country because of urgency rules, an "obligation to offer," also called a "payback," is generated, as it happens in Italy. The country that received the liver has the obligation to offer the next available liver with the same blood type to the donor country [6,7].

In the United Kingdom, the new National Liver Offering Scheme has been introduced by the National Health Service Blood and Transplant. Before the new scheme was introduced, patients with a liver disease were assessed on their need for an LT based on their United Kingdom Model for End-Stage Liver Disease score. Clinicians calculated this score by looking at 4 different characteristics of the patient with liver disease.

The new scheme is designed to be more detailed and takes into account 7 characteristics from the donor that are then matched with 21 patient characteristics. The patient with the best match will be shown at the top of the list and will have the highest transplant benefit score. Priority will always be given to those patients on the super-urgent list,

Table 3A. Trend of Requests per Year

Year	Satisfied Requests	Not Satisfied Requests	Total
2014	50 (71.4%)	20 (28.6%)	70
2015	69 (82.1%)	15 (17.9%)	84
2016	76 (76%)	24 (24%)	100
2017	96 (82.7%)	20 (17.3%)	116
Total	291 (78.7%)	79 (21.3%)*	370

*21.3% of the requests throughout the period were not processed, but this percentage falls to 13.1% if we remove from the analysis, the de-listing for clinical improvement (n. 35) and we consider only the effective failures of the system, such as patient death or clinical worsening (n.44). Similarly, the percentage of fulfillment of the effective requests increases to 86.9%.

Table 3B. Non-fulfilled Requests (n.79): Delisting Causes

Deaths	Clinical Worsening	Clinical Improvements	Total
6	5	9	20
8	1	6	15
8	4	12	24
6	6	8	20
28	16	35*	79
	Effective Failures		
28	16	—	44

*21.3% of the requests throughout the period were not processed, but this percentage falls to 13.1% if we remove from the analysis, the de-listing for clinical improvement (n. 35) and we consider only the effective failures of the system, such as patient death or clinical worsening (n.44). Similarly, the percentage of fulfillment of the effective requests increases to 86.9%.

which includes patients with severe medical conditions who will not survive for long without LT. Patients with hepatoblastoma and those waiting for a multiorgan transplant are also included on the list. If there is no patient on the super-urgent list, or there is no good match, the available liver is then offered to patients on the liver transplant list with the highest transplant benefit score. The highest ranked patient with the best match will be the first to be offered the liver [8,9]

HU IN ITALY

Since 2003 in Italy, a national protocol for liver HU has been in force. This means that in codified clinical conditions, such as fulminant hepatitis (FH) of a healthy liver, the primary nonfunction (PNF) within 10 days from LT, hepatic artery thrombosis (HAT) within 15 days from LT, acute liver failure from Wilson' disease (WD), and hepatectomy following trauma, the LT centers can ask to access this protocol and enroll patients on this priority list. Each request is collected and evaluated by the Italian National Transplant Center that endorses the access to the list of liver HU, if the HU criteria are met.

When a HU request is activated, it has priority over the first available liver at the national level. When multiple requests are active, a temporal priority criterion is applied.

In the last year, we noted the appearance of a new indication of access to the HU program, the "agreed

Table 4. Mean Waiting Days between the Date of Registration of the Request and the Date of the LT

	Mean Waiting Days for HU - LT				
	2014	2015	2016	2017	Total
AD	1,8	1,9	2,6	2,0	2,1
HEPATECTOMY	1,5	5,0	0,0	2,3	2,1
FH	1,7	1,4	1,7	1,5	1,6
WD	*	3,3	2,0	2,7	2,5
PNF	1,9	1,5	1,6	1,6	1,6
HAT	1,0	1,4	1,1	1,3	1,3
Total	1,7	1,7	1,8	1,7	1,7

Abbreviations: HU, high urgency; LT, liver transplantation; AD, agreed derogation; FH, fulminant hepatitis; WD, wilson disease; PNF, primary non function; HAT, hepatic artery thrombosis.
*no cases in the year.

Table 5. Number of Requests With Mean Waiting Days ≤ 2 days

	Requests With Mean Waiting Times Within 2 Days									
	0	1	2	3	4	5	6	7	8	Total
AG		39	17	4	5	4	1	1	2	73
Hepatectomy	1	1	3	1		1				7
FH	1	51	27	6	5					90
WD	1	3	1	3	2		1			11
PNF	8	32	14	8	5			1		68
HAT	2	22	9	1						34
Total	13	148	71	23	17	5	2	2	2	283
	232									

Abbreviations: AG, agreed derogation; HAT, hepatic artery thrombosis; FH, fulminant hepatitis; PNF, primary nonfunction; WD, Wilson disease.

derogation" (AD). Increasingly, in fact, LT centers require the access to HU program for different diagnoses from the codified ones (such as fulminant hepatitis, primary non function, etc). These diagnoses, which are acute or acute-on-chronic clinical condition, are however serious conditions, worthy of a first liver available in Italy and, probably, not adequately represented by the current protocol for HU. In these cases, the National Transplant Center acquires a written report from the clinicians and assesses whether to grant access to the program. Considering these changes, we wanted to analyze the progress of the entire management process of national liver HUs, by investigating the transplantation rates for patients included in the liver HU program and the outcome of patients with HU hepatic status requiring LT over time.

METHODS

Patients on the Waiting List

We analyzed all adult recipients (≥18 years of age) registered in the waiting list (WL) for HU-LT during the 2014 to 2017 four-year period. We evaluated the recipients' age, gender, ABO blood group, request date and time, and transplantation date and time. For each patient, it was possible to receive more than 1 request of liver in urgency, in case of patient retransplant or with patients who lost and then regained HU criteria. Patients with a request for HU-LT combined with other grafts have been excluded from our analysis.

Table 6. Number of Requests With Mean Waiting Days Between the Date of the Registration of the Request and the Date of Donor Procurement ≤ 2 Days

	Requests With Mean Waiting Time Within 2 Days									
	0	1st	2nd	3rd	4th	5th	6th	7th	8th	Total
AD	39	17	4	5	4	1	1	2		73
Hepatectomy	2	3	1		1					7
FH	46	33	7	4						90
WD	4	1	3	2		1				11
PNF	40	16	7	5						68
HAT	24	9	1							34
Total	155	79	23	16	5	2	1	2		283
	257									

Abbreviations: AD, agreed derogation; HAT, hepatic artery thrombosis; FH, fulminant hepatitis; PNF, primary nonfunction; WD, Wilson disease.

The specific objective of this study is to evaluate the trend of the HU requests over time, the changing clinical conditions of the patients requiring a HU-LT, the percentage of transplants annually performed for this patient category, and the patient time-lapse waiting for a suitable liver. Furthermore, starting from the time when the HU WL was entered, the patient's outcome was evaluated by comparing the patient's intention to treat (ITT) survival rate according to the indications to transplant and to the group to which they belong: whether they are on the urgency list or not and whether they have undergone a transplant or not.

Donors

We recorded date and time of the donor reporting, that is, the donor without opposition to organ donation and who fulfilled the LT-HU requests. We registered donor age, sex, and ABO blood group. The analyses relating to the match between donor and recipient were conducted on the fulfilled requests, only for the first LT for each patient.

Registered Requests

We considered the overall number of the received HU liver requests, date and time of request registration, patient indication for HU-LT, and the causes for patient delisting (transplant, clinical worsening, death, or clinical improvement). We considered the average value of days between requests' registration date, donor reporting, and LT. Furthermore, to refine the analysis, we measured the average hours between the registration of the request and the donor reporting. Waiting times and survival analyses were conducted only for the first HU-fulfilled request. However, we provided a snapshot of the patients undergoing late HU retransplantation (Fig 1).

Statistical Analysis

The HU-LT outcome has been evaluated by Kaplan-Meier univariate method and survival values are shown both for overall cases and stratified by indication for HU.

Survival analysis includes the overall patient survival rate, the overall graft survival rate, and the overall, death-censored, graft survival rate.

In addition, we compared patient' survival rates (by Kaplan-Meier analysis) among 4 different groups: (1) patients on the HU list, (2) patients on the standard list, (3) patient receiving transplants, and (4) patients who did not receive a transplant.

In this case, we analyzed the patient's ITT survival rate, following each patient from the enrollment date on the standard list to their last follow-up (during the period of 2014-2017). Each patient belongs to 1 of the 4 previously described groups.

Statistical analyses have been performed using the SPSS Statistics, version 22.0 (IBM, Chicago, IL, United States) statistics program.

RESULTS

Patients

Between 2014 and 2017, we enrolled on the HU-LT-WL, 360 patients (244 men, 116 women; mean age 48.4 years ± 12.3 SD). Four patients were excluded from our analysis because they needed an LT combined with other organs (3 liver-kidney and 1 heart-liver). Three hundred fifty-six patients (241 men, 115 women; mean age 48.2 years ± 12.3

Table 7. HU-LT Mean Waiting Time in Hours

	Mean Waiting Hours Between the Request and the Donor Reporting								
	0	1-5	6-12	13-24	25-48	>48	Requests Number	Mean Waiting Hours < 48	Mean Waiting Hours (All)
AD	32	6	1	12	9	13	73	6	22
Hepatectomy	2		1	2	1	1	7	10	22
FH	31	12	4	21	18	4	90	10	13
WD	1	2	1	1	3	3	11	21	39
PNF	32	7	1	10	13	5	68	8	13
HAT	18	6	–	8	2	–	34	5	5
Total	116	33	8	54	46	26	283	8	16

Abbreviations: AD, agreed derogation; FH, fulminant hepatitis; HAT, hepatic artery thrombosis; HU, high urgency; LT, liver tranplantation; PNF, primary nonfunction; WD, Wilson disease.

SD) were included in our study and 370 requests for LT-HU have been managed. Two hundred eighty-three patients have been transplanted (277 with a single LT in HU and 6 retransplanted in HU). The data on the donor-recipient match are shown in Table 1.

Seventy-three patients have not been transplanted (Fig 1). In particular, 32 patients have been delisted from the HU list as a result of clinical improvement. Of these, 24 were then definitively deleted from the WL for LT due to nonsuitability for transplantation, 3 were previously

Case Processing Summary (283 PZ)

Indication to HU-LT	Total N	N of Events		Surv(%)	SE
FH	82	19		70,2	5,9
AD	59	12		73,1	7,1
EPATECTO	6	0		100,0	,0
PNF	60	27		50,7	7,0
HAT	27	3		84,6	8,4
WD	11	3		50,0	20,4
Overall	245	64		67,1	3,5

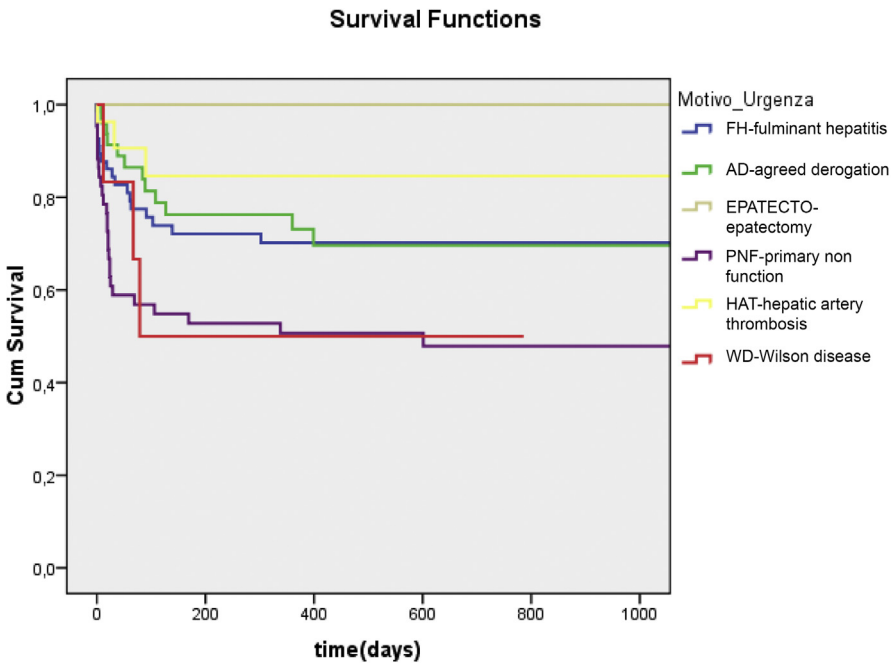

Fig 5. Patient overall survival and for indication for LT. LT, liver transplantation.

Case Processing Summary (283 TX)					
Indication to HU-LT	Total N	N of Events		Surv(%)	SE
FH	82	22		67,1	5,9
AD	59	12		73,1	7,1
EPATECTO	6	1		75,0	21,7
PNF	60	27		50,7	7,0
HAT	27	4		80,1	9,1
WD	11	3		50,0	20,4
Overall	245	69		65,2	3,5

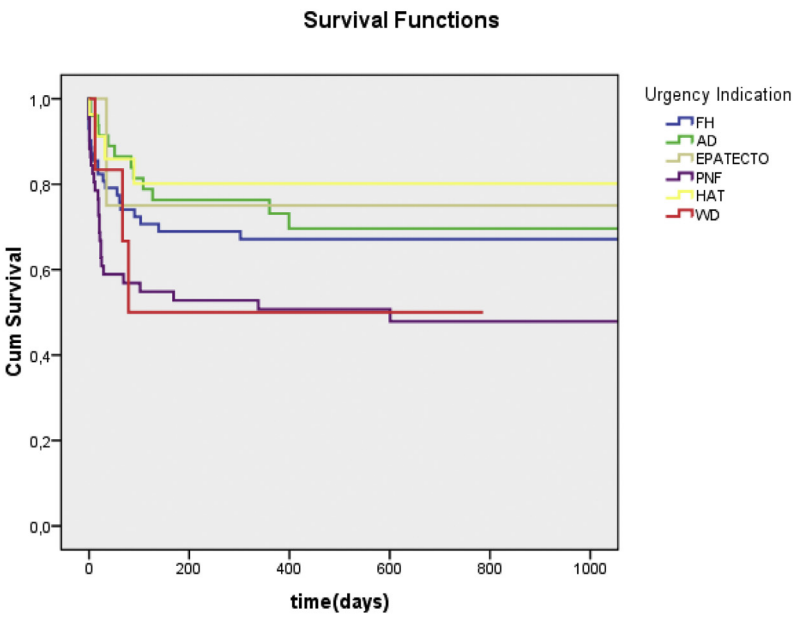

Fig 6. Organ overall survival and indication for LT. LT, liver transplantation.

transplanted, with an initial poor function that later improved, and 5 were transplanted subsequently not in HU. Thirteen patients have been delisted from the HU list for clinical deterioration (8 of them died on the standard list and 5 were excluded from the list due to nonsuitability for transplantation). Finally, 28 patients died on the HU list before receiving a suitable liver.

Requests

Out of the 356 enrolled patients, 370 requests were managed (Fig 1). FH has been shown to be the most frequent indication (n = 114; 30.8%) during the whole period, followed by PNF (n = 105; 28.4%), AD (n = 86; 23.2%), HAT (n = 43; 11.6%), WD (n = 12; 3.3%), and hepatectomy for trauma (n = 10; 2.7%) (Fig 2). Two hundred ninety-one requests were satisfied with the first available liver on the national territory, with a LT rate of 78.7% (Figs 3–4). Two hundred seventy-seven (95.2%) requests have been received for the first transplant and 14 (4.8%) for retransplant. Details about the requests for retransplantation are shown in Table 2. Seventy-nine requests (21.3%) throughout the period were not met (Tables 3A and 3B). In particular, 35 requests (44.3%) have not been managed for clinical improvement, 16 (20.2%) due to clinical deterioration, and 28 (35.5%) for death on the list.

Waiting time and survival analysis were performed considering 283 requests for first transplant (Fig 1). The average waiting time between the date of request registration and the date of transplantation was 1.7 days (Table 4). Two hundred thirty-two requests were satisfied within 2 days and this number increased to 257 considering the time between the request registration and the donor reporting (Tables 5–6). Considering the requests that were satisfied within the first day of enrollment, the average waiting time from request to transplant was 8 hours. Furthermore, in 116 cases, requests were promptly satisfied, since a compatible donor was already available at the time of patient referral. The average waiting time for all the requests has been of 16 hours (Table 7).

Survival Analysis

We analyzed 283 transplants, 277 of which were first transplants and 6 retransplants (2.1%). Out of the latter, 3 patients died after the second or third LT, 2 are alive to date and 1 was lost to follow-up.

We focused only on the first transplants, to avoid the mixing effect on the same patient with different indications for HU-LT. Survival analysis was applied on 245 transplants for which follow-up data were available (86.6%).

The overall 1-year patient survival rate is 67.1%; the indication for HU-LT that appears to perform better over time is HAT (84.6%), followed by AD (73.1%), HF (70.2%), and WD (50%) (Fig 5).

The overall 1-year graft survival rate (Fig 6) was 65.2%; according to urgent transplant indication, the best results were obtained for HAT (80.1%), followed by hepatectomy for trauma (75.0%) and AD (73.1%).

The overall 1-year graft survival rate (death-censored), measured on all the patients, was 85.4%; the indications for HU-LT that appear to perform better over time were HAT and WD (94.4%) followed by HF (87.4.9%), AD (83.3%), PNF (79.3%), and hepatectomy (75%) (Fig 7).

The ITT patient survival analysis was performed on 6282 total patients on the WL for LT in the examined period: 4191 received a liver in the standard list and 283 in the HU list [10]. Their 1-year patient survival rate (mean survival rate ± SD [%]) was 93 ± 0.4 and 69.2 ± 3.4, respectively; 1735 patients were not transplanted on the standard list and 73 were not transplanted on the HU list. The 1-year patient survival rate (mean survival rate ± SD [%]) was 74 ± 1.1 and 20.8 ± 8.2, respectively (Fig 8).

DISCUSSION

In Italy, the management of emergency WLs is of national competence and includes the definition of criteria for patient inclusion. Included patients have allocation priority on a national basis, regardless of the donor's procurement area.

Case Processing Summary (283 TX)

Indication to HU-LT	Total N	N of Events		Surv(%)	SE
FH	76	8		87,4	4,4
AD	57	6		83,3	6,3
EPATECTO	6	1		75,0	21,7
PNF	51	9		79,3	6,3
HAT	26	1		94,4	5,4
WD	10	0		100,0	
Overall	226	25		85,4	2,8

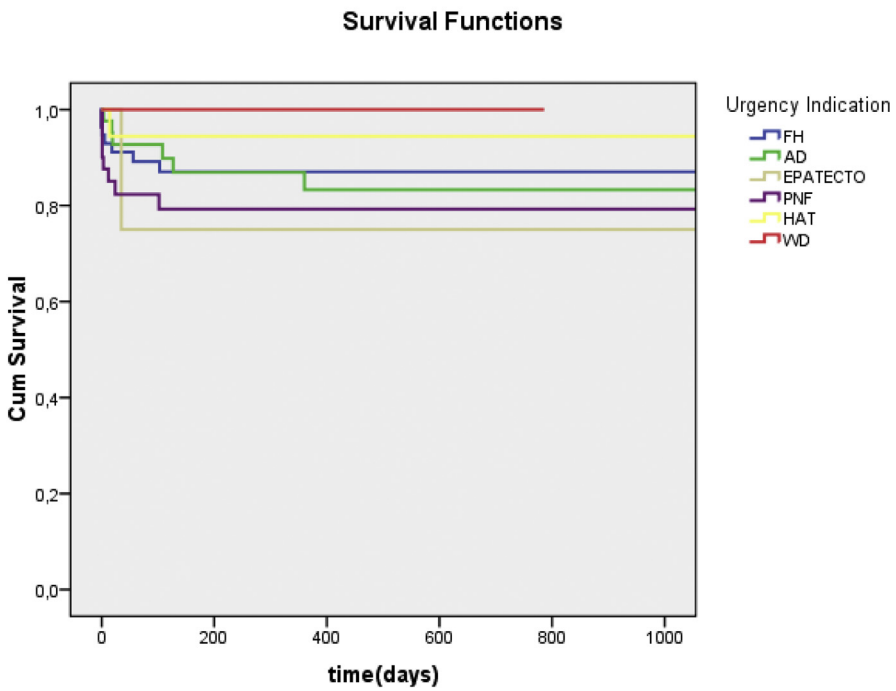

Fig 7. Organ overall survival (death-censored) and indication for LT. LT, liver transplantation.

The lists are usually specific to the types of organ and transplant needed (kidney, liver, lung, heart, pancreas, small bowel) and are also specific for pediatric transplants.

There are no uniform rules or systems for organ allocation in Europe or within the European Union and there are several organ exchange organizations for different countries and geographic areas. In Italy, the AD has been included among the criteria to access to the HU-WL, in order to give to the recipients who do not meet codified criteria, the possibility to quickly find a compatible liver. From a first review of transplant indications, these are young recipients, in acute clinical conditions on chronic pathologies, not represented by codified criteria but for which the transplant is necessary or mandatory in a short time as a life-saving procedure. A more in-depth analysis would be necessary to try to evaluate the possibility of resorting to a larger category.

This study merely represents a snapshot of HU-LT requests in Italy, showing an analysis about the efficacy of organ allocation in a short time, rather than a modification of the indications for transplant.

In Italy, between 2014 and 2017, 6425 adult patients passed through the LT WL, and 4361 LT were performed (67.9%), of which 291 were in HU conditions (6.7%). This initially lower percentage (5% in 2014), remained stable at around 6.7% during the 2015 to 2016 period and then gradually increased between 2016 and 2017 up to 7.8%. This happened despite the simultaneous increase in LTs, which in the same period went from 1001 in 2014 up to 1219 in 2017 (+17.9% increase) [10].

The number of the requests for HU-LT have been increasing over the years. The indications for HU-LT including FH and other diagnosis have remained stable over time except for PNF, which peaked in 2016, and HAT, which has increased in the last year. On the contrary, requests for AD have been increasing more and more over the years reaching, in the last year, the FH levels. This means, most likely, that something is changing in the LT landscape.

Most of the requests received have been satisfied with an LT (78.7%), and if we evaluate the trend during the study period, we can notice that this percentage of transplants has increased from 71% in 2014 to 82% in the 2017 (up 13%) and remained stable at 80% during the period of 2015 to 2016. Even as far as the requests received for the patients to be retransplanted are concerned, they have all been fulfilled, even more than once.

A total of 21.3% of the requests throughout the period were not processed, but this percentage falls to 13.1% if we remove from the analysis, the delisting for clinical improvement (n = 35) and we consider only the effective failures of the system, such as patient death or clinical worsening (n = 44). Similarly, the percentage of fulfillment of the effective requests increases to 86.9% (Fig 5). In reality, even these failures should not be linked to a failure of the system, if we consider that the event of death or nonsuitability for transplantation occurred within 48 hours, which is also the average waiting time for an urgent liver, as shown by our analysis. This means that, probably, the patient's clinical condition was too compromised at the time of referral, and the patient soon lost the indication for transplant.

The waiting time analysis has been conducted on 2 levels: first of all, we considered the waiting days between the registration of the request and the LT for year and indication.

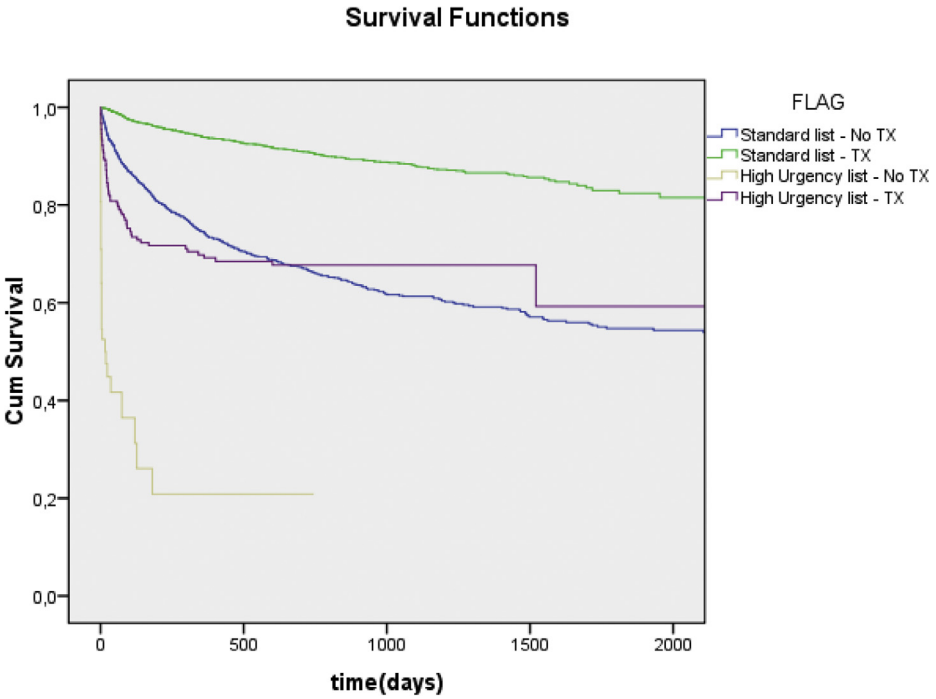

Fig 8. ITT patient survival (groups: combinations of transplanted and HU vs not transplanted and not HU). HU, high urgency; ITT, intention to treat.

Due to the short waiting times, this first analysis appeared immediately inaccurate. Therefore, we limited the evaluation to the requests that awaited transplantation, no longer than 2 days. For these, we evaluated the average time between the request registration and donor reporting for each request that was fulfilled. Also in this case, for 257 times, the request has been fulfilled within 2 days (Table 6). In order to investigate more precisely, we have evaluated the average waiting time between the hour of registration request and the hour of donor reporting. Since these times are very close, reckoning this timing in terms of days might have significantly affected our analysis, because of those patients who potentially waited less than 24 hours. The most important piece of information obtained was that a large part of the requests (41% of the total fulfilled requests) are all immediately met because they were registered when the donor's organ was already available and that most requests (74% of the total fulfilled requests) were met in less than 24 hours. This demonstrates the high efficiency of the allocation system in Italy.

As for the comparison between transplanted and non-transplanted patients, in HU and not in HU, it is clear that there are better results both in terms of graft and patient survival for transplanted patients compared with non-transplanted patients (Fig 8). The aspect that should be highlighted is that the survival rate of patients on the HU list who did not receive transplants is significantly lower than that of the patients on the standard list who did not receive transplants. This is due to the lack of available organs for transplant and also the result of acute diseases, too severe to be successfully treated.

CONCLUSIONS

In our experience, the fulfillment rates of the HU-LT requests remained steadily high over the years, thanks to an efficient system, which features the centralization of management as a decisive step. The survival analysis shows that the indication for LT is confirmed to be life-saving in patients in HU, compared to conventional treatments.

The number of HU requests in our country have been increasing over time, and this is probably due to a growing need to add other indications to those already codified. This certainly depends on the changes in the clinical landscape that we have been witnessing in recent years.

In fact, the reduction of liver demands in other fields, such as for example for hepatitis C virus–related liver diseases, is opening new indications to LT and some may suggest an extension to the limits of access to clinical urgency. However, this is to be carefully evaluated, taking into account the present shortage of livers available from cadaveric donors, and the need to guarantee excellent long-term results.

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