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Liver transplant recipients and prioritization of anti-HCV therapy: an Italian cohort analysis

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Abstract

Background and Aims—In patients with hepatitis C virus (HCV), recurrence of infection after liver transplant (LT) is universal and associated with worst survival. We present the results of an Italian cohort to compare the 3-year outcome of HCV-Ab-positive and HCV-Ab-negative LT recipients and to assess the potential interaction between HCV-Ab sero-status and other risk factors for LT failure.

Methods—The study is a multicentre cohort including a sample of liver transplant centres. Participant's information was collected at the local level. The best functional form of variables was decided according to the objective methods based on information theory. Association between transplant failure and potential risk factors was assessed in univariate and multivariate Poisson regression model with random intercept.

Results—Between June 2007 and May 2009, 1164 LT recipients were enrolled in 16 Italian transplant centres, of them 275 (23.63%) experienced LT failure. Incidence rates of LT failure was 0.32 and 0.23 per 1000 person-days in HCV-Ab-positive and HCV-Ab-negative recipients respectively ($P = 0.003$). Inferential models according to Akaike information criterion indicated that donor–recipient age difference and donor–recipient sex matching were more informative to predict LT failure than the age and the sex as separate variables. Multivariate analysis provided evidence that HCV-Ab sero-status, time after LT, donor–recipient age difference, donor–recipient sex matching and recipient's MELD score were significantly associated with LT failure. Moreover, the effect of HCV-Ab sero-status on LT failure was modified by the simultaneous action of time after LT and donor–recipient age difference. No interaction was found between recipient's HCV-Ab sero-status and either recipient's MELD or donor–recipient sex matching.

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Conclusion—In view of the imminent introduction of new anti-HCV therapies, our study provides information to assess which LT recipients should be prioritized for receiving these highly effective, but expensive, new treatments. This is particularly relevant for those clinical settings where healthcare prioritization is endorsed by national authorities.

Keywords

Donor; recipient age difference; donor; recipient sex matching; liver graft failure; MELD score; multicentre study

Hepatitis C virus (HCV) is one of the leading causes of end-stage liver diseases and liver transplantation (LT) worldwide (1). Official data from the Italian authority for organ transplant [Centro Nazionale Trapianti (CNT)] indicates that at the beginning of April 2014, a total of 958 patients were waiting for LT in Italy and 410 (43%) of them were chronically infected with HCV (unpublished).

Recurrence of infection is universal in LT recipients chronically infected with HCV (1) resulting in significantly higher mortality and lower quality of life. In particular, the median time to HCV-related cirrhosis is about 30 years for immunocompetent individuals, while 10–30% of HCV-positive LT recipients develop cirrhosis in less than 5 years and the majority experience graft loss in 9–12 years (2). Therapy with interferon is poorly tolerated in LT recipients and contraindicated in patients with decompensated cirrhosis waiting for LT (3, 4). Moreover, there is no clear evidence that interferon therapy is an effective intervention either when used as pre-emptive therapy right after LT or when moderate to severe fibrosis is already established (5).

The recent approval of drugs with direct antiviral activity (DAAs) against HCV has paved the way for interferon-free regimens. Because of their extraordinary efficacy and low drug–drug interactions with immuno-suppressants, these new antiviral drugs are the ideal candidates for anti-HCV therapy in LT recipients. However, given the early stage of clinical implementation, there are limited ‘real life’ data on safety and efficacy of DAA in LT recipients; moreover, the best time to start therapy post-transplant and the overall therapy duration are, as yet, a matter of discussion (3, 4).

This study aimed to describe and to compare the early post-transplantation outcome of HCV-positive and HCV-negative LT recipients and to assess the potential interaction between the HCV status of the recipient and the other risk factors for LT failure with the goal of identifying those LT recipients who should be prioritized for receiving highly effective antiviral therapy with new DAAs. This is particularly relevant for those clinical settings and in those countries where healthcare prioritization is endorsed by national health authorities.

Methods

Setting

Italy has a central authority (CNT) that is responsible for co-ordinating organ donation and transplantation activities throughout the Country. About 1000 LTs are performed each year in Italy, 45% of which are carried out on anti-HCV Ab-positive recipients.

Study design

This study has been designed as a national, multicentre cohort. Patients were considered at risk from the day of transplantation until: (a) the day of death; (b) the day of retransplantation or (c) 1080 days (i.e. 3 years) after LT.

Participants

All patients aged 18 or older who received their first LT or dual liver–kidney transplant between 1 June 2007 and 30 May 2009 in Italy were eligible. Patients who received multi-organ transplant, other than dual liver–kidney, and those who underwent liver retransplantation were excluded. Patient information was collected at the local level using predefined forms and forwarded to the CNT every 6 months.

Outcome and risk factors

Transplant failure was considered as the primary outcome of this study, defined as either: (a) recipient death or (b) liver retransplantation.

We analysed the association between the outcome and 13 potential risk factors (Table 1). The functional form of the association between the outcome and either donor's age, recipient's age, recipient–donor age difference, recipient–donor sex matching and year of transplantation was decided according to their information power assessed by Akaike information criterion (AIC) (6) (see Appendix S1 for details). Time after transplant, was divided into the following intervals: 0–89, 90–359, 360–719 and 720–1080 days. Recipient's MELD score (7) at the time of transplant was categorized in a three-level variable based on the distribution of scores in our sample. The remaining six risk factors were analysed as binary variables.

Statistical methods

Rates were calculated according to events per 1000 person- days and hazard ratio (HR) was used as the measure of association. Association between the outcome and risk factors was assessed in univariate and multivariate Poisson regression model with random intercept to incorporate the potential effect of latent variable related clinical centres (i.e. multilevel Poisson model with gamma frailty) (8). *P*-values were calculated according to Wald's method.

The best set of variables for the multivariate model was chosen according to simplicity and fitness criteria through a manual stepwise approach with backward elimination (see Appendix S2 for details). Potential interaction between HCV-Ab and all variables included in the multivariate final model was assessed by model-based likelihood ratio test (LRT) and interaction term(s) were included when the LTR *P*-value was <0.100.

Statistical evidence for the association between the outcome and risk factors was inferred either as: no evidence ($P \geq 0.100$), weak evidence ($0.100 > P \geq 0.050$), good evidence ($P < 0.050$) (9).

STATA 13.0 (StataCorp, College Station, TX, USA) package was used for the analysis and to generate plots.

Ethics

Data have been collected by the Italian Transplant Informative System established by law 91/1999 in a mandatory National Registry as part of the quality assurance programme, according to current Italian regulations and guidelines for safety and quality in solid organ transplants.

This is an observational study and no patient underwent any medical intervention for this study. Authors of this article did not have access to the personal information of the enrolled patients.

Results

Descriptive and univariate analysis

At the time of the enrolment, 22 clinical units were authorized to perform LTs in Italy and 16 participated in this study. Of the 1508 LTs performed in the participating clinical units, 1270 were eligible for this study and for 1164 (91.6%) all data were available for analysis (Fig. 1). Table 1 reports the participants' characteristics.

By day 1080 after LT, a total of 275 transplant failures had occurred among the 1164 participants for a crude cumulative risk of 23.63%. Causes of transplant failure either for HCV-negative or HCV-positive recipients are reported in Table 2. The overall survival 1080 days after LT was 72.96% and 79.33% among HCV-positive and HCV-negative recipients respectively.

Univariate analysis (Table 1) showed that time after transplantation, HCV-Ab status, recipient's MELD score, donor's age, donor–recipient sex-matching and donor–recipient age difference were significantly associated with transplant failure.

Multivariate analysis

The final multivariate model found an association between transplant failure and time after LT, HCV-Ab status, recipient's MELD, recipient–donor sex matching and recipient–donor age difference (Table 3). It is worthy of notice that the stepwise approach indicated that recipient–donor age difference has a predictive power for transplant failure greater than donor's age and recipient's age as separate variables (see Appendix S1 for details). In addition, we found that male (donor) to female (recipient) sex matching may result in worse LT outcome than all other sex matching pairs.

The analysis of interaction provided good evidence that the effect of HCV-Ab on LT failure was not homogeneous over time after transplantation (P for interaction 0.006) and across recipient–donor age difference classes (P for interaction 0.004). No evidence of interaction was found between HCV-Ab and either recipient–donor sex matching (P for interaction 0.139) or recipient's MELD (P for interaction 0.775).

The analysis of interaction between HCV-Ab and time after LT or donor–recipients age difference is shown in Fig. 2. The analysis indicated that HCV-Ab serum status is strongly associated with an increased risk of LT failure when the donor was ≥10 years older than the recipient. Among these recipients, the association between HCV and LT failure appeared very early and it was already strongly significant by day 90 after transplantation (Fig. 2C). In addition, the effect of HCV on LT failure seems to be the highest between day 90 and 359 in all the three classes of donor–recipient age differences. In particular, during this period of time, recipients who received LT from a donor ≥10 years younger had and an increased risk of LT failure (Fig. 2A). Finally the effect of HCV on LT failure seems to be minimal when age difference between the recipients and donor is less than 10 years (Fig. 2B).

Discussion

Recurrent hepatitis C is a major issue after LT. In our study, recurrence of HCV infection directly caused more than 28% of all LT failures in HCV-positive recipients in the first 3 years after transplantation. The recent introduction of DAAs has the potential for new therapeutic options to prevent and treat HCV recurrence in LT recipients before and after LT respectively (10). Current guidelines suggest that LT candidates may receive DAAs while on the waiting list (3, 4). However, the real impact of these treatments cannot be predicted at present. Timing of pretransplant therapy can be challenging when organ availability is not precisely predictable. Moreover, it cannot be assumed that, to optimize resource allocation, local health authorities will be willing to defer treatment of these patients until after transplant. Indeed, the treatment of all candidates on the waiting list may produce resource wasting because of the treatment of patients who will die as a result of organ unavailability, despite a successful therapy. It is noteworthy that in our sample the median time to transplant was 103 days (interquartile range 37–306 days) and that about 43% of all recipients would not have been able to receive 12 weeks of DAA therapy even if they had started therapy the same day they entered the waiting list. Therefore, it is likely that clinicians will be dealing with the treatment of recurrent HCV following LT in the DAA era.

Our study confirmed, as expected, that HCV infection considerably increases the risk of LT failure. Univariate analysis indicated that 1080 days after transplantation, the global risk to experience a LT failure, either as recipient death or graft loss, was about 44% higher among HCV positive recipients than in those without infection. The observed 3-year graft survival was about 73% and 79% among HCV-positive and HCV-negative recipients respectively. These figures are slightly lower than those reported by Thuluvath *et al.* (i.e. 75% and 81%) who carried out a similar study between 1998 and 2007 in USA (11). This marginal difference may be because of Thuluvath *et al.* used patients instead of graft survival as primary outcome. In contrast, our figures are better than those reported by Forman *et al.* for the United Network for Organ Sharing who found that 3 years after LT, graft survival was about 66% in HCV-positive patients. Nevertheless, it must be considered that this study was carried out with the data of patients who received LT between 1992 and 1998 (12).

Our study shows that the influence of HCV is not homogeneous over time after LT and it can be modified by other risk factors, specifically, the age difference between donor and recipients. There is minimal effect of HCV in the very early post-transplant period (i.e. the

first 90 days in our study). This is consistent with other published studies which indicate that in this period, transplant failures are mainly because of causes other than HCV (13–15). Indeed, we found that between day 0 and 89 after LT, HCV-positive patients may have a better LT outcome than HCV-negative recipients, though this result must be interpreted with caution as it may be the consequence of the interplay of several unanalysed conditions such as: (a) a better matching for latent infection, as mentioned below; (b) the fact that HCV-positive patients may receive less aggressive immunosuppressive schemes (16) or (c) a loss of inferential power as a result of the introduction of simultaneous interaction terms in the regression model. It is noteworthy that a similar trend was also found by Thuluvath *et al.* (11).

Beyond the first 90 days, HCV does have a negative effect on transplant survival but the magnitude of this effect is modified by both recipient and donor ages. Several published studies have established that recurrence of HCV infection is far more severe in recipients of old donors than in the those who receive liver from the younger ones (17, 18). However, in this study, we found that the age difference between the recipient and donor may be an even more better predictor of LT failure than the donor's age itself. This is a new finding which has been proved through fully objective likelihood-based inferential techniques, such as AIC (6), and it can be useful to better inform about potential recipient-graft interaction and organ allocation. The identification of the biological reasons of this new finding are beyond the scope of our study. However, it is possible that the age difference is a good proxy for recipient donor matching with regard to age-related endemic latent infections (e.g. Cytomegalovirus, Epstein–Barr virus) which are known to produce more severe clinical manifestations when a mismatch for such infections are present (19, 20). These results would argue that young HCV-positive patients should not receive grafts from older donors while having detectable HCV RNA in the blood; as this would result in aggressive graft re-infection or if such a donor is used, that these recipients be targeted for very early treatment with highly active DAA therapy post-LT. Interestingly, the effect of HCV seems to be minimal in the first 1080 days after transplantation when age difference between recipient and donor is less than 10 years. This information may be useful in prioritizing LT recipients for HCV treatment, with those recipients with age difference less than 10 years being deferred for treatment, whereas those with age difference more than 10 years offered treatment as soon as possible.

This study has some limitations. There are a lack of data about immunosuppressive regimens, though there are no conclusive evidence about the effect of different immunosuppression schemes on early post-LT outcome in HCV-infected recipients (21). Not all Italians centres chose to participate and voluntary enrolment might have introduced a selection bias. However, 73% (16 out of 22) of all LT centres were included and with a loss of less than 9% of potentially eligible participants. In addition, the six centres which did not participate this study were similar to the included centres with regard to geographical location and median number of transplants carried out.

In summary, this national study of LT provides insights into the primary determinants of transplant loss (graft and patient) among HCV patients and provides potential guidance on how selecting patients to anti- HCV therapy in settings who decide to endorse prioritization

scheme for access to new DAA. Newly approved or soon-to-be approved DAA combinations are highly effective in almost all LT patients, despite previous failure to interferon and the stage of liver diseases, but cost is limiting in some clinical settings. Guidance based on 'real life' data is critical in guiding prioritization programmes. Based upon our results, a key factor to be considered is the age difference between donor and recipient and the time from LT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

95% CI	95% confidence interval
CNT	Centro Nazionale Trapianti (Italian authority for organ transplant)
DAA	drugs with direct antiviral activity
F	female
HCV-Ab	serum antibody against hepatitis C virus
HCV	hepatitis C virus
HR	hazard ratio
LRT	likelihood ratio test
LT	liver transplant
MELD	model for end-stage liver disease
M	male
RNA	ribonucleic acid

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Key points

- Hepatitis C virus (HCV) remain a significant clinical transplant medicine.
- Our study provides evidence that the effect of HCV recurrence on transplant failure is strongly affected by donor's and recipient's sex and age.
- Through an approach based on information theory we find that age and sex matching, rather than ages and sexes as separate variables, can at best predict early transplant failure in HCV positive recipients.
- This study provides insights into the primary determinants of transplant loss among HCV patients and provides potential guidance on how selecting patients to anti-HCV therapy in settings who decide toendorse prioritization scheme for access to new DAA.

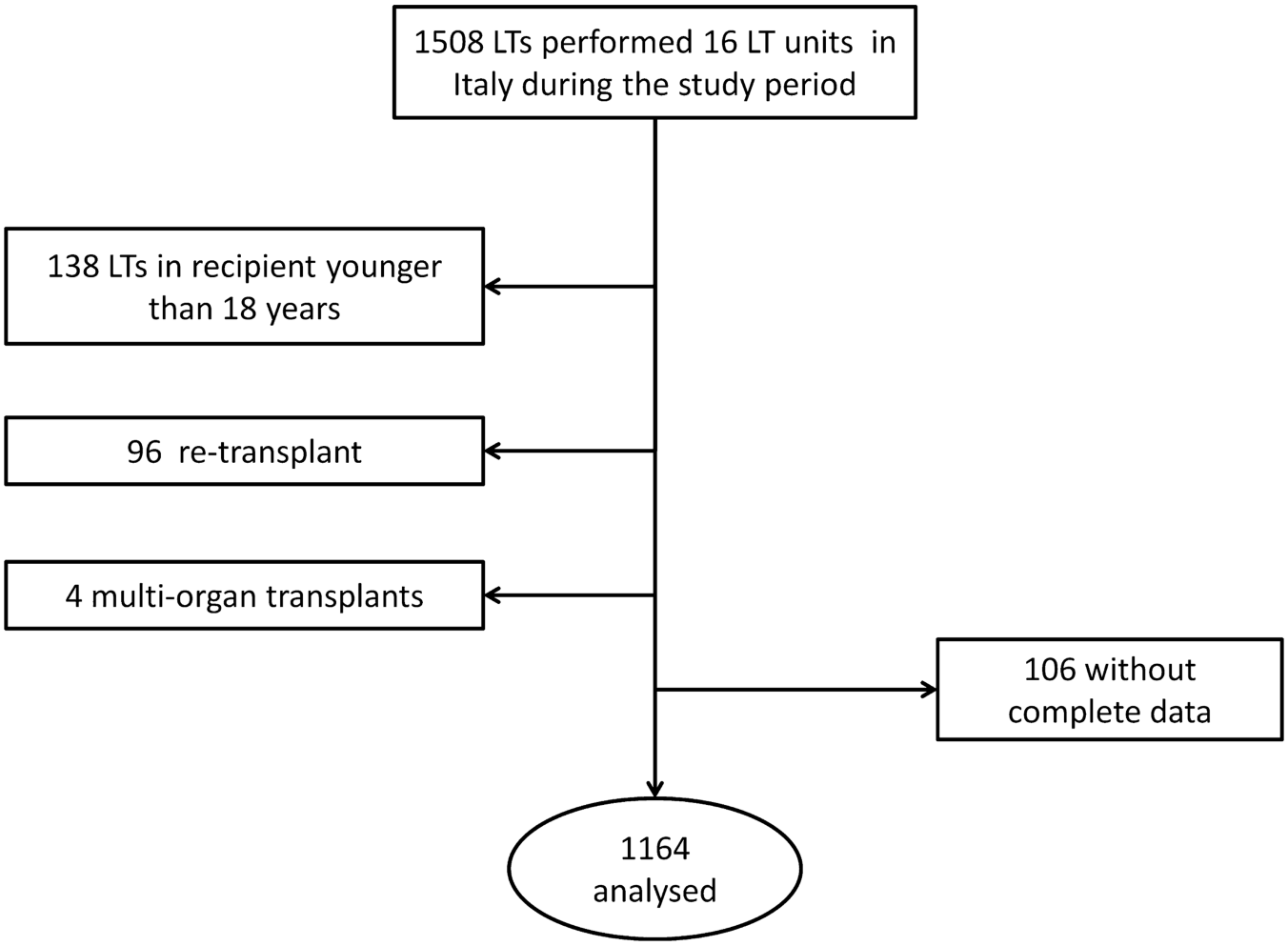

Fig. 1.
Sampling of study population flow chart.

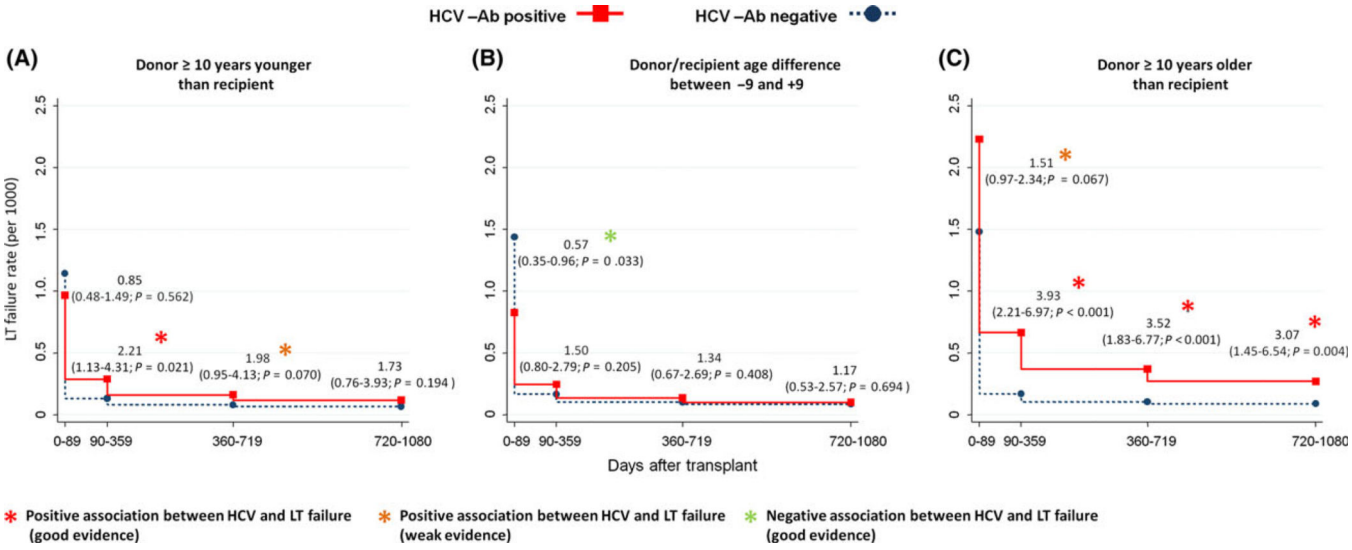

Fig. 2.

Analysis of interaction between time after liver transplant, recipient–donor age difference and recipient's HCV status. Figures above dots represent punctual estimates of hazard ratios, the 95% confidence interval and *P*-values.

Table 1

Cohort characteristics and univariate analysis

	Descriptive analysis			Univariate analysis	
Risk factor	**Events**	**Time at risk**	**Rate (95% CI)**	**HR (95% CI)**	***P*-value**
Overall	275	1 005 918	0.27 (0.22–0.34)	–	–
Time after liver transplant (days)					
0–89	130	96 653	1.35 (0.98–1.88)	Base	–
90–360	**67**	**269 022**	**0.25 (0.20–0.32)**	**0.19 (0.14–0.25)**	**<0.001**
360–719	**46**	**332 769**	**0.14 (0.11–0.19)**	**0.10 (0.07–0.15)**	**<0.001**
720–1080	**32**	**307 474**	**0.10 (0.07–0.15)**	**0.08 (0.05–0.12)**	**<0.001**
HCV-Ab					
Neg.	129	552 153	0.23 (0.17–0.32)	Base	–
Pos.	**146**	**453 765**	**0.32 (0.26–0.41)**	**1.44 (1.13–1.83)**	**0.003**
Recipient's age (years) *					
18–47	71	231 238	0.31 (0.23–0.42)	Base	–
48–55	**57**	**266 001**	**0.21 (0.16–0.29)**	**0.69 (0.49–0.98)**	**0.040**
56–61	73	256 255	0.28 (0.21–0.40)	0.97 (0.70–1.35)	0.861
62–70	74	252 424	0.29 (0.21–0.41)	0.92 (0.66–1.28)	0.619
Recipient's MELD					
0–19	171	713 662	0.24 (0.19–0.30)	Base	–
20–29	67	221 437	0.30 (0.22–0.43)	1.21 (0.90–1.61)	0.203
≥30	**37**	**70 820**	**0.52 (0.38–0.74)**	**2.17 (1.50–3.14)**	**<0.001**
Dialysis †					
No	263	975 416	0.27 (0.22–0.34)	Base	–
Yes	12	30 502	0.39 (0.16–1.46)	1.46 (0.81–2.62)	0.205
Hepatocellular carcinoma					
No	211	787 252	0.27 (0.22–0.33)	Base	–
Yes	64	218 666	0.29 (0.18–0.46)	0.93 (0.67–1.29)	0.670
Split liver					
No	265	953 124	0.28 (0.22–0.35)	Base	–
Yes	10	52 794	0.19 (0.13–0.29)	0.70 (0.37–1.33)	0.280

	Descriptive analysis			Univariate analysis	
Risk factor	**Events**	**Time at risk**	**Rate (95% CI)**	**HR (95% CI)**	***P*-value**
Dual liver–kidney transplant					
No	269	971 599	0.28 (0.22–0.34)	Base	–
Yes	6	34 319	0.17 (0.06–0.70)	0.62 (0.28–1.41)	0.257
Donor with infection[‡]					
No	264	955 086	0.28 (0.22–0.35)	Base	–
Yes	11	50 832	0.22 (0.13–0.35)	0.75 (0.41–1.399	0.363
Donor age (years)	**275**	**1 005 918**	**0.27 (0.22–0.34)**	**1.01 (1.00–1.02)**	**0.003**
Transplant year	275	1 005 918	0.27 (0.22–0.34)	0.90 (0.76–1.07)	0.234
Sex matching					
M to M	115	472 672	0.24 (0.18–0.34)	Base	–
F to M	90	300 639	0.30 (0.23–0.40)	1.30 (0.98–1.71)	0.066
M to F	**34**	**82 020**	**0.41 (0.32–0.55)**	**1.71 (1.16–2.51)**	**0.006**
F to F	36	150 588	0.24 (0.17–0.34)	0.97 (0.67–1.42)	0.893
Donor/recipient age difference (years)					
≥−10	64	283 336	0.23 (0.17–0.31)	Base	–
−9 to 9	83	378 022	0.22 (0.18–0.28)	1.03 (0.74–1.43)	0.873
≥10	**128**	**344 560**	**0.37 (0.29–0.47)**	**1.75 (1.29–2.37)**	**<0.001**

HR, hazard ratio; 95% CI, 95% confidence interval; HCV-Ab, serum antibody against HCV; M, male; F, female.

[*]Age classes are reported according to quartile distribution.

[†]Recipient needed for renal dialysis at least twice a week while on the waiting list.

[‡]recipient received transplant from a donor who was diagnosed with septicaemia or meningitis on the donation day.

Risk factors with good evidence of association with outcome (i.e. $P < 0.05$) are reported in bold.

Table 2

Causes of liver transplant failure

Cause of transplant failure	HCV Ab negative Num. (%)	HCV Ab positive Num. (%)	Overall Num. (%)
Recurrence of primary diseases other than HCV *	19 (14.7)	12 (8.2) †	31 (11.3)
Recurrence of primary HCV cirrhosis	–	42 (28.8)	42 (15.3)
Conditions other than primary disease *	106 (82.2)	88 (60.3)	194 (70.5)
Not reported	4(3.1)	4(2.7)	8(2.9)
Overall	129 (100.0)	146 (100.0)	275 (100.0)

The table reports causes for the 275 liver transplant failures (i.e. 224 deaths and 51 retranplant) recorded between day 0 and day 1080 after transplantation in the 1164 patients enrolled in this study.

* Primary diseases: main reason for liver transplantation.

† Two patients had cirrhosis caused by alcoholism and 10 had recurrence of primary cancer without cirrhosis.

Table 3

Multivariate analysis

Risk factor*			HR (95% CI)*	*P*-value
Donor ≥10 years younger than Recipient	Time after LT 0–89 days	HCV-Ab neg.	Base	–
		HCV-Ab pos.	0.85 (0.48–1.49)	0.562
	Time after LT 90–359 days	HCV-Ab neg.	Base	–
		HCV-Ab pos.	**2.21 (1.13–4.31)**	**0.021**
	Time after LT 360–719 days	HCV-Ab neg.	Base	–
		HCV-Ab pos.	1.98 (0.95–4.13)	0.070
	Time after LT 720–1080 days	HCV-Ab neg.	Base	–
		HCV-Ab pos.	1.73 (0.76–3.93)	0.194
Donor–recipient age difference between −9 and +9 years	Time after LT 0–89 days	HCV-Ab neg.	Base	–
		HCV-Ab pos.	**0.57 (0.35–0.96)**	**0.033**
	Time after LT 90–359 days	HCV-Ab neg.	Base	–
		HCV-Ab pos.	1.50 (0.80–2.79)	0.205
	Time after LT 360–719 days	HCV-Ab neg.	Base	–
		HCV-Ab pos.	1.34 (0.67–2.69)	0.408
	Time after LT 720–1080 days	HCV-Ab neg.	Base	–
		HCV-Ab pos.	1.17 (0.53–2.57)	0.694
Donor ≥ 10 years older than Recipient	Time after LT 0–89 days	HCV-Ab neg.	Base	–
		HCV-Ab pos.	1.51 (0.97–2.34)	0.067
	Time after LT 90–359 days	HCV-Ab neg.	Base	–
		HCV-Ab pos.	**3.93 (2.21–6.97)**	**<0.001**
	Time after LT 360–719 days	HCV-Ab neg.	Base	–
		HCV-Ab pos.	**3.52 (1.83–6.77)**	**<0.001**
	Time after LT 720–1080 days	HCV-Ab neg.	Base	–
		HCV-Ab pos.	**3.07 (1.45–6.54)**	**0.004**
MELD Score		0–19	Base	–
		20–29	1.25 (0.93–1.67)	0.139
		30 or more	**2.30 (1.58–3.34)**	**<0.001**
Recipient and donor sex matching		M to M	Base	–
		F to M	1.21 (0.91–1–60)	0.186
		M to F	**1.67 (1.13–2.47)**	**0.011**
		F to F	0.98 (0.67–1.44)	0.931

HR, hazard ratio; 95% CI, 95% confidence interval; LT, liver transplantation; HCV-Ab, serum antibody against hepatitis C virus; M, male; F, female.

*HR estimates are provided according to simultaneous interaction between HCV-Ab status, donor–recipient age difference and time after LT.

Risk factors with good evidence of association with outcome (i.e. $P < 0.05$) are reported in bold.