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Journal:	*Liver International*
Manuscript ID	LIVint-15-01041.R1
Wiley - Manuscript type:	Original Articles
Date Submitted by the Author:	06-Mar-2016
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Keywords:	Liver transplantation, Survival, International comparison

International comparison of liver transplant programmes: differences of indications, donor and recipient selection, and outcome between Italy and UK

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**See supplementary file

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Number of figures and tables: 3 figures and 3 tables

Manuscript word count: 5,216

Keywords: Liver Transplantation, Survival, International Comparison.

Conflict of interest: Non conflict of interest to disclose

Financial support: This study has been supported by the *Liver Match Study* and by the NHSBT.

List of abbreviations in the order of appearance:

LT, liver transplantation

UK, United Kingdom

ELTR, European Liver Transplant Registry

AISF, Associazione Italiana Studio Fegato

CNT, Centro Nazionale Trapianti

DBD, donation after brain death

ODT, Organ Donation and Transplantation

NHSBT, National Health Service Blood and Transplant

DCD, donation after circulatory death

HCV, hepatitis C virus

ALD, alcoholic liver disease

HBV, hepatitis B virus

PSC, primary sclerosing cholangitis

PBC, primary biliary cirrhosis

HCC, hepatocellular carcinoma

MELD, model for end-stage liver disease

UKELD, UK model for end-stage liver disease

INR, international normalised ratio

BMI, body mass index

CIT, cold ischemic time

IQR, interquartile range

HR, hazard ratio

ECD, extended criteria donor

Tac, tacrolimus

CyA cyclosporin A

MMF, mycophenolate mofetil

Aza, azathioprine

Abstract

Background: Comparing liver transplant (LT) programmes internationally can improve outcomes by stimulating cross-national learning. Yet, comparison of crude outcomes, by using registry data, is limited by missing data, not allowing proper risk-adjustment for donor and recipient-related factors. The objective of this study was to compare two European LT programmes based on high-quality national longitudinal databases prospectively collected in Italy and UK, respectively.

Methods: We undertook a multicentre, international cohort study including all adults who underwent a first single organ LT in Italy (N = 1,480) and the UK (N = 1,003) between June 2007 and May 2009.

Results: Italian donors were much older compared to the UK ones. Hepatitis C virus infection and hepatocellular carcinoma had higher prevalence in the Italian cohort compared to the UK one (47.5% vs 23.1%, and 47.2% vs. 17.1%, respectively). Centres volume differed significantly, with 5 centres out of 7 in UK vs. only 2 out of 20 in Italy performing >60 transplants per year. No national strategies to drive the donor-recipient matching were identified in both countries. After appropriate adjustment, a higher risk of early transplant loss was identified in the Italian cohort, while no differences were found in the three-year survival rates.

Conclusions: International comparison of LT programmes provides the opportunity for benchmarking between heterogeneous healthcare systems and should ideally become a vital part of national quality assurance programmes. This requires the implementation of a standardized methodology for data collection to appropriately weigh each country's patient case-mix and donor and recipients risk factors.

Abstract work count: 250

Key points

- Comparing liver transplant performances internationally can stimulate cross-national learning by identifying gaps in the healthcare delivery and should therefore be routinely implemented.
- An appropriate adjustment of such comparisons for confounding factors, such as donor and recipient-related factors, would allow the identification of differences strictly related to the transplant procedure.
- Currently, international registeries are not sufficiently comprehensive to allow detailed comparisons between countries.
- To enable such comparisons, national registries should agree a common database, agreed definitions and ensure laboratory variables are standardised. To reduce the rate of missing data it is advisable to use longitudinal databases.

Background

Many developed countries are interested in measuring and improving the quality of health care for their citizens. Comparing quality of care internationally should stimulate cross-national learning and collaboration to improve this quality, and generate hypotheses defining the questions for future epidemiological research (1). The standardised nature of liver transplantation (LT) practice makes it uniquely placed to allow undertaking of reliable international comparisons of health care outcomes. International comparison of survival after LT is particularly difficult for the many differences that exist between countries in terms of aetiology of the liver diseases, quality of the donors, level of co-morbidities of the transplant candidates, policies of acceptance to the transplant waiting list and allocation system.

International comparisons of LT outcomes between the United Kingdom (UK) and United States have been carried out and have highlighted areas for further research and quality improvement in the two countries (2). In Europe, the European Liver Transplant Registry (ELTR) provides an invaluable resource in comparing outcomes between countries. However, missing data are common for some measurements in large registries, such as the ELTR. This might prevent an appropriate adjustments for confounding factors and therefore comparisons might not provide reassurance that outcomes are acceptable (4).

We performed a comparison of LT programmes between two European countries with a universal health care system, Italy and UK, by using two nationwide longitudinal databases with the aim to describe and appropriately analyse: characteristics of the donors and recipients, trends in prevalence of end-stage liver disease, allocation of donor livers and outcomes at short- and medium-terms between the two countries.

Materials and Methods

Study population

In order to compare the two LT programmes, data were obtained from the Italian *Liver Match* database (3) and the '*UK Transplant'* registry. The *Liver Match* database is the result of the *Liver Match Study*, a prospective, multicentre, observational study carried out in Italy and sponsored by the Associazione Italiana Studio Fegato (AISF) and the Centro Nazionale Trapianti (CNT).

The *UK Transplant Registry* is held by National Health Service Blood and Transplant (NHSBT). Detailed descriptions of both databases have been previously reported (3, 4).

Characteristics of the processes of selection and allocation policy in the two LT programmes are reported in the **Supplementary Box S1**.

The population selected for this comparative study included all adults (aged 15 years or older) who received a first, non-urgent LT from DBD and donation after circulatory death (DCD) donors (DCD performed in UK only) in the two countries between 1 June 2007 and 31 May 2009. Patients who underwent multiorgan transplantation, retransplantation, LT for fulminant hepatitis and the few with missing survival data were excluded from the analysis.

Patient consents were not required since data were collected entirely anonymised.

The study was approved by the *Ethics Committees* of both AISF and NHSBT.

Data management

The two databases were harmonised to ensure that liver disease classification and risk factor definitions were comparable. We adopted a 8-category liver disease classification system. In the event of multiple diagnoses, patients were assigned to the diagnosis which was deemed most likely to influence their prognosis; disease classification was undertaken in a hierarchical order (**Supplementary table S1**). The diagnosis of hepatocellular carcinoma (HCC) was considered as a separate variable in order to analyse the specific effect of each aetiology, irrespective of the presence of HCC.

The model for end-stage liver disease (MELD) score (5) was calculated using serum creatinine, serum total bilirubin, international normalised ratio (INR) of prothrombin time obtained immediately before transplantation. In those with lower values of creatinine who received renal support immediately prior to transplantation, creatinine was set to 4.0 mg/dl.

The percentage of individuals with missing values for each variable is shown in the **Supplementary Table S2**. All these data were missing at random, except for the variable 'portal vein patency' in the UK. Data on portal vein patency status in the UK has been collected since December 2007, and so this variable was not included in the analysis.

Statistical analysis

Since several continuous variables showed a skewed distribution, median, first and third quartiles were used as summary statistics. Categorical variables were described by frequencies. Continuous variables were compared by t-test or Wilcoxon rank-sum test in case of any significant departure from normality. Associations between categorical variables were evaluated by Chi-square test; Fisher exact test was preferred in case of sparse tables.

The outcomes in the survival analysis were the patient and the transplant survival. The latter was defined as time from transplant to either graft failure or patient death, whichever occurred first.

Three year unadjusted survival curves were calculated using the Kaplan-Meier method. The log-rank test was used to compare groups.

Multivariate analysis was based on the Cox model (6). To identify the relative risk of transplant loss and patient death in one country compared to the other a merged 'Italy-UK' dataset was used. Recipient, donor and transplant variables that were well recorded to a comparable degree in both databases with non-missing values of >95% were included in the regression models (**Table 1**). The variable representing allocation system was taken to have three levels, which were different for the two countries, to take account of the different distribution of the transplant centres (regional [with possibly > one centre per region], national and international in Italy; and local [including only one

centre], national, international in UK). Aetiology was analysed using six disease categories (HBV as baseline; HCV; ALD; PSC+PBC; autoimmune and cryptogenic; other) in order to increase the power of the analysis in the small disease categories. Immunosuppression (IMS) variables were treated as categorical ones (calcineurin inhibitors: Cyclosporin/Tacrolimus; steroids: yes/no; antimetabolites: Azathioprine/Mycophenolate/No).

Predictors of graft loss were identified by a backward selection procedure, taking correlation structure among covariates and clinical interpretation of their effects into account. We separately investigated short-term and mid-term survival. The former was limited at 90 days of follow-up from LT, considering patients alive at this date as censored. The latter was carried out at three years. To avoid the carry-over effect of early mortality, three years analysis was conditioned on being alive with functioning graft at 90 days.

All continuous variables were represented in the Cox model as a linear effect. This assumption was verified by plots of martingale residuals for a null model against covariate values (7); no evidence of non-linear effects was observed. Possible time dependent effects were evaluated by plots and test statistics based on Schoenfeld residuals (8). A time depending effect was detected in the medium-term model for the donor HBcAb status. Since this effect was not of primary interest, no attempt was made to model it. However, in order to preserve the interpretation of the corresponding regression parameter as an average population effect in presence of censoring, we used a weighted Cox regression as suggested by Xu and O'Quigley (9). Weights correspond to the increments of a consistent estimate of the marginal failure time distribution and, in practice, they are based on the jumps of the Kaplan-Meier curve at the observed failure times. In this case covariance matrix was estimated by the robust Lin-Wei estimator (10).

We explored possible interactions with a theory-driven approach.

All analyses were performed using SAS version 9.3 and R.

Results

Cohort characteristics

Clinical characteristics of recipients, donors and grafts are reported in **Table 1.**

The most common primary indications for LT were HCV (n=682, 47.5%) in Italy, and ALD (n=251, 28.4%) in the UK. In Italy, there was a high prevalence of HCC (n=677, 47.2%), likely related to the high prevalence of HCV and HBV; indeed, 55.7% (381/677) of those with HCC in Italy had HCV as underlying aetiology. Prevalence of HCC was relevant also in the UK (n=151/885, 17.1%), with 43.7% (66/151) of those with HCC having HCV.

Recipient age distribution was similar in the two cohorts for recipients of DBD grafts (median age: 55 years [interquartile range, IQR: 48-61] vs. 54 years [IQR: 46-60] in Italy and UK, respectively). Male gender was more common in the Italian recipient cohort (79.1% vs. 65.1%). Compared with their UK counterparts, LT recipients in Italy had lower median BMI (25 [IQR: 23-28] vs. 26 [IQR: 23-30]) (although no account was taken of ascites), a slightly lower median MELD score at the time of transplant (15 [IQR: 10-20] vs. 16 [IQR 12-20]), were less likely to receive a split liver (5.5% vs. 12.3%), had a lower requirement for preoperative renal support (1.1% vs. 3.6%), had a significantly shorter donor organ CIT (median CIT in hours: 7.3 [IQR: 6.0-8.8] vs. 9.5 [IQR: 7.7-11.2]), were more likely to receive grafts from older donors (median age: 56 [IQR: 41-68] vs. 47 [IQR: 35-58]), and from donors died as a result of a trauma (25.4% vs. 13.0%), as opposed to cerebrovascular accident (**Table 1).**

Among the 20 Italian Transplant Centres participating to this study, the median number of transplants performed per year was 40 (range 14-108). In the UK the national transplant activity is distributed in 7 centres with a median number of transplants performed per year of 152 (range 76-268).

In the UK, 144 recipients were transplanted using DCD donors compared to none in Italy, where there is no DCD donor programme. Of note, these recipients were more likely to have HCV (27.2% vs. 22.3%) and less likely to have HCC (6.3% vs. 19.2%), compared to recipients of livers from DBD donors; furthermore, they had a lower MELD score (14 vs. 16), less requirement for

preoperative renal support (0.7% vs. 3.6%), a shorter CIT (6.9 h vs. 9.5 h) and did not receive split livers compared with recipients of DBD donors.

Organ allocation

No difference was found in the donor age in HCV positive vs. HCV negative recipients in both cohorts (median donor age: 46 years in UK and 56 years in Italy in both groups). However, transplantation using a split graft was less frequent in HCV-positive than in HCV-negative recipients in Italy (3.7% vs. 7.2%, respectively; $p = 0.0036$) while no significant difference was observed in the UK (8.3% vs 10.9%, p=0.2934).

Donors allocated to recipients with HCC were significantly older in both cohorts. In the Italian cohort the median donor age in HCC recipients was 58 (IQR: 44-70) vs. 55 (IQR: 39-67) in non-HCC (p=0.0002). In the UK cohort the median donor age in HCC was 48 (IQR 37-58) vs. 46 (IQR: 33-56) in non-HCC (p=0.0889). No correlation was found between the donor age and the MELD score at transplant in both cohorts, as shown in the non-parametric regression curves in **Supplementary Figure S1**.

Post-transplant mortality

Short- and medium-term survivals in both countries were consistent with the post-transplant outcomes reported by the ELTR (11).

The unadjusted transplant survival at three years (**Fig. 1a**) in Italy was slightly lower than that observed in UK (0.76 vs. 0.82, p=0.0004). Disease-specific sub-analysis showed that such lower survival was limited to patients transplanted for HCV, **Fig. 2a** (0.72 and 0.79 in Italy and UK, respectively, p=0.0357) and for ALD, **Fig. 3a** (0.73 and 0.86 in Italy and UK, respectively, p=0.0018). Survival was similar in those transplanted for other causes of liver disease (data not shown).

Similar patterns were observed for patient survival (Figg. 1b, 2b and 3b).

Multivariate regression analysis of the 'combined Italy-UK' cohort (**Table 2 and Table 3**) generated overall adjusted hazard ratios (HR) for transplant loss and patient death in one country compared to the other. The adjusted risk of transplant loss at 90 days was significantly higher in Italy (HR=2.45 [1.75-3.44], $p<0.0001$) (**Table 2**). The adjusted risk of patient death at 90 days was significantly higher in Italy (HR=2.44 [1.63-3.66], $p<0.0001$) (**Table 2**). DCD donor status, donor BMI, recipient creatinine, aetiology, HCC and INR were included in the risk-adjustment, significantly affecting transplant and patient survival.

In the multivariate analysis at three years, aetiology was initially analysed using six disease categories. However, since only the HCV category was statistically associated with outcome, in the final Cox model (**Table 3**) we treated the aetiology only based on the HCV status (HCV positive and HCV negative) to increase the power of the analysis. The risk of transplant loss and patient death at three years, restricted to those with a transplant survival of 90 days or more, was similar in the two cohorts (**Table 3**). Adjustment included donor HBcAb status, DCD status and age, and recipient HCV status. Interaction between donor age and HCV aetiology was statistically significant. The effect of age as continuous variable (x 10 years) in HCV positive and HCV negative patients is shown in **Table 3** as well as the hazard ratio for the HCV status (positive vs. negative) in old (defined as age = 70 years) and young (defined as age = 40 years) donors.

The variable 'high volume centre' added to the final model, setting up a cut-off at 60 LT per year (this is consistent with the literature and the distribution of the number of LT recipients per year in the two cohorts) was non-significant both at 90 days ($p=0.6147$) and at three years ($p=0.7661$).

A sub-analysis including DBD LT only (i.e. excluding 144 recipients of DCD graft) was performed. The Kaplan-Meier curves showed similar results with an unadjusted transplant and patient survival at three years slightly lower in Italy than in UK (**Supplementary figures S2.A and S2.B**). Multivariate regression analysis of the combined 'Italy-UK' cohort after excluding recipients of

DCD grafts (**Supplementary table S3 and S4**) confirmed the same variables found in the analysis including both DBD and DCD graft recipients being associated with the outcome.

To further investigate differences in the outcome at 90 days, we also analyzed the rate of re-transplantation (re-LT) and the causes of death in the two countries. The rate of overall re-LT in Italy was higher compared to UK (7.2% vs 5.0%, p=0.0347) and the rate of patient death within 90 days was not significantly different in the two countries, despite being slightly higher in Italy (19.4% vs 11.4%, p=0.2428).

Finally we explored the role of IMS on the short-term outcome. When the IMS variables, were included in the final model, the HR for transplant loss in one country compared to the other remained consistent with the original results (**Supplementary table S5**). Specifically, the risk of transplant loss at 90 days was significantly higher in Italy (HR=4.62, p<0.0001). DCD donor status, donor BMI, recipient creatinine, aetiology, and HCC were included in the risk-adjustment.

Discussion

This was the first study that compared LT programmes between two European countries with an appropriate adjustment for confounding factors. A major difference highlighted was the donor age. Despite a higher rate of trauma as donor cause of death, Italian donors were much older compared to the UK ones. This might reflect a different demographic of populations, as well as different approaches in organ procurement (12). Donor age, in both cohorts, represented a risk factor for transplant loss in HCV positive recipients, with an increased risk of mid-term graft loss of ~23% for every ten years of the donor (**Table 3**). Also, an older donor population in Italy might explain, at least in part, the higher prevalence of donor HBcAb positivity (13, 14). This is relevant since HBcAb status was significantly associated with higher risk of graft loss both in Italy and UK.

The spectrum of indications for LT varied enormously between the two countries: HCV was the indication of 47.5% of LT in Italy, while only 22.3% in UK. HCC was more prevalent in the Italian cohort that in the UK one (47.2% vs. 19.2%, respectively). It is unclear whether the high prevalence

of HCC was related to a truly higher prevalence of HCC, possibly related to a higher prevalence of HCV and HBV, or to the priority given to transplant candidates with HCC in Italy. ALD and chronic cholestatic liver disease were more common in the UK, accounting for 48.0% of the indications vs. 21.1% in Italy.

Other differences were found in the CIT and the split rate. The CIT was significantly longer in the UK without, though, representing a risk factor for transplant loss. This might be related to the fact that in 85.8% of cases in UK and 97.3% in Italy the CIT was lower than 12 hours, generally considered a safe threshold (15). The lower rate of 'splitting' in Italy might be related to the characteristics of the Italian donors (3), i.e. older and with a high rate of HBcAb positivity; and to the high proportion of HCV recipients, less likely to receive a split liver due to the concern of an increased risk of severe HCV recurrence after partial LT (4).

An additional relevant point identified is the lack of national strategies to drive the donor-recipient matching in both countries. Only exceptions were split livers, which were mainly allocated to non-HCV recipients, and HCC patients who received grafts from older donors. The latest was visible both in the UK and Italy and appeared to be the result of a precise allocation strategy; however, considering that half of the HCC population in Italy is HCV positive it would be warranted to assess the impact of this allocation strategy on overall survival.

We found that both Italy and UK had good short- and medium-term transplant survival after LT, consistent with the outcomes reported by the ELTR registry. This reassures about the high-quality performance of the transplant recipient care in both countries. In the unadjusted analysis, risk of transplant loss at three years was higher in Italy for patients transplanted for HCV and ALD. After an appropriate risk-adjustment, a higher risk of transplant loss was identified in the Italian cohort only at 90 days while, after conditioning the analysis to those surviving up to 90 days, no differences were found in the three-year survival rates between the two countries. When the analysis was restricted to recipients of DBD grafts, it showed similar findings. When the analysis

was repeated considering aetiologies as dicotomous variables the results were consistent in that the hierarchy of etiologies remained the same.

Factors that could explain the higher risk of early transplant loss in the Italian cohort are not entirely clear. When IMS was added to the final Cox model, the HR for transplant loss in one country compared to the other remained consistent with the original results (**Supplementary table S5**). A reduced graft survival was observed in Italy in those who were not taking corticosteroids at 90 days compared to those on corticosteroids (89.7% vs 92.6%, p=0.0561). However, a causal relationship cannot be assumed as this may reflect patient selection. *Angelico* et al. (6) already showed that steroid-free immunosuppression at baseline in a subgroup of recipients with ALD was a remarkable risk factor for early transplant loss (HR = 4.89) in the Italian *Liver Match* cohort (16). Some of these patients might have experienced severe adrenal insufficiency, with a consequent impact on early survival. This issue had been already identified and promptly addressed by the relative LT centres.

The rates of overall re-LT in Italy were higher compared to UK and the rate of failure of the second graft or patient death was slightly higher in Italy at 90 days. Reasons for that are unclear and conclusions cannot be drawn. An appropriate analysis of re-LT survival should include donor variables of the second graft and the recipient variables at the time of the re-LT, which unfortunately were not available in our databases.

We attempted to analyze the cause of death in the two cohorts but unfortunately, this information is not collected in a standardized fashion; it is therefore not possible to interpret differences and to carry out a robust analysis of causes of death.

Local organ availability and centre volume might be implicated in the different short-term outcome (15). Of note, among the twenty Italian Transplant Centres enrolled in this study, only two centres out of twenty-one (vs. five out of seven in UK) performed > 60 transplants per year.

It is also possible that the differences in the early survival described here are far more likely to originate from multiple medical and non-medical factors than to have one clear-cut explanation.

Of note, introduction of an interaction term in the analysis between donor age and HCV aetiology (HCV positive vs. HCV negative) showed as HCV aetiology is a major risk factor for transplant loss particularly in those receiving grafts from older donors. Age has a linear effect on transplant survival, but this effect is different based on the HCV status (as shown in **Table 3**). Indeed the risk of graft loss increases of 24% per decade of donor age in those HCV positive while only of 3% in HCV negative. On the other hand, HCV status has a much higher impact in older vs. younger donors; e.g. the HR is equal to 2.6 if donor age is = 70 while the HR is equal to 1.4 if donor age = 40. Since the differences in medium-term survival between the two countries disappeared after adjusting for confounding factors (i.e. donor age, HCV aetiology, donor HBcAb among the others), we hypothesize that the interaction between a higher age of the donor and a higher prevalence of HCV in Italy, along with a higher donor HBcAb positivity, contributed partially to this difference.

It is worth to mention that the current availability of interferon-free antiviral therapies against HCV, with much greater efficacy, tolerability and absence of relevant drug-to-drug interactions, will provide extraordinary tools in the management of both pre- and post-transplant HCV infection. Needless to say that it might change the present clinical scenario, with potential considerable consequences in the allocation policy.

In this study we compared the performance of the two transplant programs using the transplant and patient survival from the time of LT as outcome. Comparing survival from the time of listing, which considers also the death on the waiting list and therefore assess the ability to allocate organs and select recipients, would have been an alternative approach. However, this approach was not feasible in our study since these data are not complete in both datasets. We believe this does not represents a

major limitation of our study since the current policy of recipient selection is based on the need (urgency) as assessed by UKELD/MELD in both countries (rather than on transplant benefit).

The main strength of this study consisted in its nationwide dimension, its observational nature and the prospective patient enrolment. Studies based on large registries, such as the ELTR, have made enormous contributions to the field of LT. However, because data collection for registries is often more passive than data collection in longitudinal research databases (such as the *Liver Match Study* database), missing data may be a potential problem, which affects the overall quality of the evidence and the development of risk-adjustment models. Also, entry into a registry may not be as strictly monitored compared with longitudinal research databases; this creates the potential for ineligible patients to enter the registry and may weaken the generalizability of findings obtained from analysis of registry data.

This study presents some limitations. It is conceivable that the observed differences in survival could be explained by residual confounding not included in the databases because they are difficult to identify and quantify (e.g. organ perfusion, appearance and steatosis). Variations between laboratories in the measurement of analytes used to prioritize patients for LT, and the lack of standardized definitions may represent an additional limitation to the robustness of the risk-adjustment (17). Efforts are therefore required to standardise biochemical test measurements within and across countries.

In conclusion, this study highlighted areas for additional research and quality improvement. There is enormous potential for further comparative studies of LT programmes, although we should not overlook the risk that comparison of outcomes could become a competition: a quest to claim the highest ranking or avoid the embarrassment of an unfavourable rank. However, this must not obscure the opportunity to draw appropriate lessons from other countries and jeopardize the

discussion of policy failings. Finally, it should be remembered that optimal use of scarce organs should also consider transplant benefit as well as post-transplant survival.

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Figures

Fig. 1. Kaplan-Meier estimate of transplant (1a) and patient survival (1b) for liver transplant recipients in Italy and UK.

The unadjusted transplant survival at 3 years in Italy was slightly lower than that observed in UK.

Fig.2 Kaplan-Meier estimate of transplant and patient survival for liver transplant recipients with HCV in Italy and UK.

Unadjusted comparison at 3 years showed a lower graft (**2a**) and patient survival (**2b**) in Italy in patients transplanted for HCV.

Fig.3 Kaplan-Meier estimate of transplant and patient survival for liver transplant recipients with ALD in Italy and UK.

Unadjusted comparison at 3 years showed a lower graft (**3a**) and patient survival (**3b**) in Italy in patients transplanted for ALD.

Table 1. Characteristics of recipient, donor and graft of first adult liver transplantations in UK and Italy between 01 June 2007 and 31 May 2009

	United Kingdom - DBD (n=741)	United Kingdom - DCD (n=144)	Italy - DBD (n=1435)
Variables	**Median or n (Q1-Q3 or %)**		
Donors characteristics			
Age (years)	47 (35-58)	42 (23-51)	56 (41-68)
BMI (Kg/m^2)	26 (23-29)	24 (21-27)	25 (23-28)
Gender (male)	389 (53.5)	79 (54.8)	792 (55.2)
Cause of death			
Trauma	94 (13.0)	38 (27.9)	365 (25.4)
Haemorrhagic and thrombotic stroke	444 (61.3)	58 (42.7)	825 (57.5)
Other	186 (25.7)	40 (29.4)	245 (17.1)
HBcAb status (pos)	26 (3.6)	3 (2.1)	231 (16.1)
Recipients characteristics			
Age (years)	54 (46-60)	54 (47-61)	55 (48-61)
BMI (Kg/m^2)	26 (23-30)	26 (23-29)	25 (23-28)
Bilirubin at transplant (mg/dl)	2.86 (1.5-6.1)	2.11 (1.26-4.68)	2.6 (1.3-5.7)
Creatinine at transplant (mg/dl) *	1.0 (0.9-1.2)	1.0 (0.9-1.2)	1.0 (0.8-1.1)
INR at transplant	1.4 (1.2-1.7)	1.4 (1.2-1.6)	1.4 (1.2-1.7)
Sodium at transplant (mEq/L)	137 (134-140)	137.0 (134-140)	137 (134-140)
MELD score at transplant	16 (12-20)	14 (11-19)	15 (10-20)
CIT (h)	9.5 (7.7-11.2)	6.9 (5.7-7.98)	7.3 (6.0-8.8)
Portal vein thrombosis	31 (6.3)	NA	36 (2.5)
Preoperative renal support	27 (3.6)	1 (0.7)	15 (1.1)
Split liver	91 (12.3)	-	79 (5.5)
Gender (male)	482 (65.1)	110 (76.4)	1135 (79.1)
Aetiology			
Hepatitis C	165 (22.3)	39 (27.2)	682 (47.5)
Alcohol	208 (28.1)	43 (30.1)	237 (16.5)
Hepatitis B	26 (3.5)	9 (6.3)	285 (19.9)
Primary sclerosing cholangitis	65 (8.8)	10 (7.0)	30 (2.1)
Primary biliary cirrhosis	82 (11.1)	14 (9.8)	36 (2.5)
Autoimmune + Cryptogenic	70 (9.5)	8 (5.6)	83 (5.8)
Metabolic	52 (7.0)	10 (7.0)	24 (1.7)
Other	73 (9.9)	10 (7.0)	58 (4.0)
HCC status**	142 (19.2)	9 (6.3)	677 (47.2)
Allocation			
Local	591 (80.2)	121 (84.0)	1056 (73.6)
National	134 (18.2)	23 (16.0)	351 (24.5)
Inter-national	12 (1.6)	-	28 (2.0)

Abbreviations: BMI, body mass index; MELD, model for end-stage liver disease; UKELD, United Kingdom model for end-stage liver disease; CIT, cold ischemic time
*Patients with preoperative renal support were excluded
**HCC was considered as separate variable

Table 2. Graft and patient survival at 90 days: results from the Cox model

	Graft survival (n=2309)			Patient Survival (n=2309)		
Variable	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Country (Italy vs UK)	2.45	(1.75, 3.44)	<0.0001	2.44	(1.63, 3.66)	<0.0001
DCD (yes vs no)	2.24	(1.32, 3.81)	0.0030	2.14	(1.08, 4.24)	0.0292
Aetiology (HBV baseline)			0.0004			0.0041
HCV	2.09	(1.22, 3.56)	0.0070	2.26	(1.19, 4.30)	0.0125
ALD	2.79	(1.59, 4.91)	0.0004	3.36	(1.73, 6.54)	0.0004
PSC + PBC	4.12	(2.19, 7.75)	<0.0001	3.88	(1.78, 8.46)	0.0006
Autoimmune + Cryptogenic	2.79	(1.59, 4.91)	0.0029	2.99	(1.33, 6.70)	0.0079
Other	1.94	(0.97, 3.89)	0.0605	1.94	(0.83, 4.57)	0.1284
Ln creatinine* (x unit)	1.68	(1.25, 2.28)	0.0007	1.94	(1.37, 2.75)	0.0002
HCC (yes vs no)	0.73	(0.53, 0.99)	0.0468			NS
Donor BMI (x 5 units)	1.24	(1.06, 1.44)	0.0080	1.28	(1.07, 1.54)	0.0086
INR			NS	1.29	(1.03, 1.61)	0.0241

Note:
- Missing variables = 0.5 %

Table 3. Graft and patient survival at three years: results from the Cox model

	Graft survival (n=2061)			Patient Survival (n=2121)		
Variable	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Country (Italy vs UK)	1.25	(0.89, 1.75)	0.2033	1.18	(0.85, 1.62)	0.3220
DCD (yes vs no)	1.98	(1.16, 3.39)	0.0119			NS
Donor HBcAb status (pos vs neg)	1.54	(1.07, 2.22)	0.0194	1.58	(1.10, 2.27)	0.0131
Recipient HCV status (pos vs neg)			0.3934			0.4562
Donor age			0.7393			0.8094
Donor age * Recipient HCV status			0.0150			0.0074
Donor age (x 10 years) in HCV neg	1.02	(0.91, 1.12)		0.98	(0.88, 1.09)	
Donor age (x 10 years) in HCV pos	1.23	(1.04, 1.42)		1.21	(1.09, 1.35)	
HCV (pos vs neg) at donor age 70 ys	2.61	(1.74, 3.58)		2.98	(2.06, 4.31)	
HCV (pos vs neg) at donor age 40 ys	1.45	(1.00, 1.98)		1.63	(1.16, 2.29)	

Note:
- Analysis was conditioned to be alive with functioning graft at 90 days. Patients who died, were re-transplanted (graft survival) or censored before 90 days were excluded.
- Missing variables = 1.2 %

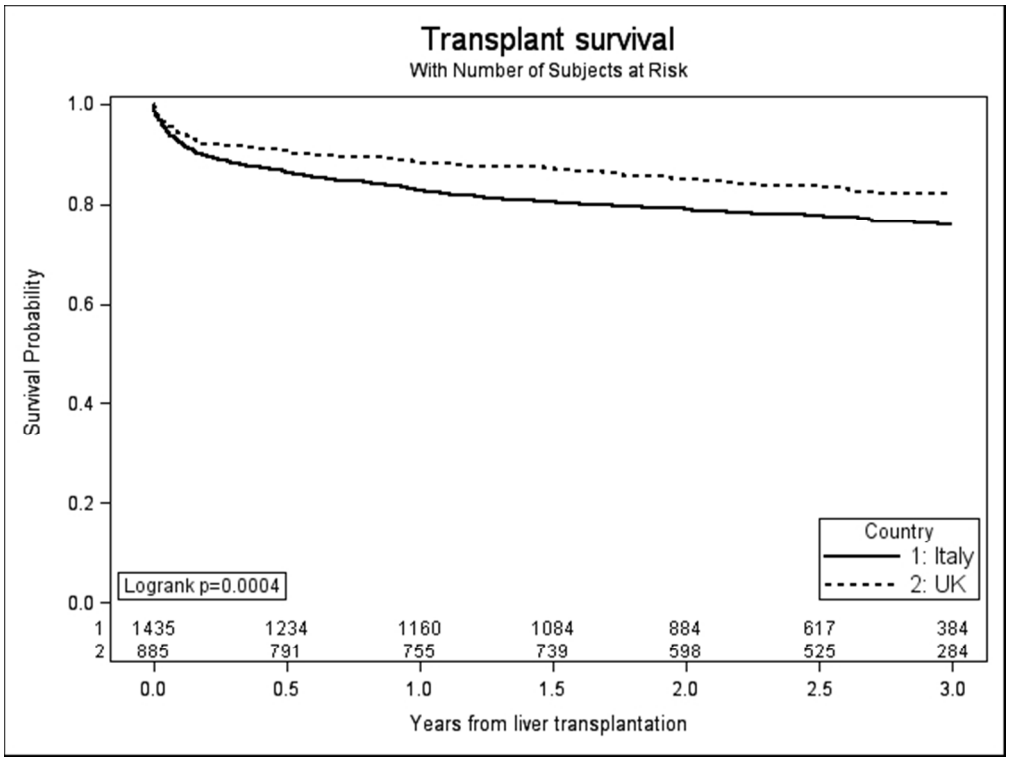

Figure 1a
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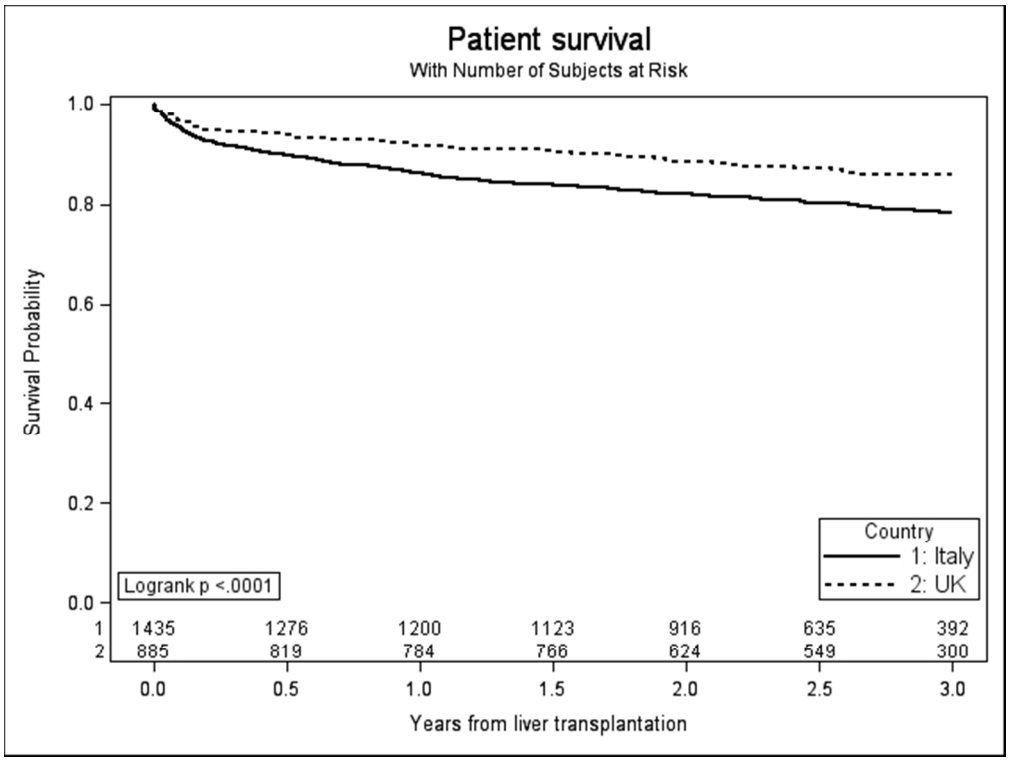

Figure 1b
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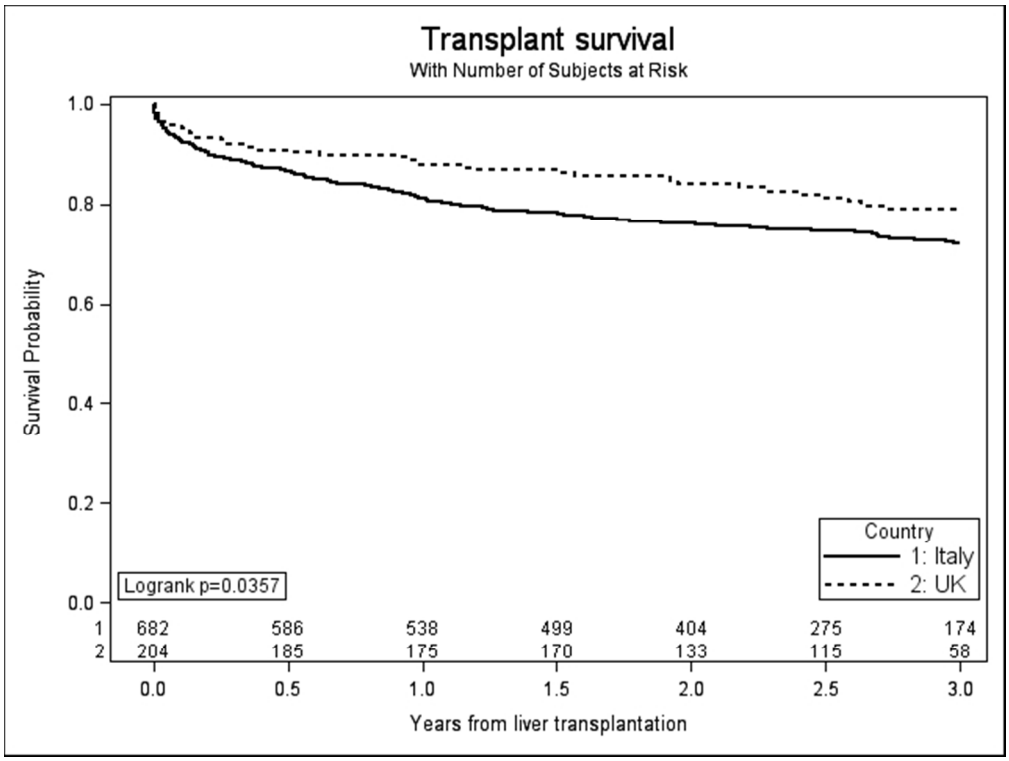

Figure 2a
169x127mm (96 x 96 DPI)

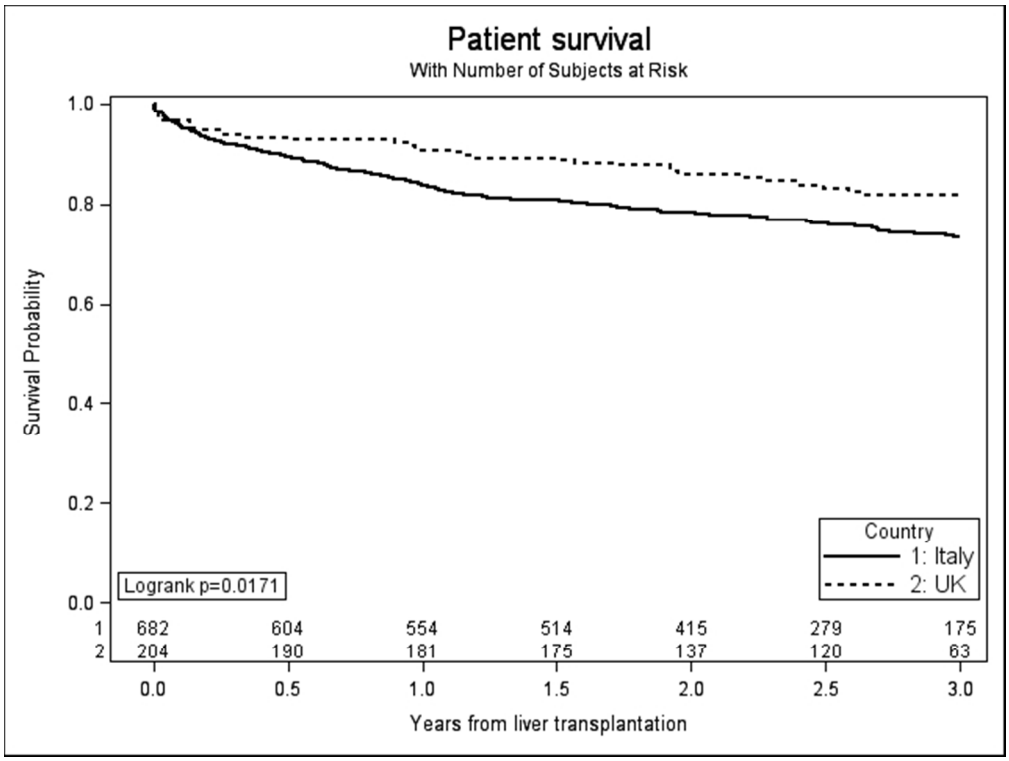

Figure 2b
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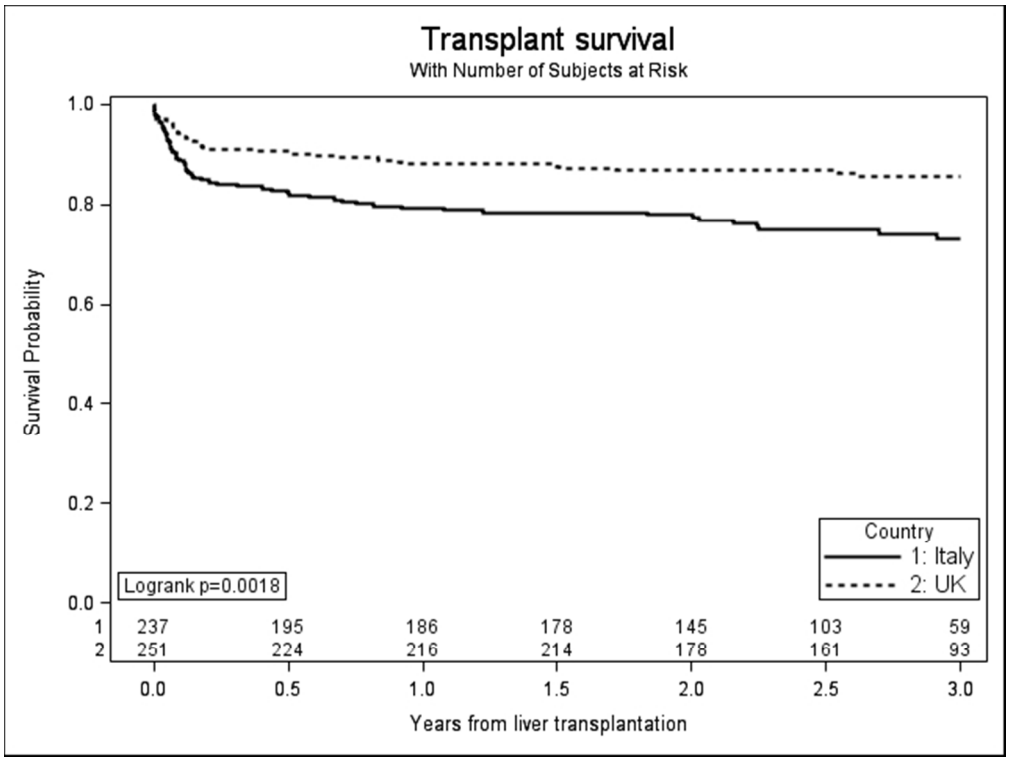

Figure 3a
169x127mm (96 x 96 DPI)

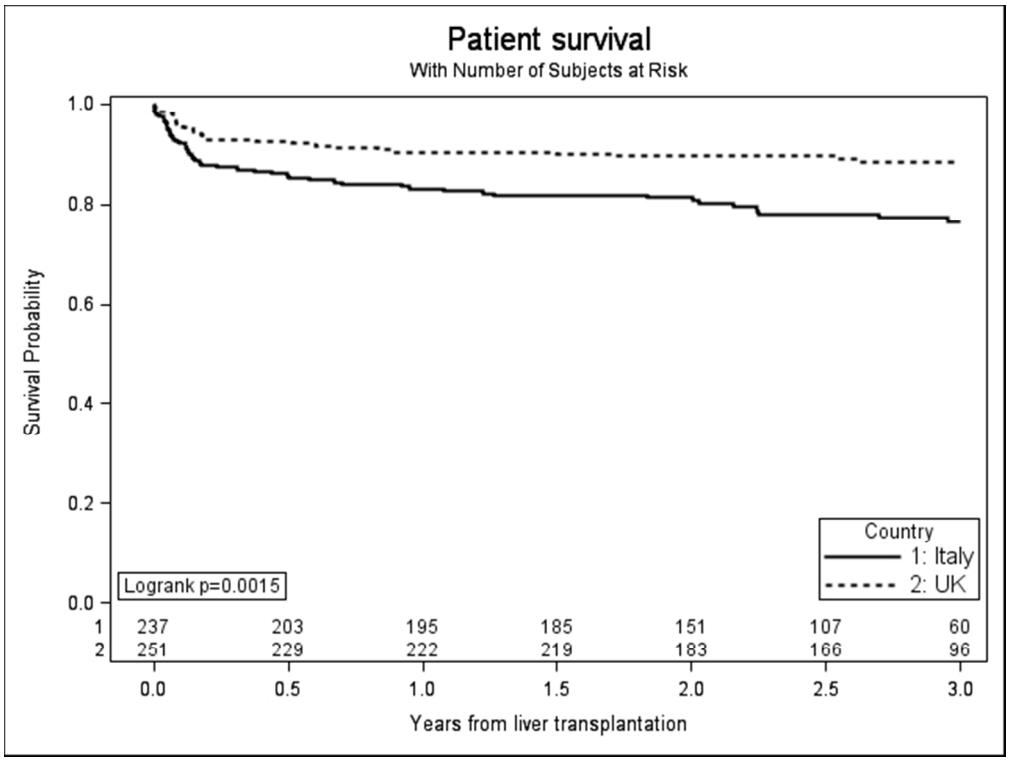

Figure 3b
169x127mm (96 x 96 DPI)