Transplant International

ORIGINAL ARTICLE

Inferior outcomes in young adults undergoing liver transplantation – a UK and Ireland cohort study

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All authors have given final approval for this manuscript to be submitted for publication to Transplant International.

SUMMARY

Graft loss incidence is reported to be inversely related to recipient age. We used a national cohort of liver transplant (LT) recipients from the United Kingdom and Ireland to compare the age-dependent risk of graft failure in different post-transplantation time-periods ('epochs'). A cohort of first-time LT recipients (1995–2016) were identified (11 006). Cox regression was used to estimate hazard ratios (HR) comparing graft loss between age-groups (18–29, 30–39, 40–49, 50–59 and 60–76 years) and graft loss in different post-transplant epochs: 0–90 days, 90 days–2 years and 2–10 years. The risk of graft failure was highest in those transplanted between age 18 and 29 (adjusted HR 1.25, 95% CI: 1.00–1.57, $P = 0.04$) and in those aged 30–39 (adjusted HR 1.31, 95% CI: 1.11–1.55, $P = 0.02$). Graft failure in those under the age of 40 was similar in the first 90 days but worse 2–10 years' post-LT (18–29 years HR 1.36, 95% CI: 0.96–1.93, $P < 0.001$). Graft failure because of chronic rejection (CR) was more common in recipients aged 18–29 ($P < 0.001$). Adults transplanted between age 18 and 39 are at risk of late graft loss. CR is a concern for young adults (18–29 years). Our data highlights the need for specialist young adult services within adult healthcare.

Transplant International 2021; 34: 2274–2285

Key words
adult, age, liver, transplant, young

Received: 13 April 2021; Revision requested: 8 July 2021; Accepted: 1 September 2021; Published online: 13 October 2021

Introduction

Worldwide, there is an increasing disparity between the number of patients requiring liver transplantation (LT) and the availability of suitable donor livers. Inevitably, this has resulted in difficulties transplanting would-be recipients in an acceptable time-frame [1]. Rising re-transplantation rates and the development of expanded criteria for LT have increased the demand on LT services [2]. In response, extended criteria donor organs are increasingly being utilized and – evidenced by the development of organ perfusion techniques – huge importance is being placed on the preservation of primary graft function both short term and in the long term [3].

The impact of donor quality on the longevity of liver graft function has already been established – livers

doi:10.1111/tri.14033

donated following circulatory death (DCD) or heavily steatotic grafts are at an increased risk of early graft failure [4]. The impact of recipient characteristics on graft function is less well explored. In the context of kidney transplantation, an inverse relationship between recipient age and graft failure has been demonstrated with those receiving a donated kidney in their second and third decades consistently experiencing higher rates of graft loss than those transplanted later in life [5,6]. Poorer adherence to immunosuppressant medication resulting in higher rates of chronic rejection (CR) is a plausible explanation [7-9].

In liver transplant recipients, we do know that there are age-related differences in the presentation of the primary liver diseases that are predisposed to post-transplant recurrence and possible graft failure [10]. For example, primary sclerosing cholangitis (PSC) and autoimmune liver disease (AILD) have been shown to be more prevalent in the younger transplant recipients [10-12]. Most importantly young adults (YA) – aged 18–29 years – are usually transplanted for the complications of portal hypertension and porto-systemic shunting rather than liver failure per se [13]. There is a suggestion that persistence of portal hypertension after liver transplantation may influence long-term graft survival [14].

There is increasing appreciation that in liver transplantation, age may have an inverse relationship with graft failure. We, therefore, investigated the impact of different age-ranges on post-transplant graft failure. Using data from the UK Liver Transplant Registry, including all patients who had a liver transplant between 1995 and 2016 in the United Kingdom and Ireland, the impact of age on post-transplant graft loss was estimated in the short and long term and according to the indication for transplantation and the type of donor graft used (DBD, donation after brain death vs. DCD, donation after cardiac death).

Materials and methods

UK Liver Transplant Registry

Since 1968, the UK Liver Transplant Registry contains information about all liver transplants performed in the six liver transplant centres in England, and single centres in Scotland and Ireland. The dataset is managed by National Health Service Blood and Transplant (NHSBT) [11], and regular checks indicate that the data are consistently more than 93% complete and accurate and results from several studies confirm the validity of the dataset [15-17].

Study population

All patients aged 18 years or older who had received a first-time liver transplant for chronic liver disease between 1st January 1995 and 31st December 2016 were eligible for inclusion. To limit heterogeneity of the study cohort, those who underwent multi-visceral, super-urgent, domino or living-related liver transplantations were excluded (Fig. 1) as well as those who received a liver transplant for acute liver failure (including auxiliary transplantation). We also excluded patients whose survival data were missing. We did not have information on explant pathology. Patients were grouped according to their age at the time of transplantation: 18–29, 30–39, 40–49, 50–59 and 60–76 years. YA for the purpose of this paper were defined as 18–29 years of age. Ten-year age bands were chosen, with wider age-ranges in the youngest and oldest groups to ensure sufficient graft failure events in each group. Donor steatosis and capsular damage were dichotomized at the time of transplantation as either present or not. Recipients' functional status at the time of transplantation was assessed using a 5-point scale ranging from 'able to carry out normal activity without restriction' to 'completely reliant on nursing/medical care' [17]. The UKELD score, derived from international normalized ratio (INR), serum creatinine, serum bilirubin and serum sodium, was used to score the recipients' severity of the liver disease [18]. Age-specific mean platelet counts and the presence of previous variceal bleeding were included as proxy markers of portal hypertension. Ethnicity was dichotomized into Caucasian and non-Caucasian groups. Chronic rejection – as a cause of graft failure – was defined separately by each transplant unit.

UK allocation policy 1995–2016

During the study period from 2008 to 2016, donated liver allocation in the United Kingdom was organized by centre and patients on the waiting list were prioritized according to a scoring system – the United Kingdom Model for end-stage liver disease (UKELD) – that was designed to predict waiting list mortality [18,19]. This urgency-based scoring system was adapted from the US Model for end-stage liver disease (MELD) but unlike the US did not award exception points for

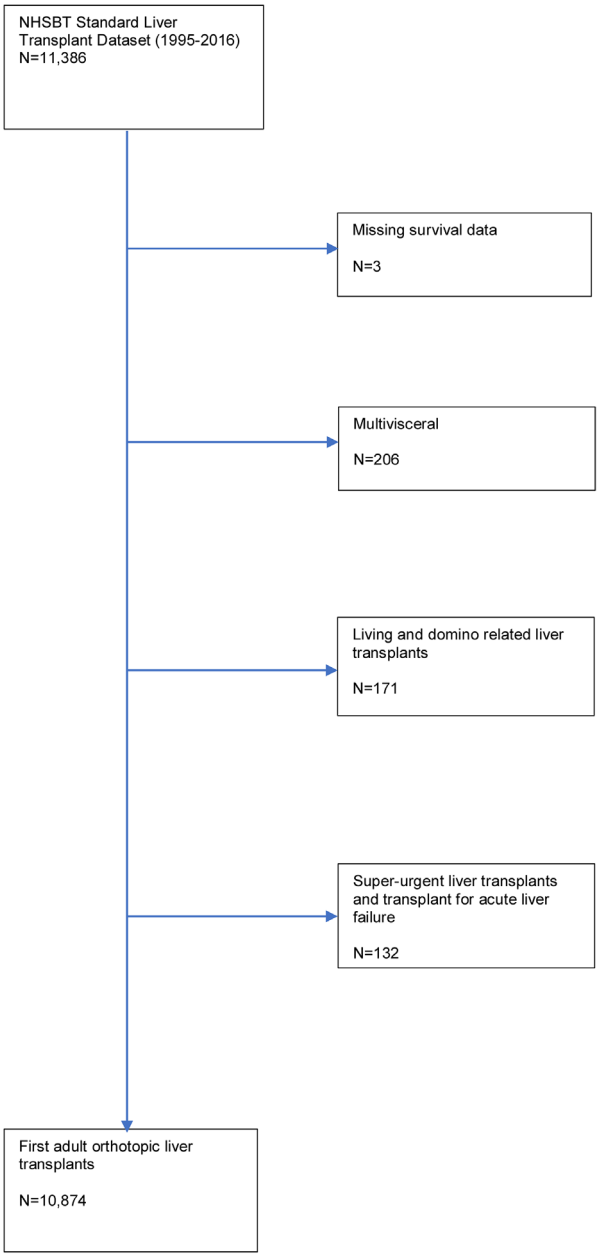

Figure 1 Flow chart presenting the selection of the study population.

patients with hepatocellular carcinoma (HCC) on the waiting list.

Statistical analysis

Categorical variables were presented as proportions and compared using chi-squared tests and continuous variables were presented as means with standard deviations and compared using the Kruskal–Wallis test. Patients transplanted for non-HCC indications who may subsequently have been found to have a HCC in their explant pathology, were analysed on an intention-to-treat basis and remained in the non-HCC group.

Kaplan–Meier methods were used to compare graft failure between age groups. Follow-up was censored at 10 years after transplantation or on the last follow-up visit before 7th April 2017, whichever occurred earlier. Graft failure was defined as the time from transplantation to re-transplantation or patient death.

Multivariable Cox regression models were used to estimate hazard ratios (HRs) that represent the relative differences in the hazard of post-transplant graft failure between the age-groups. Age-group 50–59 was used as the baseline category as it contained the largest number of recipients and graft failure events. Interaction terms were included in the Cox regression models to determine whether the impact of age differed significantly according to indication for transplantation, donor type (DCD or DBD) and era of transplantation (1995–2008 and 2009–2016). In the first model, hazard ratios (HRs) comparing post-transplant graft failure in liver transplant recipients were estimated without adjustment for the donor and recipient characteristics. In the second model, HRs were estimated with adjustment for donor factors only, and in the final model, HRs were estimated after adjustment for both donor and recipient factors. Interaction terms were tested using the Wald test. The donor and recipient factors that were included in the multivariable models were decided a priori based on their clinical plausibility of being a risk factor for the outcome [2,4,14,15,16,19,20]. Case-mix adjustment included donor factors – sex, age, body mass index (BMI, kg/m^2), donor cause of death, donor type (donation after circulatory death or donation after brain death), steatosis, capsular damage, organ appearance, graft type and cold ischaemic time (CIT) – and recipient factors – sex, age, ethnicity, BMI, functional status, ascites, varices, encephalopathy, hepatitis C virus (HCV) status, UKELD, pretransplant inpatient status, pretransplant renal support, pretransplant ventilator status, previous abdominal surgery, disease aetiology and era of transplantation (1995–2008 & 2009–2016). A sensitivity analysis using this model was also performed where all recipients in the disease indication group 'others' – including those with biliary atresia-failed Kasai – were excluded and the hazard ratio compared with the original model.

A separate multivariable model was built to examine the prognostic association of age-group with graft survival in three post-transplant time periods ('epochs'): the first 90 days after transplantation reflecting the occurrence of surgical complications, acute rejection

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and primary nonfunction [20-22], from 90 days to 2 years reflecting long-term outcomes, including recurrence of the primary liver disease [20,21], and from 2 to 10 years reflecting long-term adherence to immunosuppressive medications [19-21].

Missing donor and recipient characteristics were multiply imputed using chained equations creating 10 complete datasets [23]. In the imputation procedure, the donor and recipient variables used in the case-mix adjustment were used to predict missing values, as were the outcome variables [24]. The Cox regression results for each of these datasets were pooled using Rubin's rules [23]. STATA V15 (StataCorp, College Station, TX, USA) was used for all statistical analyses. A *P*-value smaller than 0.05 was considered statistically significant.

Results

Donor and recipient characteristics

A total of 10 874 adult liver transplants were recorded as performed between 1995 and 2016 (Fig. 1). YAs were less likely to receive livers from donors who had high BMI's or whose grafts had evidence of macro-steatosis (Table 1). They were also less likely to receive DCD grafts or grafts that were documented abnormal in appearance but more likely to receive grafts that were segmental (i.e. split grafts). Younger recipients were more frequently from a non-white ethnic background and were also more frequently found to require an inpatient stay and or ventilation prior to their transplant. YAs were less likely to have evidence of HCV antibodies and were also less often found to have the sequelae of end-stage liver disease, including ascites and encephalopathy. Importantly, compared with the other age groups, common indications for LT in YA were primary sclerosing cholangitis (26.8%) and autoimmune liver disease (AILD; 25.3%). 39.6% were classified as 'others' and include 37 patients with biliary atresia post Kasai, a childhood liver disease and the most common indication for liver transplantation in children.

Kaplan–Meier survival analysis

Kaplan–Meier survival curves comparing graft failure across the different age-groups showed that outcomes in the first 5 years after transplantation are very similar (Fig. 2). After this time point, the pattern of graft failure identified in patients who were transplanted between the ages of 18 and 29 years or 30 and 39 years were observed to have worse 10-year outcomes, (27.5%; 95% CI: 23.9–34.3% and 31.3%; (95% CI: 27.5–35.5%, respectively) compared with those aged 50–59 years 24.1% (22.5–25.9%). These age-related differences in graft failure reached borderline statistical significance ($P = 0.05$). It was also observed that those in the younger age groups more often underwent re-transplantation (15.4% vs. 5.1% for 60–76 years).

Multivariable Cox regression

In the multivariable Cox model adjusting for both donor and recipient characteristics patients who were transplanted in the younger age-groups were found at 10 years to have a significantly increased risk of graft loss (18–29 years: HR 1.25, 95% CI: 1.00–1.57 and 30–39 years HR 1.31, 95% CI: 1.11–1.55, $P = 0.02$, Table 2). In these models, adjusting sequentially for donor and then recipient characteristics did not markedly the impact of age on graft failure (Table 3). There was also no evidence that the impact of age on the graft failure differed according to the era of transplantation (P for interaction = 0.54), donor type (DCD vs. DBD, P for interaction = 0.06) or underlying liver disease (P for interaction = 0.28). The pattern of results from the sensitivity analysis that compared the impact of age on graft failure having excluded the disease indication group 'others' were almost identical to the results of the main analysis described above.

In the multivariable Cox model comparing the impact of age-group on graft failure in the different epochs of follow-up, there was evidence that the impact of age on graft failure differed according to the time period after transplantation ($P = 0.03$, Table 4). For example, compared with those who were 50–59 years, the hazard ratio in those aged 18–29 years and 30–39 years was greatest for the 2–10-year follow-up period (adjusted HR: 1.36, 95% CI: 0.96–1.93 and adjusted HR: 1.62, 95% CI: 1.26–2.09, $P < 0.001$, respectively).

Cause of graft failure

Compared with older recipients, patients transplanted between the ages of 18 and 49 who lost their graft were more likely to do so from chronic rejection (CR, $P < 0.001$, Table 5), recurrence of primary liver disease ($P < 0.001$) and acute ($P = 0.02$) and late vascular occlusion ($P = 0.03$).

Discussion

Similar to other reports, young adults in the United Kingdom and Ireland who are aged 18–29 years are up

Table 1. Donor and recipient characteristics according to age-group (n = 10 874).

	Age at transplantation						
	18–29 years	30–39 years	40–49 years	50–59 years	60–76 years	*P*-value[§]	Missing values (%)
Number	533	868	2448	4050	2975		
Donor characteristics							
Female	49.5%	47.5%	46.8%	43.9%	47.4%	0.007	0.0 (0)
Age	39.6 (15.7)	43.0 (15.6)	45.5 (15.4)	46.2 (15.5)	48.3 (15.8)	<0.001	0.0 (0)
BMI (kg/m^2) mean (SD)	23.4 (4.5)	25.0 (4.9)	26.5 (5.2)	27.2 (5.0)	27.0 (4.8)	<0.001	5.5 (601)
Trauma as cause of death	19.0%	18.2%	14.1%	15.1%	13.5%	0.001	0.0 (0)
DCD donor*	6.6%	7.3%	10.5%	12.9%	14.6%	<0.001	0.0 (0)
Hepatic steatosis	31.5%	36.9%	42.0%	43.9%	45.5%	<0.001	21.7 (2 364)
Presence of capsular damage	10.8%	14.1%	13.7%	13.7%	13.8%	0.56	22.2 (2 418)
Abnormal donor liver appearance	14.0%	16.1%	19.7%	21.7%	22.0%	<0.001	9.5 (1 035)
Segmental graft type	14.3%	9.7%	5.8%	6.0%	5.3%	<0.001	0.0 (0)
CIT (mins) mean (SD)	582.2 (194.4)	595.0 (193.5)	590.4 (184.1)	584.4 (184.5)	566.8 (184.7)	<0.001	6.0 (652)
Recipient characteristics							
Female	49.7%	40.3%	35.7%	32.3%	37.5%	<0.001	0.9 (1)
Non-Caucasian ethnicity	17.8%	17.9%	17.3%	11.8%	8.0%	<0.001	0.02 (6)
BMI (kg/m^2) mean (SD)	24.3 (4.1)	25.0 (4.2)	25.7 (4.8)	25.9 (4.8)	26.1 (4.8)	<0.001	5.9 (643)
UKELD[†] mean (SD)	55.4 (6.3)	56.0 (6.4)	56.1 (6.0)	55.0 (5.7)	54.2 (5.5)	<0.001	5.3 (574)
Blood group O	40.3%	46.8%	42.0%	43.2%	41.3%	0.01	0.0009 (1)
Functional status: self-care[‡]	45.0%	48.0%	53.2%	53.0%	51.4%	0.006	0.0 (0)
Platelet count ($\times 10^9$/l) mean (SD)	126.5 (123.7)	134.5 (117.3)	112.2 (86.3)	108.5 (73.1)	114.8 (72.5)	<0.001	2.6 (279)
Ascites	43.7%	48.3%	59.0%	57.5%	53.8%	<0.001	2.4 (260)
Previous variceal bleed	27.6%	28.6%	31.2%	30.7%	26.1%	<0.001	3.0 (330)
Encephalopathy	14.7%	19.2%	25.5%	26.4%	27.2%	<0.001	0.8 (92)
Presence of HCV antibodies	1.9%	14.3%	26.2%	25.9%	15.5%	<0.001	10.1 (1 097)
Inpatient prior to transplant	20.3%	16.9%	16.1%	13.6%	13.8%	0.001	0.02 (2)
Renal support prior to transplant	5.8%	6.3%	5.5%	5.3%	5.0%	0.64	0.3 (32)
Ventilator support prior to transplant	1.5%	1.3%	0.9%	0.4%	0.6%	0.01	0.05 (5)
Previous abdominal surgery	17.9%	15.1%	14.4%	14.2%	15.6%	0.13	0.3 (41)
Indication for transplant							
HCC	2.3%	4.8%	10.4%	21.2%	27.9%	<0.001	0.0 (0)
HCV	1.1%	12.1%	19.9%	14.0%	7.0%	<0.001	0.0 (0)
PSC	26.8%	19.9%	11.2%	7.4%	8.0%	<0.001	0.0 (0)
HBV	1.9%	4.7%	3.5%	2.8%	1.9%	<0.001	0.0 (0)

Table 1. Continued.

	Age at transplantation					*P*-value[§]	Missing values (%)
	18–29 years	30–39 years	40–49 years	50–59 years	60–76 years		
PBC	1.1%	9.2%	12.6%	12.6%	16.8%	<0.001	0.0 (0)
ALD	1.7%	14.6%	24.0%	26.5%	10.5%	<0.001	0.0 (0)
AILD	25.3%	14.3%	8.5%	6.5%	8.8%	<0.001	0.0 (0)
Metabolic	0.19%	0.46%	1.2%	2.5%	5.2%	<0.001	0.0 (0)
Others	39.6%	19.8%	8.7%	6.4%	6.0%	<0.001	0.0 (0)

*Liver donated following circulatory death.
†United Kingdom Model for end-stage liver disease.
‡3rd level of 5-point scale assessing patient's pre-transplantation functional status.
§Categorical variables compared using chi-squared tests and continuous variables compared using the Kruskal-Wallis test.

to 30% more likely to lose their graft after LT, compared with other age cohorts [25,26]. In this study, we were able to highlight the differences between this cohort and older transplant recipients, up to 76 years of age. YAs were less likely to receive grafts with evidence of steatosis, capsular damage or other signs of abnormal organ appearance and were more likely to receive a LT for conditions such as PSC, AILD and 'Others' – including biliary atresia. At the time of transplantation, the prevalence of the sequelae of end-stage liver disease, including ascites and encephalopathy was found to be less common in YA's. Our analysis therefore demonstrates that, despite more often receiving more optimal quality grafts, YA have a greater risk of graft loss.

The reasons for inferior graft survival appear to be multi-factorial. CR is a leading cause of graft failure in the YA group (4.8%). The definition of CR can be imprecise and within this database like other studies, it is as per the reporting centre's interpretation. Sagar *et al.* [27] found a higher prevalence of CR (7.3%) when comparing a group of 110 YA's transplanted between the ages of 18 and 35 years with younger cohort of 137 young people transplanted during childhood. Risk factors for CR include autoimmune aetiology, cytomegalovirus infection and low levels of immunosuppression [28]. However, poor adherence to medication/clinic attendance is recognized as one of the strongest risk factors for CR and had the highest incidence amongst YA [7,29]. The prevalence of nonadherence in adolescents post organ transplantation has been estimated to nearly 50% [30,31]. Poor adherence or nonadherence is often complex, multifactorial, fluctuating and requires regular monitoring also in patients with graft function within normal limits. The role of alcohol and even illicit drug use may also lead to medication nonadherence [32]. Unfortunately, data on the reasons for non-adherence is not recorded by the database.

The benefits and positive impact of transition services are well established and can help negate nonadherence [27]. A multi-disciplinary approach focused on exploring adherence patterns and beliefs as well as mental health problems is recommended as these are particular prevalent in this population [33]. Disclosure of nonadherence should be encouraged and met with a nonjudgmental stance as patients are often concerned about the repercussions of their disclosure in particular in the setting of graft loss and discussions regarding re-transplantation [8]. Other reasons for inferior graft survival could be because of disease aetiologies such as AILD or PSC, both of which are known to recur in the post-transplant period, thus leading to graft dysfunction

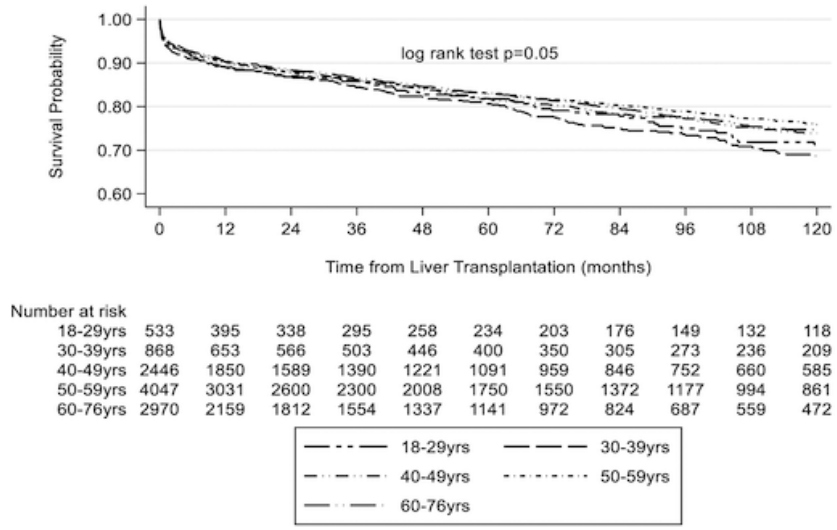

Figure 2 10-year graft survival stratified by age-group (n = 10 874).

and graft failure [10]. However, we must acknowledge that in our analysis the impact of age on graft failure did not differ according to liver disease aetiology (P = 0.28). Further investigation into the impact of disease aetiology on graft failure in YA's is therefore, warranted.

In the United Kingdom, this is the first study that has highlighted that graft survival is inferior in YA. Internationally, this is the first study that has identified that the effect of age on graft survival differs according to epoch of follow-up. Other literature that has explored this association is both sparse and conflicting [26,34]. Using the United Network for Organ Sharing (UNOS) database including 17 181 patients between 1988 and 2013, inferior liver graft survival rates were reported in this age group (17–29 years) [26]. In contrast, in another study of 12 161 liver recipients between 1987 and 2012, no difference in liver graft failure rates was reported between 17 and 24-year olds and younger or older cohorts [34]. Differing definitions of graft failure and differing partitioning of age-bands may have led to differing results in these analyses [26,34].

Another study which also utilized the UNOS database demonstrated no difference in graft failure between three different age groups, 0–17, 18–24 and 25–34 years [24]. However, the authors demonstrated increased rates of late graft loss in the 18–24 group and the cohort were less likely to be re-transplanted and more likely to die after developing graft failure [24]. An increased waiting list drop-out rate when awaiting LT was also observed [25]. These patients were less likely to be granted an exception score on the waiting list, had lower MELD scores and had inferior waiting list outcomes despite having the highest mean MELD scores at time of listing and LT. These data further accentuate the vulnerable status of YA undergoing liver transplantation.

Inferior outcomes in the 30–39 age group were also highlighted in our study. This group share similar recipient characteristics with the YA group, as well as underlying disease aetiologies. However, in contrast to the YA group, the leading cause for graft failure is recurrent disease and would be more likely to encompass recurrent HCV. With the introduction of direct antiviral agents (DAA) pre- and post-LT, the impact of recurrent HCV on inferior graft survival will likely become negated [35]. The prevalence of CR in this age group of 2.9% is still relevant and higher than the older age groups. In contrast to adolescents and YA where non–adherence to treatment is typically suspected and perceived to be developmentally appropriate, nonadherence or sub-optimal adherence to treatment is rarely explored in older age groups post LT [36]. A meta-analysis however showed that 22.6/100 adult transplant patients failed to take their medications correctly [32]. Variation in tacrolimus immunosuppression levels, suggestive of variable adherence to treatment, were associated with the rejection in group of 150 adult LT recipients (age 18–80 years) and have shown similar results in children and young people post LT [37]. Adherence management should be an integral part of a patient's management irrespective of their age. Routine calculation of Medication level variability index (MLVI) could be used routinely in a clinic setting to monitor adherence [38].

Table 2. Association of age at transplantation with 10 year graft survival (n = 10 874).

Age group	Hazard ratio	*P*-value	95% CI
18–29 years	1.25	0.04	1.00–1.57
30–39 years	1.31	0.02	1.11–1.55
40–49 years	1.07	0.28	0.95–1.21
50–59 years	1	1	1
60–76 years	1.05	0.44	0.93–1.18
Donor factor			
Female sex	1.01	0.863	0.91–1.11
Donor age	1.01	0.001	1.00–1.01
Donor BMI	1.01	0.030	1.00–1.02
Cause of death: CVA	0.91	0.200	0.80–1.05
Cause of death: other	0.89	0.148	0.76–1.04
DCD donor	1.75	0.000	1.49–2.04
Presence of steatosis	1.00	0.935	0.89–1.11
Presence of capsular damage	1.05	0.627	0.87–1.26
Abnormal organ appearance	1.33	0.000	1.18–1.50
Segmental graft type	1.48	0.000	1.22–1.79
Cold ischaemic time	1.00	0.002	1.00–1.00
Recipient factor			
Female sex	1.11	0.533	1.00–1.24
Non-white ethnicity	0.99	0.925	0.86–1.14
BMI	0.99	0.187	0.98–1.00
ECOG score			
Restricted	1.02	0.893	0.80–1.28
Self-care	1.10	0.408	0.88–1.38
Reliant	1.17	0.250	0.90–1.53
Dependent	1.40	0.063	0.98–2.00
Prescence of ascites	0.96	0.415	0.86–1.06
Prescence of varices	1.02	0.767	0.91–1.13
Encephalopathic	0.94	0.272	0.83–1.05
Presence of HCV antibodies	1.36	0.000	1.15–1.61
UKELD score	1.01	0.154	1.00–1.02
Inpatient	1.13	0.143	0.96–1.32
Renal support	0.98	0.831	0.79–1.20
Ventilated	0.39	0.02	0.17–0.88
Previous abdominal surgery	1.19	0.004	1.06–1.35
Indication for transplant			
HCC	1	1	1
HCV	0.85	0.086	0.71–1.02
PSC	1.06	0.580	0.87–1.27
HBV	0.62	0.005	0.45–0.87
PBC	0.61	0.000	0.50–0.76
ALD	0.90	0.236	0.76–1.07
AILD	0.72	0.003	0.58–0.89
Metabolic	1.21	0.280	0.85–1.71
Others	0.86	0.141	0.69–1.05
Era of transplant 2008–2016	0.79	0.000	0.71–0.88

Our data found that UKELD were comparable across the different age groups although mean platelet counts were lowest in the YA and the 50–59 group. Portal hypertension was a predominant feature amongst YA at the time of liver transplantation although, as our data suggests, it is not necessarily clinically evident; 43% had ascites and only 28% had suffered a previous variceal bleed, the lowest prevalence across the different groups. A leading aetiology in the YA group is biliary atresia post Kasai, a condition which is characterized by portal hypertension and cholangitis. The UKELD score therefore, does not appear to be a sensitive descriptor of the

Table 3. Association of age at transplantation with 10-year graft survival sequentially adjusted for donor and then recipient characteristics (n = 10 874).

	Age at transplantation					
	18–29 years	30–39 years	40–49 years	50–59 years	60–76 years	*P*-value‡
Unadjusted	1.15 (0.94–1.41)	1.26 (1.07–1.48)	1.05 (0.94–1.19)	1	1.02 (0.91–1.14)	0.05
Adjusted for donor characteristics*	1.24 (1.00–1.52)	1.31 (1.12–1.54)	1.08 (0.96–1.21)	1	1.01 (0.90–1.13)	0.01
Adjusted for donor and recipient characteristics†	1.25 (1.00–1.57)	1.31 (1.11–1.55)	1.07 (0.95–1.21)	1	1.05 (0.93–1.18)	0.02

*Adjusted for donor characteristics: sex, age, BMI (kg/m^2), donor cause of death, donor type (donation after circulatory death or donation after brain death), steatosis, capsular damage, organ appearance, segmental graft type and cold ischaemic time.

†Adjusted for donor characteristics listed above and recipient characteristics: sex, ethnicity, BMI (kg/m^2), functional status, ascites, varices, encephalopathy, HCV status, UKELD, pretransplant inpatient status, pretransplant renal support, pretransplant ventilator status, previous abdominal surgery, disease aetiology and era of transplantation (1995–2008 & 2009–2016).

‡*P*-value to determine whether the HR's representing the impact of different age-groups on graft failure differs significantly.

Table 4. Assessing the time-varying impact of age-group at transplantation on graft survival at 90 days, 2-years and 10 years, adjusted for donor and recipient characteristics (n = 10 874).

	Age at transplantation				
Epoch of follow-up*	18–29 years	30–39 years	40–49 years	50–59 years	60–76 years
0–90 days	1.10 (0.77–1.59)	1.26 (0.96–1.66)	0.94 (0.77–1.15)	1	0.91 (0.75–1.10)
90 days to 2 years	1.31 (0.88–1.94)	0.96 (0.68–1.37)	1.02 (0.81–1.29)	1	1.07 (0.86–1.33)
2–10 years	1.36 (0.96–1.93)	1.62 (1.26–2.09)	1.07 (0.86–1.33)	1	1.19 (0.99–1.46)
P for interaction between for all age groups and epoch †*P* = 0.03					

*Adjusted for donor characteristics: sex, age, BMI (kg/m^2), donor cause of death, donor type (donation after circulatory death or donation after brain death), steatosis, capsular damage, organ appearance, segmental graft type and cold ischaemic time and recipient characteristics: sex, ethnicity, BMI (kg/m^2), functional status, ascites, varices, encephalopathy, HCV status, UKELD, pretransplant inpatient status, pretransplant renal support, pre-transplant ventilator status, previous abdominal surgery, disease aetiology and era of transplantation (1995–2008 & 2009–2016).

†Wald test to determine whether the hazard ratios from 0 to 90 days, 90 days to 2-years and 2-years to 10 years for all age-groups differ significantly from each other.

severity of liver disease in YAs [13]. The development of more sensitive scores and models are therefore needed in YAs that will describe the severity of their liver disease and help identify those that will benefit from LT.

There are several limitations to our study. First, our dataset lacked complete information on several clinically plausible risk factors including immunosuppression, changes over time and differences between centres in immunosuppression regimens, immunosuppression levels, adherence rates, rejection episodes and peri-operative complications and causes of graft failure. However, given that we adjusted for donor and recipient characteristics that have previously been proven to be risk factors for graft loss [2,4] it is unlikely that residual confounding fully explains our results. Second, the donor and recipient characteristics that we did include in our model may not have fully captured variations in how patients were selected for liver transplantation over the 20-year study period but again given the extensive risk adjustment that was performed it is unlikely that changes over time in patient selection would explain such variation in age-related outcomes. Third, the relatively small number of recipients in the youngest age-group (18–29 years) may have affected the statistical power of the study and in particular in the time-

Table 5. Cause of graft failure stratified by age-group (n = 1927).

	Age at transplantation					
Cause of graft failure	18–29 years 105 failures (%)	30–39 years 191 failures (%)	40–49 years 447 failures (%)	50–59 years 694 failures (%)	60–76 years 490 failures (%)	P-value‡
Acute rejection	0.0 (0)	2.1 (4)	0.5 (2)	1.2 (8)	0.4 (2)	0.05
PNF	5.7 (6)	4.2 (8)	7.6 (34)	11.1 (77)	9.6 (47)	0.17
Acute vascular occlusion	17.1 (18)	14.7 (28)	12.5 (56)	12.0 (83)	10.4 (51)	0.02
Late vascular occlusion	5.7 (6)	5.8 (11)	6.3 (28)	4.5 (31)	2.9 (14)	0.03
Non-thrombotic infarction	1.0 (1)	2.1 (4)	2.9 (13)	2.0 (14)	1.2 (6)	0.30
Ductopenic rejection	1.9 (2)	1.6 (3)	0.7 (3)	0.9 (6)	0.6 (3)	0.39
Recurrent disease*	11.4 (12)	20.4 (39)	21.7 (97)	17.6 (122)	16.5 (81)	<0.001
Biliary complications	3.8 (4)	5.2 (10)	3.4 (17)	4.9 (34)	6.9 (34)	0.42
Other†	15.2 (16)	15.2 (29)	17.2 (77)	22.2 (154)	23.3 (114)	0.60
Unknown	12.4 (13)	17.3 (33)	17.5 (78)	14.8 (103)	21.0 (103)	0.006

*Includes the recurrence of HCV and the cholestatic liver diseases (PSC & PBC).

†Specified only as 'other cause of graft failure' in Standard National Liver Transplant Registry.

‡Categorical variables were presented as proportions and compared using chi-squared tests.

dependent analysis. The impact of age on graft failure in this study may therefore be an underestimation. Finally, used predefined post-transplant epochs (up to 90 days, between 90 days and 2 years and between 2 and 10 years) to investigate the impact of age on graft failure in different epochs. This approach assumes that the prognostic impact of age on graft survival is constant within each of these epochs. The advantage of this approach is that the hazard ratios can be estimated using standard Cox regression methods and, more importantly, that the results are relatively easy to interpret. Its disadvantage is that that the partitioning of the survival time in distinct epochs needs to be chosen in advance and that the number of separate epochs as well as their duration is arbitrary.

Our data confirms that YA's form a unique cohort of patients, supported by the concept that adolescent development, a period of significant neuro-biological changes continues into the mid-20s [39]. It is likely that some of the behaviours associated with this developmental phase such as risk taking and impulsivity, will impact on graft outcome in YA liver transplant recipients. Our data suggests that more support is required for YA undergoing liver transplantation to help them preserve their graft function especially from two years onwards [27,40]. As demonstrated by the paediatric experience of transitional care for children post-transplantation, adult liver transplant professionals should be encouraged to seek support from allied health professionals including clinical psychologists, transplant coordinators, social workers and youth workers, experienced in working with young people [30].

Currently in the United Kingdom, there is a huge inter-centre variability with regards to patient care for young people with liver disease, including for those transitioning from paediatric to adult services. Currently, young people are expected to be looked after by adult services at 18 years of age, irrespective of whether this is developmentally appropriate for the individual. Whereas most services focus on providing support for young people aged 16–18 years moving from paediatric to adult services, at King's College Hospital, we have developed a unique multi-disciplinary service supporting YAs during the ages of 16–25 years hence including young people presenting to the adult service with de novo liver disease [41]. In stark contrast, in most centres patients between the ages of 18 and 29 years would be managed by adult services they will not necessarily have been exposed to transition services. It is therefore likely, that the needs of this 'vulnerable' age groups are not being met. YA services are limited but are available in certain UK transplant centres, providing a multidisciplinary team approach, addressing the physical, social and mental health needs of the patient [33,41].

In summary, we have demonstrated inferior graft outcomes for YA (18–29 years), with chronic rejection identified as the leading cause for long-term graft failure. This increased risk is more evident from two years after liver transplantation. YA require supportive multidisciplinary care, which can help improve long-term outcomes.

Authorship

GB: conception of project, literature review, data analysis, interpretation of results and write up of the manuscript. DW: conception of the project, data analysis, interpretation of results and write up of the manuscript. SF: conception of the project, data analysis, interpretation of results and write up of the manuscript. KW: conception of the project, data analysis, interpretation of results and write up of the manuscript. TC: interpretation of results and write up of the manuscript. NH: conception of the project, interpretation of results and write up of the manuscript. JM: conception of the project, interpretation of results and write up of the manuscript. MS: conception of the project, interpretation of results and write up of the manuscript. DJ: conception of the project, interpretation of results and write up of the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Dr Stefan Flasche is supported by a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society (Grant number 208812/Z/17/Z). JvdM is partly supported by the NHS National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care North Thames at Bart's Health NHS Trust. The remaining authors declare no financial support.

Conflict of interests

All authors declare no conflict of interests.

Acknowledgements

The authors would thank all liver transplant centres for providing data to the Standard National Liver Transplant Registry. The authors also to thank all those involved in collecting and handling liver transplant data at NHSBT. The UK Liver Transplant Audit is supported by the NHS National Specialised Commissioning Group and NHS England.

Data availability statement

The UK Liver Transplant Registry is available on request from National Health Service Blood and Transplant.

REFERENCES

1. Bruix J, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. *Gut* 2014; **63**: 844.
2. Wallace D, Cowling TE, Walker K, *et al.* Short- and long-term mortality after liver transplantation in patients with and without hepatocellular carcinoma in the UK. *Br J Surg* 2020; **107**: 896.
3. Nasralla D, Coussios CC, Mergental H, *et al.* A randomized trial of normothermic preservation in liver transplantation. *Nature* 2018; **557**: 50.
4. Callaghan CJ, Charman SC, Muiesan P, *et al.* Outcomes of transplantation of livers from donation after circulatory death donors in the UK: a cohort study. *BMJ Open* 2013; **3**: e003287.
5. Wallace D, Robb M, Hughes W, *et al.* Outcomes of patients suspended from the national kidney transplant waiting list in the United Kingdom between 2000 and 2010. *Transplantation* 2020; **104**: 1654.
6. NBATAhttps://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/12256/nhsbt-kidney-transplantation-annual-report-2017-2018.pdf. Accessed 8th October 2018.
7. Dobbels F, Van Damme-Lombaert R, Vanhaecke J, De Geest S. Growing pains: non-adherence with the immunosuppressive regimen in adolescent transplant recipients. *Pediatr Transplant* 2005; **9**: 381.
8. Dobbels F, Hames A, Aujoulat I, Heaton N, Samyn M. Should we retransplant a patient who is non-adherent? A literature review and critical reflection. *Pediatr Transplant* 2012; **16**: 4.
9. Shemesh E, Duncan S, Anand R, *et al.* Trajectory of adherence behavior in pediatric and adolescent liver transplant recipients: the medication adherence in children who had a liver transplant cohort. *Liver Transpl* 2018; **24**: 80.
10. Montano-Loza AJ, Bhanji RA, Wasilenko S, Mason AL. Systematic review: recurrent autoimmune liver diseases after liver transplantation. *Aliment Pharmacol Ther* 2017; **45**: 485.
11. http://odt.nhs.uk/pdf/advisory_group_papers/LAG/Provision_of_Standard_Data_Set_for_Liver_Transplant_v4.pdf. Accessed 2nd August 2018.
12. Joshi D, Gupta N, Samyn M, Deheragoda M, Dobbels F, Heneghan MA. The management of childhood liver diseases in adulthood. *J Hepatol* 2017; **66**: 631.
13. Jain V, Burford C, Alexander EC, *et al.* Prognostic markers at adolescence in patients requiring liver transplantation for biliary atresia in adulthood. *J Hepatol* 2019; **71**: 71.
14. Gomez Gavara C, Bhangui P, Salloum C, *et al.* Ligation versus no ligation of spontaneous portosystemic shunts during liver transplantation: audit of a prospective series of 66 consecutive patients. *Liver Transpl* 2018; **24**: 505.
15. van der Meulen JH, Lewsey JD, Dawwas MF, Copley LP, UK, Ireland Liver Transplant A. Adult orthotopic liver transplantation in the United Kingdom and Ireland between 1994 and 2005. *Transplantation* 2007; **84**: 572.
16. Dawwas MF, Gimson AE, Lewsey JD, Copley LP, van der Meulen JH. Survival after liver transplantation in the

United Kingdom and Ireland compared with the United States. *Gut* 2007; **56**: 1606.
17. Jacob M, Copley LP, Lewsey JD, *et al*. Functional status of patients before liver transplantation as a predictor of posttransplant mortality. *Transplantation* 2005; **80**: 52.
18. Barber K, Madden S, Allen J, *et al*. Elective liver transplant list mortality: development of a United Kingdom end-stage liver disease score. *Transplantation* 2011; **92**: 469.
19. Collett D, Friend PJ, Watson CJ. Factors associated with short- and long-term liver graft survival in the United Kingdom: development of a UK donor liver index. *Transplantation* 2017; **101**: 786.
20. Tovikkai C, Charman SC, Praseedom RK, Gimson AE, van der Meulen J. Time-varying impact of comorbidities on mortality after liver transplantation: a national cohort study using linked clinical and administrative data. *BMJ Open* 2015; **5**: e006971.
21. Wallace D, Walker K, Charman S, *et al*. Assessing the Impact of suboptimal donor characteristics on mortality after liver transplantation: a time-dependent analysis comparing HCC with non-HCC patients. *Transplantation* 2019; **103**: e89.
22. Lehr S, Schemper M. Parsimonious analysis of time-dependent effects in the Cox model. *Stat Med* 2007; **26**: 2686.
23. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011; **30**: 377.
24. Sterne JAC, White IR, Carlin JB, *et al*. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009; **338**: b2393.
25. Ebel NH, Hsu EK, Berry K, Horslen SP, Ioannou GN. Disparities in waitlist and posttransplantation outcomes in liver transplant registrants and recipients aged 18 to 24 years: analysis of the UNOS database. *Transplantation* 2017; **101**: 1616.
26. Foster BJ, Dahhou M, Zhang X, Dharnidharka VR, Conway J, Ng VL. High risk of liver allograft failure during late adolescence and young adulthood. *Transplantation* 2016; **100**: 577.
27. Sagar N, Leithead JA, Lloyd C, *et al*. Pediatric liver transplant recipients who undergo transfer to the adult healthcare service have good long-term outcomes. *Am J Transplant* 2015; **15**: 1864.
28. Choudhary NS, Saigal S, Bansal RK, Saraf N, Gautam D, Soin AS. Acute and chronic rejection after liver transplantation: what a clinician needs to know. *J Clin Exp Hepatol* 2017; **7**: 358.
29. Dharnidharka VR, Lamb KE, Zheng J, Schechtman KB, Meier-Kriesche HU. Across all solid organs, adolescent age recipients have worse transplant organ survival than younger age children: a US national registry analysis. *Pediatr Transplant* 2015; **19**: 471.
30. Berquist RK, Berquist WE, Esquivel CO, Cox KL, Wayman KI, Litt IF. Non-adherence to post-transplant care: prevalence, risk factors and outcomes in adolescent liver transplant recipients. *Pediatr Transplant* 2008; **12**: 194.
31. Soltys KA, Mazariegos GV, Squires RH, Sindhi RK, Anand R, Group SR. Late graft loss or death in pediatric liver transplantation: an analysis of the SPLIT database. *Am J Transplant* 2007; **7**: 2165.
32. Dew MA, DiMartini AF, De Vito Dabbs A, *et al*. Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. *Transplantation* 2007; **83**: 858.
33. Hames A, Matcham F, Joshi D, *et al*. Liver transplantation and adolescence: the role of mental health. *Liver Transpl* 2016; **22**: 1544.
34. Van Arendonk KJ, King EA, Orandi BJ, *et al*. Loss of pediatric kidney grafts during the "high-risk age window": insights from pediatric liver and simultaneous liver-kidney recipients. *Am J Transplant* 2015; **15**: 445.
35. Belli LS, Perricone G, Adam R, *et al*. Impact of DAAs on liver transplantation: major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. *J Hepatol* 2018; **69**: 810.
36. Drent G, De Geest S, Dobbels F, Kleibeuker JH, Haagsma EB. Symptom experience, nonadherence and quality of life in adult liver transplant recipients. *Neth J Med* 2009; **67**: 161.
37. Christina S, Annunziato RA, Schiano TD, *et al*. Medication level variability index predicts rejection, possibly due to nonadherence, in adult liver transplant recipients. *Liver Transpl* 2014; **20**: 1168.
38. Shemesh E, Bucuvalas JC, Anand R, *et al*. The medication level variability index (MLVI) predicts poor liver transplant outcomes: a prospective multi-site study. *Am J Transplant* 2017; **17**: 2668.
39. Darcy A, Samyn M. Looking after young people with liver conditions: Understanding chronic illness management in the context of adolescent development. *Clin Liver Dis* 2017; **9**: 103.
40. Harden PN, Walsh G, Bandler N, *et al*. Bridging the gap: an integrated paediatric to adult clinical service for young adults with kidney failure. *BMJ* 2012; **344**: e3718.
41. Joshi D, Dyson J, Hudson M, Levitsky J, Heldman M, Samyn M. Paediatric to adult liver transition services: the state of play in the UK. *Clin Med* 2019; **19**: 425.