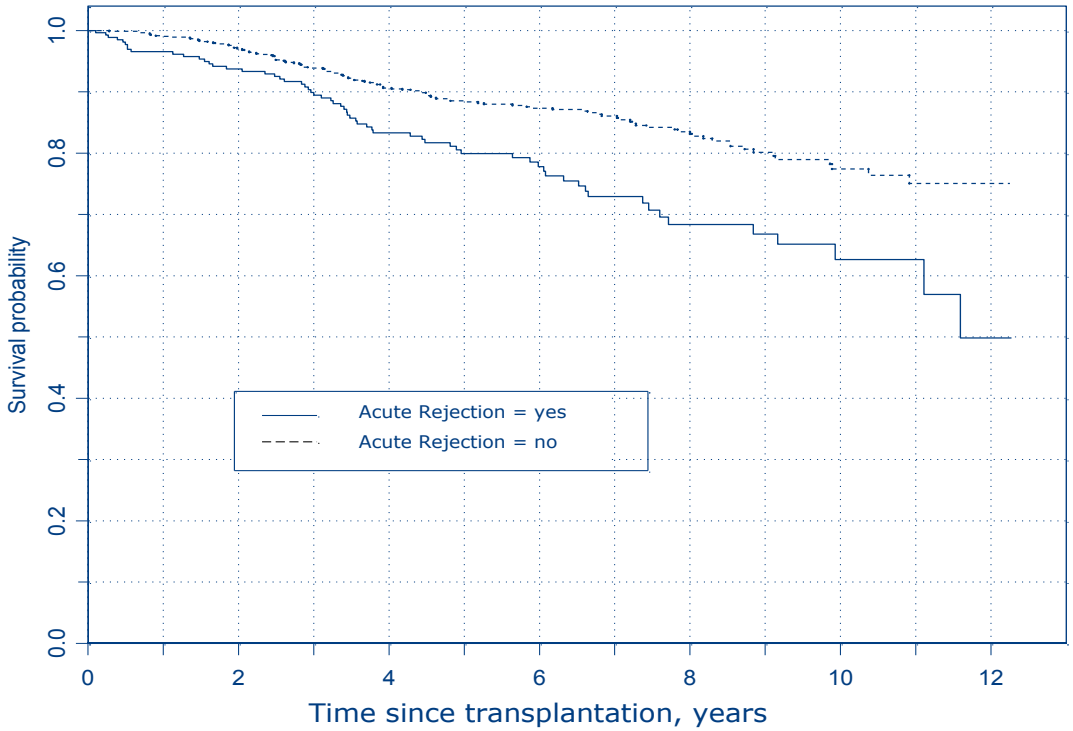
# Some Observations of The Impact of Acute and Chronic Rejection on Graft Survival in Kidney and Liver Transplantation

Markku Mikael Nurminen

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# SOME OBSERVATIONS OF THE IMPACT OF ACUTE AND CHRONIC REJECTION ON GRAFT SURVIVAL IN KIDNEY AND LIVER TRANSPLANTATION

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## ABSTRACT

*Background* Survival rates of kidney and liver transplantations have improved significantly over the last decades. Despite the progresses made especially in the 1-year graft survival and attrition rates, the developments in long-term graft survival post-transplant have not followed through.

*Data and Objectives* This paper reviews the published survival experiences of kidney and liver transplantation patients from the period 1982-2004 in Finland, reports some new observations derived from the re-analyses of the preceding datasets, and updates the discussion concerning the impact of acute rejections on the chronic deterioration of the grafts.

*Results* The half-life expectancies for renal and hepatic transplants were projected to last 15 years and 18 years, respectively. The graft survival probabilities for the liver transplant patients who had undergone an acute rejection episode were unexpectedly greater than those for their peers without such a complication. In comparison, the graft survival probabilities for the kidney transplant patients with an acute rejection were consistently smaller than for their counterparts without it.

*Concluding Remarks* It is tentatively hypothesized that: a successfully treated acute rejection in the liver graft may prolong its long-term survival; and, with the advent of modern treatments for the chronic kidney graft rejection, histological changes and decline in the renal transplant function are expected to reduce.

*Keywords* Graft survival; Kidney; Liver; Life expectancy; Modeling; Rejection; Transplantation

## INTRODUCTION

This paper is concerned with the impact of acute rejection and chronic rejection on allograft survival in the comparison of patients who received a liver transplant vs. a kidney transplant. Values of immunologic and other donor and recipient risk factors were inserted to the developed prognostic models to weigh their significance on the patient and allograft survival. I review here the previous original studies, present some new results, and discuss the timeline and importance of pathological lesions from the onset until late follow-up after transplantation.

*Acute and chronic rejection*

Acute (cellular) rejections (AR) of the liver are usually mild episodes which occur rather early, practically within 6 months after the transplantation (Tx), and can in most patients be treated with medication, whereas a severe late AR often leads to worse long-term graft and patient survival. Chronic (ductoral) rejection (CR) is defined as obliterative vasopathy and eventual loss of bile ducts, arteries and veins developing 6 months or later after liver transplantation. CR is a consequence of severe cell-mediated immunologic injury which evolves indolently in most cases and progresses inexorably through a predictable sequence of impairments. CR may be exacerbated by deteriorating conditions such as reperfusion injury, cytomegalovirus infection, hypertension, hyperlipidemia, or diabetes. The etiology of CR is still not fully known but late AR may be a vital causal risk factor of CR with worse prognosis. Currently there is no curable treatment available for the pathological lesions of the graft in a late-stage CR.[1,2]

The basic histopathological features of renal allograft undergoing CR are perivascular and intestinal inflammation, intestitial fibrosis, glomerular schelosis, tubular atrophy and concentric, generalized arteriosclerosis.[3] The first and last of these features are also shared by the liver transplants. Kidney graft failure is defined as non-life-sustaining function of the organ requiring dialysis without which patient's death is imminent unless a new transplantation is performed. Liver dialysis with the molecular adsorbent recirculating system is not indicated for treatment of chronic liver disease. The MARS support system may be approved only for patients in acute hepatic failure with encephalopathy as a bridge to transplant. An important aspect is that the liver is the only organ in which early CR is potentially reversible. This quality has been attributed to its unique immunobiological properties.

*Previous studies of kidney and liver transplantation in Finland*

The graft function as well as the graft and patient survival after kidney transplantation (KTx)[3,4] and liver transplantation (LTx)[5-7] has been previously studied at the Transplantation and Liver Surgery Clinic of Helsinki University Central Hospital (HUCH), Finland. The patient populations, data-analytic approaches, and main findings are summarized below. Details of the clinical procedures can be found in the original publications.

In a 2-year prospective clinical follow-up study[3] of 94 patients with a functioning renal graft at 2 years post-Tx, the proportion of deteriorated cases was 26%. Originally these patients belonged to a group of 128 consecutive adult recipients of first cadaveric allograft entering a randomized study from 1986 to 1987. CR was defined as the deterioration of graft function with permanent increase in serum creatinine over 20% between 2 and 4 years after the KTx and/or the deterioration of graft function leading to dialysis with characteristic signs of CR confirmed in biopsy, without signs of cyclosporin nephrotoxicity or recurrence of the original renal disease. Graft loss is due in part to death with a functioning graft, but its most common cause is chronic allograft failure.

The follow-up study[3] registered the 4-year graft and patient survival rates as 69% and 84%, respectively. The estimated risk of deterioration was greater among patients with previous AR than among those without it (33% and 21%, respectively). But the difference was not statistically significant in the small subgroups that were subjected to thorough clinical investigations. The risk ratio (RR) was 1.6 with a 95% confidence interval (CI) of 0.8-3.1.

A retrospective epidemiological-statistical study[4] of renal allograft function was based on the comprehensive register roll of 1,215 KTx patients diagnosed with an end-stage kidney disease; the transplantation surgeries were performed in the period between 1986 and 1995. In all, 36% of the patients experienced a delayed graft functioning. The median time to AR was 16 days. AR episodes within three months from KTx were recorded in 26% of the patients, 13% of which were fatal (3% of all patients). The incidence of CR was 15%. Of those patients who overcame AR, 20% developed later CR.

In a Cox regression analysis[4] for kidney graft survival, the follow-up was started from the KTx date. Covering the timeframe, two subgroups were formed: patients who were clinically treated for AR and patients without AR. Upon adjustment for the other renal risk factors selected into the prognostic model (Appendix 2), a preceding occurrence of AR proved to be a highly significant predictor for CR ($P < 0.001$, the hazard ratio (HR) was 1.8, 95% CI 1.3-2.4).

A series of 388 orthotopic LTx patients were operated during the years 1982 and 2002 due to a severe end-stage liver disease and followed until 2004.[5-7] Prognostic models for LTx were developed for analyzing which risk factors, immunological or other, predicted graft loss due to CR, or other chronic dysfunction defined as a deterioration of graft function without signs of rejection in biopsy. Covariates of graft survival time (chosen either based on prior knowledge or significance in univariate analyses) were donor's age, recipient-donor gender compatibility, recipient's blood group, intra-operative blood transfusion, size of the transplanted organ, indication for transplantation, and calendar year of transplantation.

The Cox's proportional hazards modeling evinced consistent trends toward prolonged survival over calendar time.[†] In the successive time periods 1982-1986, 1987-1991, 1992-1996, and 1997-2002, the 3-year liver allograft survival rates ascended with rapid pace: 50%, 60%, 79%, and 88%, respectively (Figure 1).[5] The overall 1- and 10-year graft survival probabilities were estimated to be 84% (CI 80-88%) and 67% (95% CI 61-75%), respectively.[‡]

The incidence of different types of ARs in liver allograft decreased sharply from 1982 to 2002. Moreover, the time period to first AR and to the occurrence of AR and CR increased, although the basic immunosuppression rate stayed mainly the same over the 20 years. The risk of chronic graft dysfunction also declined over time. The overall occurrence of AR in LTx patients was 46% in the first grafts. The median time to reactions was 16 days; half of these took place 9 to 35 days post-operative. CR was appreciably rare, 4%, and its incidence rate remained low, even when patients were followed up to 18 years. Chronic renal dysfunction was a more prevalent complication following LTx, 10%.[6]

The impact of immunological and other factors in liver transplantation is generally believed to be less important than in kidney transplantation. The significance of these factors to liver graft rejection was examined in a multivariate regression analysis. The main findings were that immunological pre-transplant factors did not have an effect on the occurrence of either AR or CR. Thus, the study supported the prior belief that immunological factors do not constitute a major risk associated with rejection after LTx.[7]

## IMPACT OF REJECTION ON GRAFT SURVIVAL

The datasets derived from the HUCH prior published clinical-epidemiological studies aimed at investigating KTx[4] and LTx[5,6], were analyzed anew. The survival time for right censored data was the follow-up time from transplantation to the ending date of the study or the censoring event, either death or re-transplantation. The graft survivor curve specifies for each follow-up day the probability that a typical graft would function beyond that day if there were no censoring. It refers to the model of an individual case with inserted average covariate values in the whole set of data records. One advantage of the applied prognostic models is that they can be used to estimate an individual patient's mortality risks under different clinical conditions.

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[†]This favorable development is likely to have come about due to the improved medication and hospital clinic/outpatient therapy. Source: Professor Krister Höckerstedt, HUS. Kidney and liver transplantations. Studia Medicina - public lecture: New life with transplantation. Biomedicum Helsinki, 23.11.2011

[‡]Of the liver transplantation recipients in the 2000s, approximately 95 % are living one year and 80% ten years after the operation. Page accessed on March 22, 2017: http://www.hus.fi/sairaanhoito/sairaanhoitopalvelut/elinsiirrot/maksansiirrot/Sivut/default.aspx

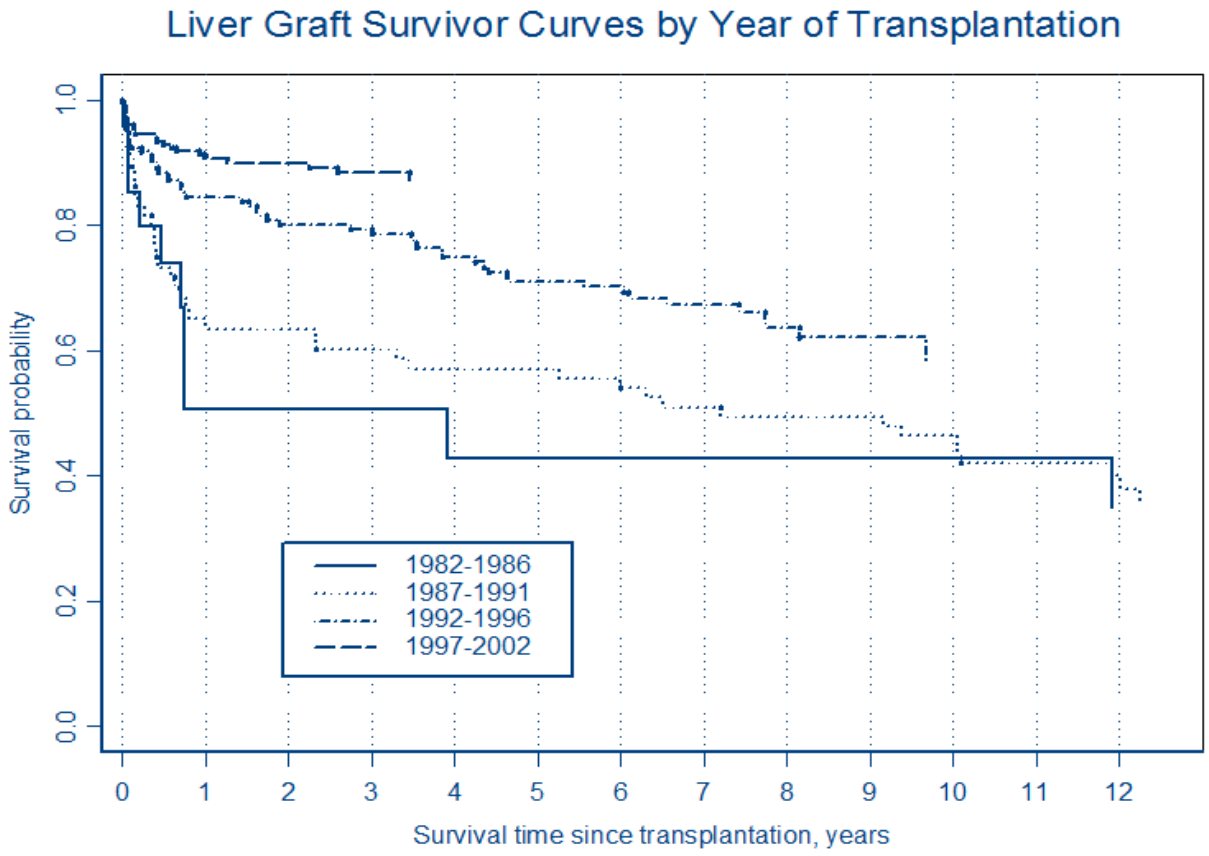


*Figure 1*. Liver graft survivor curves by calendar year of transplantation. In the successive 5-year periods, the survival rates after a 3-year follow-up were 50%, 60%, 79%, and 88%.

Contrary to expectation, the observed (unadjusted) mean graft survival time of the LTx patients who had undergone an AR episode was longer than that for their peers without such a reaction. The difference prevailed, and became significant, in the stratified Cox model that adjusted for the risk factors, estimated with separate baseline hazard functions for subjects either with AR or without AR (Appendix 1). The model accounted for unequal follow-up times in the compared strata. The model-based graft survivor curves for an 'average' patient (with average values of the included covariates) in the two subpopulations are presented in Figure 2.

A marked difference in the survivor curves formed early on following a dip during the first month after LTx. In that time span, in all 25 patients without AR and only 5 patients with AR died or received a re-transplant. The median time to first AR was 16 days, and 87% of the cases occurred within 3 months after LTx. The log-survivor functions display fairly straight lines after the first year (Figure 2), confirming the good fit of the exponential model for the hepatic transplantation data. Note also the parallelism of the log-hazards of the patients' two AR statuses as a function of follow-up after the first year. This means that that their hazards are approximately equal, up to a multiplicative constant, and their differences do not vary over time. Hence, this represents a case of multiplicative hazards in the later follow-up (> 1 year).

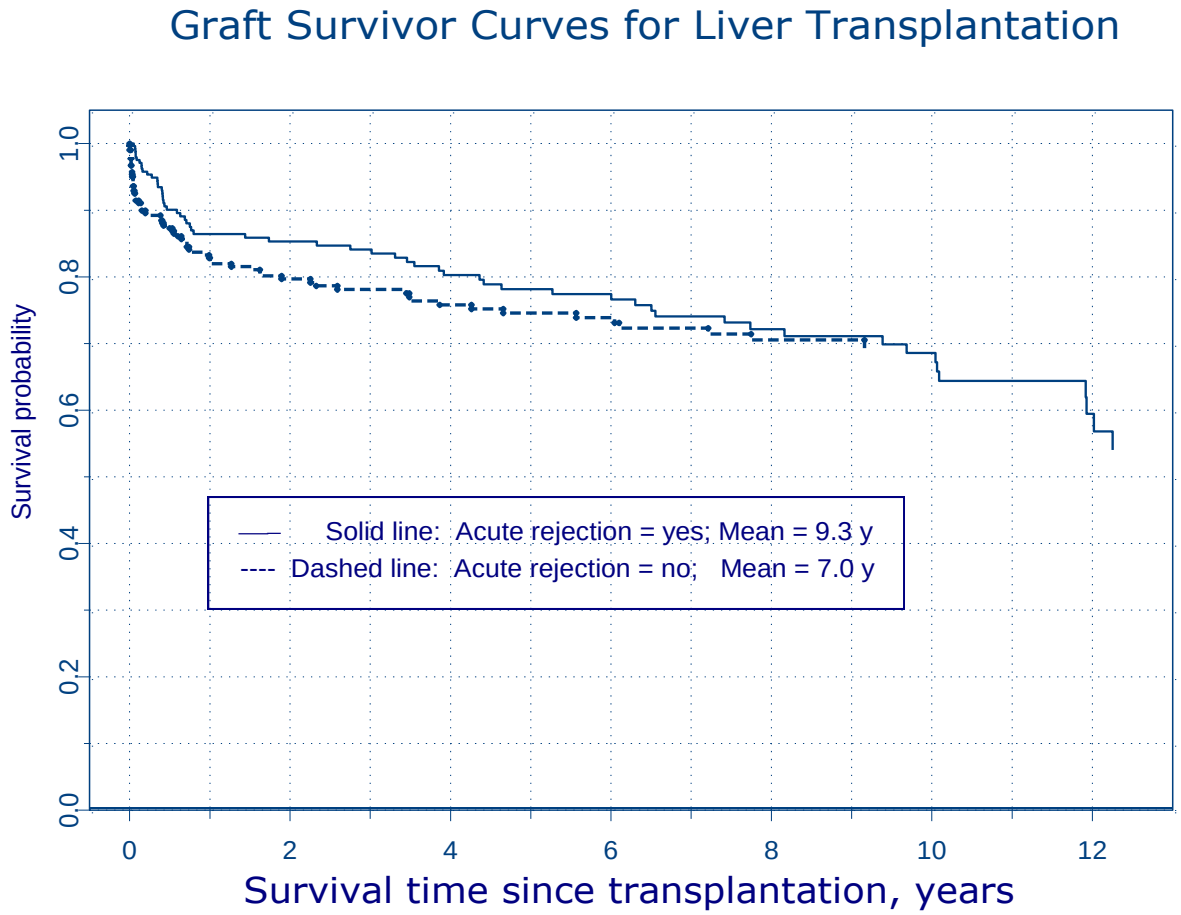


*Figure 2*. Graft survivor curves for liver transplantation patients with estimated values for risk factors by acute rejection status. The mean values refer to the length of the follow-up period.

The pivotal question is: What really made this difference in attrition rates for liver transplants? Did the therapy given to patients with AR confer them a comparative edge in immunity from complications, or was it a random cluster of patient deaths or graft failures in the AR-free subgroup? During the first month post-LTx, the commonest cause of death is infection. Be it as it may, the difference in losses remained basically the same in the timeline of one through six years and diminished thereafter. The 5-year survival probability was 4%-units higher for patients with an episode of AR than without it. There were no comparative data beyond 9 years. The overall 62% survival rate was reached after a 12-year follow-up. A projection to the 50% survival rate produced the 'half-life' of approximately 15 years expected for LTx grafts.

In stark contrast, the graft survival probabilities for subjects with KTx, who had undergone an AR episode, showed consistently less favorable outcomes than the experiences of their counterparts without such an episode. Note how straight the log-survivor functions are in Figure 3, confirming again the good fit of the exponential model for the renal transplantation data (Appendix 2). Note also that the hazards of the two AR statuses are rather parallel in the log-scale throughout the time span. This implies that their hazards are equal, up to a multiplicative constant. That is, this is also approximately a proportional hazards situation.

The compared survivor curves stayed relatively close to each other during the first 3 years of follow-up, started to grow discrepant thereafter, and reached a difference of 10%-units after a 10-year follow-up. An extrapolation to the 50% overall survival rate yielded the 'half-life' of approximately 18 years forecasted for KTx grafts.

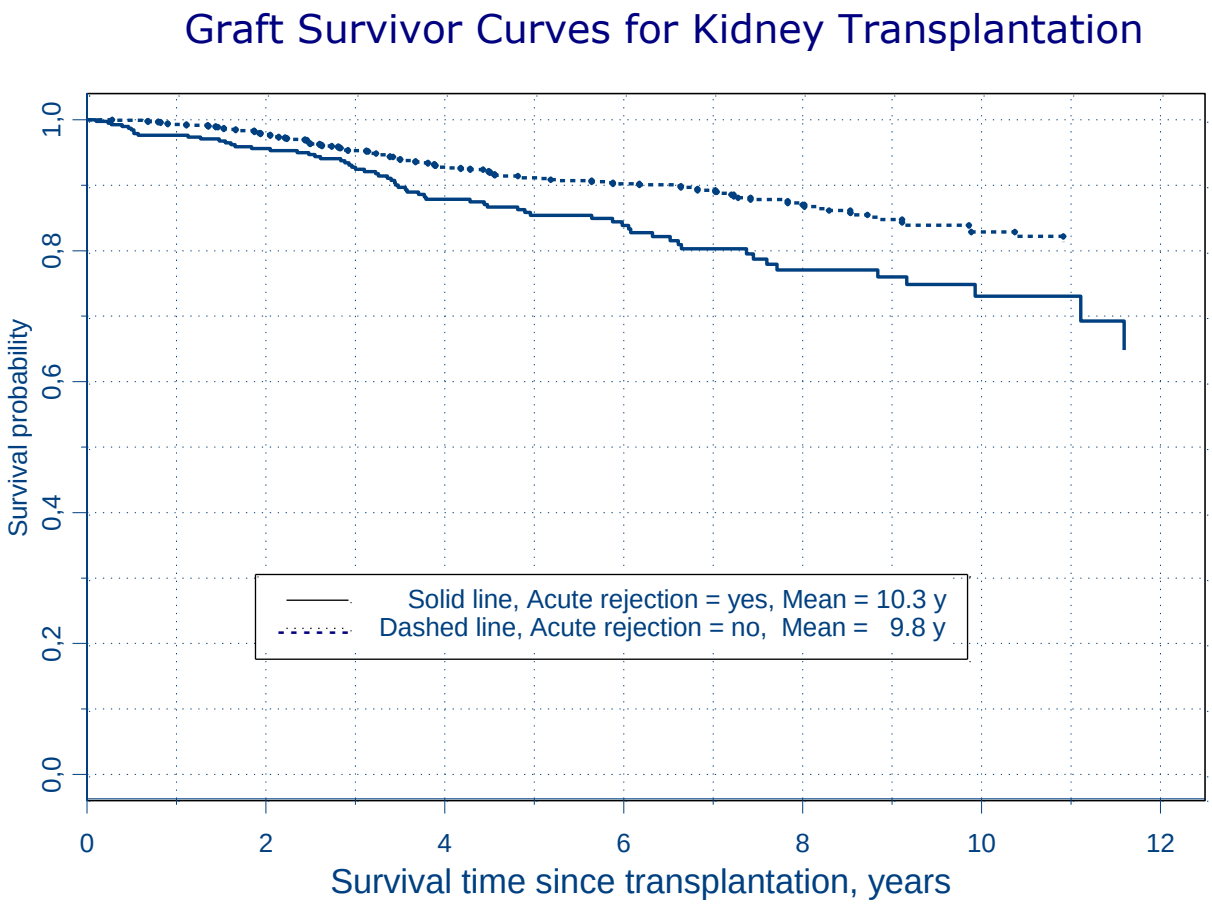


*Figure 3*. Graft survivor curves for kidney transplantation patients with estimated values for risk factors by acute rejection status. The means refer to the length of the follow-up period.

## DISCUSSION

### *Timeline of pathological lesions after liver transplantation*

Since 1982, when liver transplant surgeries were started in Finland, the 'cutting edge' in the development and research has shifted. Earlier hepatic AR complications were the foremost problems, but these have since then largely been overcome by new treatments. Acute hepatic reactions can in most cases be treated with increased corticosteroid boluses or in mild cases by raising the basal immunosuppression (the inhibition of the normal immune response) levels. Hence CR has become a more demanding concern and remains a major complication affecting long-term survival of liver transplantation. The long-term life expectancy of patients after LTx depends on many risk factor such as donor's age, post-operative therapy, and long-term toxicity caused by immunosuppressive maintenance medication. The most important adverse consequences are renal dysfunction, cardiovascular disease, and cancer;[8] see Appendix 3.

A HUCH publication of 2011 reported that with improved early-term management, and despite the long-term complications, the 10-year LTx patient survival rates in many indications exceeded 70%.[8] In the present multivariate modeling, in which the LTx year of was included as a predictor covariate, the estimated 10-year graft survival rate was 67% (CI 61-75%).[5] Hence, the long-term patient and graft survival rates after LTx are outstanding. In comparison, a U.S. study of large data sets from the Scientific Registry of Transplant Recipients in 1989-2009 estimated the unadjusted 10-year liver graft survival rate to be lower that is 51%.[9]

The most common causes of death during the first month after LTx are infections, typically bacterial infections of hospital-mediated origin, uncontrollable rejections, and multi-organ failures (sepsis). Recipients who develop an early graft dysfunction usually experience a longer intensive care unit and hospital stay and have higher graft failure and mortality rates compared with those patients without graft dysfunction. Many factors, such as donor status, organ procurement, surgical grafting, and recipient illnesses, may affect the early dysfunction of the graft, and ischemia-reperfusion injury is considered the direct cause.[10-12] However, in the dataset available herein for the analysis of individuals' underlying causes of death were not recorded.[5]

The survival model incorporated risk factors into the adjustment calculations. The significant categories included (with a significance level of 10%): donor's age (<20 years, and all advancing age groups >20 years), gender incompatibility (R=m), recipient's blood group (B and O), graft size (reduced), indication for LTx (liver tumor, ReTx), and calendar period of transplantation (latest, 1997-2002); see Appendix 1. Nevertheless, a gap was found between the early phase of the survivor curves of the LTx patients with AR and without it. The exact cause of this discrepancy in hepatic graft survival is yet to be disclosed.

*Allograft half-life expectancies and long-term forecasting*

Life expectancies for liver and kidney transplant patients have improved significantly over the last decades. Despite the dramatic progresses that have been made in the 1-year graft survival and attrition rates, the mid-and long-term survival rates after liver transplantation have hardly changed. A recent study ascribed this circumstance to be an indication of the difficulty in diagnosing chronic graft dysfunction.[13] Further progress in long-term survival is expected to come from targeting endpoints beyond the first-year rejection and survival rates.

Looking at Figures 2 and 3, it would appear that the losses in the first year and in subsequent years post-Tx are separate pathological processes that will not necessarily reflect each other's development. In the case of LTx, the discrepancy between the graft survivor curves – of the patients who had experienced AR as against those who had not – derived by and large from the attrition events during the first year. As for KTx, there were very few events during the first year after the operation, and no marked difference emerged between the survivor curves until the 4th year of follow-up. A study concluded that one-year creatinine values predict long-term kidney graft survival.[14] Thus, the improvements in renal graft half-life would appear to be basically related to the conservation of renal function in the first year post-transplantation.

In transplantation studies, it is customary to determine graft half-live expectancy as the inter-section of point of the Kaplan-Meier curve[15] for a patient population with the 50% survival. Actual half-lives can be calculated in those instances where all patients have reached the defining 50% mark, and actuarial half-lives for those cases when only a portion of them has done so. Projected half-life expectancies are extrapolated from data in which none of patients has been followed up to the 50% mark.

The Cox survival analysis deals with the problem of unequal follow-up time distributions between the compared patient series. An alternative analytic approach to avoid any bias that can arise from the different patterns of the survivor curves before and after the first year of follow-up would be to fit the survivor model starting one year after the transplantation (i.e. to exclude the first year's data from the analysis). For more on survival analysis, see Appendix 4.

The Cox survivor curve[15] refers to a given patient in a stratum (e.g. with average values for the covariates in the proportional hazards model), and is applicable to right-censored data for estimating survival probabilities as a function of post-Tx follow-up time. The projected half-lives expectancies for KTx and LTx estimated from the HUCH data[4,5] equaled 15 years and 18 years, respectively. In 1996, Häyry[16] had anticipated, "It may be possible in the next few years to develop new treatments that would double the current 7- to 8-year half-life expected for renal transplants". This forecast would have entailed an approximately 15-year renal half-life in Finland.

The projected renal allograft half-life estimate for year 1998 in Spain was similarly 18 years.[17] In the United States between 1988 and 1995, the renal graft half-life doubled from 9 to 18 years for patients who did not experience an episode of AR within the first year.[18] For patients who had at least 1 AR during the same period the half-life of renal transplants remained relatively steady at about 7-8 years. These data suggest that AR within the first year post-transplantation is a negative predictor of long-term renal allograft survival. In another U.S. study,[9] the allograft half-lives for 1998 were for LTx: 10 years and for KTx: 11 years. Thus, in international comparisons the Finnish transplantation survival results fared rather favorably.

*Risk factors that predispose to kidney graft malfunction and adverse health outcomes*

Clinical observations evince that three years to five years following kidney transplantation a large proportion of the recipients can develop a rapidly progressing coronary artery disease. Arteriosclerosis can also develop in the transplanted graft. Donor's age can also affect the development of the disease. Thus, as explicated by Häyry,[16] "An old organ should not be given to a young recipient; this is because it's expected functioning time is shorter than that of a graft received from a younger donor." (Translation from Finnish.) Older recipients are preferably transplanted with older donors' organs.[16] Whether this principle of transplantation matching from donors to recipients of similar age groups was adhered to in practice is worth checking.

In accord with this point, a classification analysis of large body of data consisting of 1,215 patients from the HUCH Transplantation Unit estimated that the probability of delayed renal allograft function was over 90 percent in a specific class of patients.[4] This subgroup was represented by a particular type of recipient whose graft's cold ischemia time was over 25 hours, who had hemodialysis more than 17 months, and when the donor was 46 years or older, whereas the risk was only 50% for a patient with similar characteristics except that the donor's age was less than 46 years. So donor's age does matter. Evidently, the recipient-donor age-matching was not carried out as the correlation coefficient between the ages of donor-recipient pairs was zero (sic). This circumstance was most probably caused by the lack of age-matching donors. The same finding of zero correlation applied to the LTx dataset (n = 388).[5]

Among suspected risk factors that predispose to the CR of kidney graft, graft function failure and its subsequent loss are the occurrence of early AR and its multiple recurrences. A study found that patients with severe renal AR had the worst prognosis for graft survival. In the absence of protocol biopsies it was not possible to judge if the kidneys were really lost to CR.[19] Graft biopsy is invasive and it cannot predict AR. For the early detection and prevention of rejection in the kidney and liver graft, a new non-invasive immunologic monitoring method has been developed, viz. ultrasound shear wave elastography assessment of fibrosis severity.

A study found that treatment of acute vascular episodes (poor prognosis) with anti-lymphocyte globulin significantly improved graft survival rate.[20] However, a prospective study conducted at the HUCH could not confirm this observation.[3] The reason for this unexpected adverse outcome may have been that, because during the initial triple immunosuppression therapy that was administered to patients undergoing their first kidney transplantation, there were very few ARs and the reactions that did occur were uniformly mild (no grafts were lost to AR).

*Immunomodulatory properties of the liver versus kidney graft regarding chronic rejection*

Several studies have shown that the CR of a liver allograft is reversible to some extent (see TPIS,[21] and references therein). This usually occurs before the duct loss, perivenular fibrosis, or obliterative arteriopathy have become severe. A review concurred: Treatments with tacrolimus and mycophenolate mofetil have shown to reverse CR, particularly when diagnosed in early histological stages.[22] Counteracting to the advances achieved in treating liver CR, the morbidity and mortality caused by the side effects of immunosuppressive therapy have been increasing. A result is that the cumulative cancer incidence by 20 years after LTx reached 16-42%.[8]

The liver is generally believed to be less susceptible than kidney for immunologic risk factors, and hence less prone to rejection (e.g. due to inflammation). Several mechanisms have been proposed to account for the liver's better immunomodulatory properties (tolerogenicity) compared to a kidney graft,[23] among which donor microchimerism, or the persistence of donor cells and nucleic acid in the blood and tissues of the recipient, have been postulated to promote long-term graft survival. Another hypothesis put forward is that bleeding and blood transfusion may both incite immunosuppression via immunoregulatory T cells.[24,25]

Interestingly, the additional survival analyses of the earlier data[3,4] showed that the experience of transplant patients was discrepant between the kidney and liver allografts. In the case of a kidney allograft, the 5-year survival probability was approximately 85% with a preceding episode of AR, while without it the proportion was higher, 91%. For liver grafts the outcome relation was reverse: the 5-year survival probability with previous AR was 78%, whereas without AR it was lower, 74%. The latter observation runs counter to the predominant hypothesis, according to which survival after LTx will be shortened because of subsequent ARs, and calls for an explanation.

Some acute episodes of liver AR resolve spontaneously, others can be overcome by administering an increased dose of calcineurin inhibitor, and only a minority leads to graft loss.[26] That immune activation in an adjuvant treatment of hepatic AR might be beneficial in inducing a degree of tolerance and improve graft survival may sound counterintuitive.[27] But there exists some evidence that a reversible AR can entail an improved long-term outcome for the graft.[28] The time to the occurrence of AR might also affect the end result. In a large retrospective study, comparing patients with and without an episode of rejection, early AR (within 30 days after LTx) was associated with better liver graft survival, and late AR (>90 days post-LTx) was associated with reduced graft survival.[29]

AR and CR have entirely different forms as immune responses. Episodes of AR are typified by the strong activation of immunocompetent anti-allograft T cells. In comparison, CR results as a response to continuing, minor injuries to the allograft vascular endothelium. The end result is that the blood vessels within the endothelium become inflamed. The best way to control CR may be to regulate the graft's local production of cytokines, growth factors, and eicosanoids.[30]

A study found that the histological severity of AR was an important prognostic factor for CR: the use of anti-lymphocyte preparations was higher, and the time to ReTx or death was shorter, for LTx patients with a severe AR.[31] CR usually leads to a irreversible hepatic graft failure, although some patients may recover from an early clinically manifesting rejection.[32] A review summarized that chronic renal rejection has likewise been considered irreversible; however, the pathophysiology is still incompletely known.[33]

In case of the older Finnish liver (1982-2002) and kidney (1986-1995) transplantation data sets the expected half-lives were projected to be as long as 15 to 18 years. There may have been several underlying causes for this improvement. Greater amount of blood transfusions were associated with the decreased incidence of AR and the early occurrence of AR among the patients of the study. Blood transfusions have been suggested to have immunomodulatory effects and to produce tolerance and allograft survival in KTx patients.[34] Development of microchimerism and anti-idiotypic antibodies were suggested to explain these immuno-modulatory effects of blood transfusions. But evidence supporting transplantation tolerance in LTx patients is less well established.

In contrast to other solid organ transplantations, liver grafts possess better immune response properties. Liver grafts contain a unique subset of 'natural killer' cells that are transferred into the recipient after LTx.[35] The cited study showed that following LTx, but not after KTx, significant numbers of donor organ-specific T cells were detected in the recipient circulation. These cells may play a vital role in regulating the immunological response of the recipient against the graft and therefore promote liver tolerogenicity. A number of other investigations have contributed to the question of recovery from hepatic CR.[36] References to these studies are available, and additional ones can be searched, e.g., through the Transplant Pathology Internet Services.[21]

## CLOSING REMARKS

Chronic rejection has been considered irreversible and its pathophysiology is not fully known. The observations presented here, supported by previous study results, induce the hypotheses: A successfully treated acute rejection in the liver allograft may prolong its long-term survival. Better recognition and treatment of the early signs of chronic rejection in liver allograft may decelerate its later progression and in some favorable cases may turn the course to reverse. With the advent of modern treatments for chronic kidney allograft rejection, biopsy-confirmed histological changes and decline in the renal transplant function are also expected to reduce.

It should be borne in mind, though, that since the time when the referenced HUCH studies were made (over 20 years ago on renal transplantation[3,4] and over 10 years ago on hepatic transplantation[5-7]) the research of acute and chronic rejection has moved forward with long leaps. Also, the terminology has changed regarding the concept of 'chronic', especially for renal allografts. The current long-term results of transplantation from investigations conducted at the HUCH are distinctly better than those once produced; the old-time data are no longer representative of today's results. (Professor Helena Isoniemi, HUCH, personal communication, March 22, 2017.)

## ACKNOWLEDGMENT

For reading the draft paper and suggesting valuable comments which led to a much improved composition and fluency of the article I am very indebted to Dr. Tuula Nurminen.

## DISCLAIMER

The article presents the author's personal opinions and does not necessarily mirror those of the co-authors of the publications on transplantation given in the references, nos. 3 & 5-7.

APPENDIX 1. *Cox proportional hazards model for liver transplantation*

Output from fitting the *coxph* function in the Statistical SPlus system:[15, Sec. 13.3]

coxph(formula = Surv(Survival time, Censoring event) ~ strata(Acute rejection)‡ + Donor's age + Recipient-donor gender compatibility + Recipient's blood group + Blood transfusion volume + Graft size + Indication for transplantation + Year of transplantation, data = Liver.Tx)

| Covariate category | β coefficient | HR | se(β) | z-test | P-value* |
|---|---|---|---|---|---|
| | | | | | |
| [a]Donor age group 10-19 y | 0.965 | 2.63 | 0.419 | 2.30 | *0.021* |
| Donor age group 30-39 y | 0.857 | 2.36 | 0.356 | 2.36 | *0.018* |
| Donor age group 40-49 y | 0.719 | 2.06 | 0.363 | 1.98 | *0.048* |
| Donor age group 50-59 y | 1.039 | 2.83 | 0.386 | 2.70 | *0.007* |
| Donor age group 60+ y | 0.876 | 2.40 | 0.585 | 1.50 | 0.13 |
| [b]Gender compat. R=f, D=f | 0.095 | 1.10 | 0.269 | 0.35 | 0.72 |
| Gender compat. R=m, D=m | 0.471 | 1.60 | 0.285 | 1.65 | *0.098* |
| Gender compat. R=m, D=f | 0.583 | 1.79 | 0.296 | 1.97 | *0.049* |
| [c]Recipient blood group AB | 0.211 | 1.24 | 0.282 | 0.75 | 0.45 |
| Recipient blood group B | 0.665 | 1.94 | 0.299 | 2.22 | *0.026* |
| Recipient blood group O | 0.492 | 1.64 | 0.232 | 2.13 | *0.034* |
| [d]Blood transf. vol. 10-19 U | -0.054 | 0.95 | 0.243 | -0.22 | 0.82 |
| Blood transf. vol. ≥20 U | 0.404 | 1.50 | 0.253 | 1.60 | 0.11 |
| [e]Graft size reduced | 1.120 | 3.06 | 0.351 | 3.19 | *0.0014* |
| [f]Tx indication Budd Chiari n=16 | 1.174 | 3.24 | 0.869 | 1.35 | 0.18 |
| Tx indication immunologic n=146 | 0.413 | 1.51 | 0.703 | 0.50 | 0.56 |
| Tx indication liver tumor n=26 | 1.715 | 5.55 | 0.715 | 2.40 | *0.016* |
| Tx indication acute failure n=74 | 0.965 | 2.63 | 0.715 | 1.35 | 0.18 |
| Tx indication ReTx n = 36 | 1.295 | 3.65 | 0.738 | 1.76 | *0.08* |
| Tx indication other disorder n=74 | 1.081 | 2.95 | 0.713 | 1.52 | 0.13 |
| [g]Years 1987-1991 | -0.131 | 0.88 | 0.442 | -0.30 | 0.77 |
| Years 1992-1996 | -0.727 | 0.48 | 0.460 | -1.58 | 0.11 |
| Years 1977-2002 | -1.562 | 0.21 | 0.488 | -3.20 | *0.0014* |

Model goodness of fit likelihood ratio test = 68.6 on 23 degrees of freedom, n = 387, P < 0.001.

‡Acute rejection-covariate is non-significant but is included in the plotting of Figure 2.

*P-value is the probability so that Pr(P < α) = α significance level. Results P< 0.10 in *italics.*

Abbreviations:
β = model regression coefficient; HR = hazard ratio = exp(β coefficient); se = standard error; z-test = β/se(β); Tx = transplantation; ReTx = re-transplantation; R=recipient; D=donor; f=female; m=male

Reference category:
[a]Donor age group 20-29 y
[b]Gender compatibility R:f & D:m
[c]Recipient blood group A
[d]Blood transfusion volume < 10 Units
[e]Full-sized graft
[f]Chirrosis (alcohol, cryptogenic, post-hepatitis)
[g]Calendar period 1982-1986

APPENDIX 2. *Cox Proportional Hazards Model for Kidney Transplantation*

Output from fitting the *coxph* function in the Statistical SPlus system:[15, Sec. 13.3]

coxph(formula = Surv(Survival time, Censoring event) ~ strata(Acute rejection)[‡] + Diagnosis + AB mismatch + DR mismatch + Recipient's age + Recipient's gender + PRA last + PRA high + Tx order + Recipient CMV + Donor CMV + Cold ischemia time + Dialysis time + Dialysis time + Donor's age + Donor's gender + Donor's CMV + Perfusion liquid, data = Kidney.Tx)

| Covariate category | β coefficient | HR | se(β) | z-test | P-value[*] |
|---|---|---|---|---|---|
| | | | | | |
| [a]Dg: Diabetes | 0.075 | 1.08 | 0.100 | 0.74 | 0.46 |
| Dg: Glomerulonephritis | 0.019 | 1.02 | 0.093 | 0.21 | 0.84 |
| Dg: Pyelonephritis | 0.059 | 1.06 | 0.064 | 0.93 | 0.35 |
| Dg: Polycystic kidneys | -1.017 | 0.36 | 1.047 | -0.97 | 0.33 |
| Dg: Amyloidosis | 0.164 | 1.18 | 0.178 | 0.92 | 0.36 |
| [b]AB mismatches 1 | 0.434 | 1.54 | 0.172 | 2.52 | *0.012* |
| AB mismatches 2 | 0.147 | 1.16 | 0.067 | 2.18 | *0.03* |
| AB mismatches 3 | 0.062 | 1.06 | 0.119 | 0.51 | 0.61 |
| DR mismatches 1 | -0.163 | 0.85 | 0.085 | -1.92 | *0.054* |
| DR mismatches 2 | -0.073 | 0.93 | 0.091 | -0.81 | 0.42 |
| Recipient age, years | -0.026 | 0.97 | 0.007 | -3.70 | *<0.001* |
| [c]Recipient gender | -0.079 | 0.92 | 0.080 | -0.99 | 0.32 |
| [d]PRA last Group 1 | 0.008 | 1.01 | 0.174 | 0.05 | 0.96 |
| PRA last Group 2 | -0.053 | 0.95 | 0.134 | -0.40 | 0.69 |
| PRA high Group 1 | -0.033 | 0.97 | 0.148 | -0.22 | 0.83 |
| PRA high Group 2 | 0.214 | 1.24 | 0.124 | 1.73 | *0.08* |
| [e]Tx order 1st | -0.114 | 0.89 | 0.125 | -0.91 | 0.36 |
| Tx order 2nd | 0.377 | 1.46 | 0.123 | 3.07 | *0.002* |
| Tx order 3rd | -0.261 | 0.77 | 0.256 | -1.02 | 0.31 |
| [f]CMV R- & D+ | -0.055 | 0.95 | 0.102 | -0.54 | 0.59 |
| CMV R+ & D- | -0.220 | 0.80 | 0.346 | -0.64 | 0.52 |
| CMV R - & D- | -0.004 | 1.00 | 0.105 | -0.04 | 0.97 |
| CMV R & D missing | 0.325 | 1.38 | 0.341 | 0.95 | 0.34 |
| Cold ischemia time, hours | 0.016 | 1.02 | 0.012 | 1.40 | 0.16 |
| Dialysis time, months | -0.002 | 1.00 | 0.005 | -0.46 | 0.65 |
| Donor age, years | 0.001 | 1.00 | 0.006 | 0.22 | 0.82 |
| [c]Donor gender | 0.016 | 1.02 | 0.081 | 0.20 | 0.84 |
| [g]Perfusion liquid | -0.349 | 0.71 | 0.192 | -1.81 | *0.07* |

Model goodness of fit likelihood ratio test = 77.6 on 29 degrees of freedom, n =2015, P < 0.001.

[‡]Acute rejection-covariate is highly significant and is included in the plotting of Figure 3.

[*]P-value is the probability so that Pr(P < α) = α significance level. Results P< 0.10 in *italics.*

Abbreviations:
β = model regression coefficient; HR = hazard ratio = exp(β); se = standard error
z-test = β/se(β); Tx = transplantation; ReTx = re-transplantation ; R=recipient; D=donor

Reference category:
[a]Chirrosis (alcohol, cryptogenic, post-hepatitis)
[b]AB-, DR-mismatches = donor-recipient pair not matching for leukocyte antigens; Ref.= none
[c]Female
[d]PRA = panel-reactive antibodies; PRA last = last value measured pre-RTx; PRA high = highest value pre-RTx; Reference 0 % = no antibodies; Group 1: > 0% and <50%;Group 2: ≥ 50%
[e]No ReTx;
[f]Cytomegalovirus-infection episode. Referent: R+ & D+
[g]Euro-Collins solution vs. Unversity of Washington liquid

APPENDIX 3. *Immunosuppressive medication in transplantation therapy*

The approval of tacrolimus (Prograf®) and mycophenolate mofetil (MMF, Cellcept®) in the mid-1990s for use in clinical liver and renal transplantation yielded new therapeutic approaches for rejection. The superiority of tacrolimus over conventional calcineurin inhibitors (CNIs), e.g. cyclosporine (Gengraf®), in preventing rejection has been demonstrated, e.g., in three large, randomized controlled trials[37-39] and in one animal experiment of the effect of platelet-derived fibrogenic growth factor expression for later outcome of the kidney graft.[40] Tacrolimus 'rescue' therapy has been found successful in cases of acute and chronic rejection in LTx.[41] MMF also prevents acute liver rejection. Combination therapy with tacrolimus and MMF (vs. tacrolimus only) may significantly reduce the incidence of acute liver allograft rejection, allow a significant reduction in a tacrolimus dosage protocol, and decrease the incidence of nephrotoxicity.[42] On the other hand, a recent review evaluated that converting patients to non-CNI-based regimen may improve renal function.[43] Yet, long-term analysis is needed to assess, e.g., any increased risk of opportunistic infections caused by pathogens in a weakened immune system.

Immunosuppressive medication involves numerous serious long-term complications. Most importantly, tacrolimus-based immunosuppression treatment can cause kidney dysfunction, hypertension, diabetes, and neurological disorders, and while MMF can cause infections, anemia, various gastrointestinal pains, and influenza-type symptoms as complications. With advancing life expectancy the burden of some of these diseases is added for being age-related. Moreover, the drug weakens patient's resistance and thus raises significantly the risk of cancer. Post-transplant malignancies have become a serious long-term complication after transplantation, of which the most common cancer types are non-melanoma skin cancer and non-Hodgkin lymphoma.[44] Cancer incidence was found to be less increased among patients with a history of AR vs. those without AR; this association was strongest with lymphomas. There exists also evidence suggesting that immunosuppression can increase the risk of the occurrence (or recurrence) of liver cancer via the contribution of hepatic B or C virus infection.[45]

With advances of immunosuppressive medication the side effects may not always present themselves. These may also be limited to minor or mild conditions, such as postural hand tremor (without hepatic encephalopathy). For example, the survival rates following orthotopic liver transplantation (OLT) have improved markedly with CNIs serving as the cornerstone of post orthotopic liver transplantation maintenance immunosuppression therapy.[e.g.38] With these new medications, acting both as immunosuppressive and vasculoprotective compounds, the histological changes and decline in renal function present in CR may be reduced.[33] A recent HUCH study concluded,[46] "Among OLT patients with preserved renal function at 1 year posttransplant, our findings challenge the clinical impact of chronic progressive CNI nephrotoxicity and highlight the importance of a tight control of blood pressures, glucose and lipid levels, and other modifiable risk factors in order to preserve long-term renal function."

In the HUCH studies,[3,5-7] during the earlier era immunosuppression treatment was based on cyclosporine, methyl-prednisolone, and azathioporine. Certain patients were converted to MMF if immunologically unstable or if calcineurin inhibitor-based renal insufficiency was suspected. In the later period, some patients received tacrolimusine-based treatment in trials of the efficiency and safety of immunosuppression.

APPENDIX 4. *Applied statistical methods for modeling, analysis, and inference of survival*

Before embarking on multiple regression modeling, preliminary testing of the examined risk factors of graft survival time and time to AR was first performed by entering each risk factor as a term in a univariate model. A recommended model selection strategy is to set the significance level around 10%. To study the joint effect of multiple factors on graft survival, we used the *Cox regression*[47] reformulated as a counting process with a robust variance for the time-dependent model. A patient's vital status indicator (0 = alive, 1 = dead or graft lost) was entered in the model because of 'censoring', i.e. patients are not observed through-out the whole follow-up period, and this circumstance must be accounted for in the survival analysis. Because the outcome event was a discretized time covariate (representing separate categories along a continuum), some patients shared the same day of the occurrence of the outcome ('tied' event times). For handling ties, the accurate Efron[48] approximation to the partial likelihood function was applied. The idea behind Efron's approach is to spread the contributions of right-censored observations out over all the possible times to their right.

In the *Cox proportional hazards regression model*,[†] the exponentials of the coefficients, exp($\beta$), are interpreted as *hazards.* Thus, the hazard ratio (HR) of graft survival at days after the transplantation for any two patients, with covariate values $x_1$ and $x_2$, was specified as $exp[\beta(x_1 - x_2)]$. However, in case the outcome actually is a favorable event (e.g. onset of graft function), it is preferable to interpret the complement measure, $exp[-\beta(x_1 - x_2)]$, as the HR of time to graft function at days after transplantation. In case of binary coding for the covariate ($x_1 = 1$ & $x_2 = 0$), HR = $exp(\beta)$.

The assumption of proportional hazards of the Cox regression model over time was checked by examination of the Schoenfeld residuals[15, p.371] separately for each of the potential predictor covariates. The multivariate analysis was performed separately for the 1st Tx and the 2nd Tx when analyzing patient survival. In the graft survival analysis, data on re-transplantations were also included (1st Tx: n = 352, 2nd Tx: n = 31, 3rd Tx: n = 5). The check indicated no severe non-proportionality, except for blood transfusion volume due to interaction with ReTX.

When the outcome was the occurrence of graft rejection, we applied a *generalized linear model*[49,‡] to these data. For dichotomous risk factors with a binary coding ('treatment contrasts'),[15, p.146] the multiple exponential regression has the interpretation that its beta, $\beta$, coefficients are expressed simply in terms of risk ratio (RR) parameters, exp($\beta$). Here risk refers to the probability of graft rejection. Therefore, RRs were estimated using the *quasi-likelihood estimation*[‡] with a log link function and an estimated scaling factor (dispersion parameter) of the variance.

The 95% lower and upper limits of a confidence interval (CI) for the hazard/risk ratio parameter were computed as $exp(\beta \pm 1.96\ s.e.(\beta))$, where $s.e.(\beta)$ is the standard error of the regression coefficient. A lower/upper limit of the CI that exceeds/falls below unity implies a raised/reduced survival probability. All computations were done using the S-Plus system.[15, Ch. 1]

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[†] *Hazard* is an instantaneous risk at a given point in time or during a short period of time, e.g., a daily risk. The concept is needed in the mathematical derivation of the estimates of the *proportional hazards regression model*. The *Cox regression model* is semi-parametric, because no parametric assumptions are made about the baseline hazard. However, the hazard is represented parametrically by the exponential function; the survivor function at time *t*, $S(t) = exp(-H(t))$, where $H(t)$ is the hazard function. When the hazards are parallel in the log-scale, this implies that their hazards are equal, up to a multiplicative constant. This corresponds to a *proportional hazards* situation.

[‡] For a *generalized linear model*, *quasi-likelihood estimation* allows one to estimate regression relations without fully knowing the error distribution of the response variable. The theoretical likelihood function need not be exactly specified, and fewer assumptions are made in the statistical estimation (e.g. regarding over-dispersed variance) and inference.

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