Renal Transplant Outcomes in Amyloidosis

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Abstract

Background

Outcomes after renal transplantation have traditionally been poor in AA and AL amyloidosis, with high mortality and frequent recurrent disease. We sought to compare outcomes to matched transplant recipients with autosomal dominant polycystic kidney disease (ADPKD) and diabetic nephropathy (DN), and identify factors predictive of outcomes.

Methods

We performed a retrospective cohort study of 51 systemic AL and 48 systemic AA amyloidosis patients undergoing renal transplantation. Matched groups were generated by propensity score matching. Patient and death-censored allograft survival were compared via Kaplan Meier survival analyses, and assessment of clinicopathological features predicting outcomes via Cox proportional hazard analyses.

Results

One, five, and ten-year death-censored unadjusted graft survival was 94%, 91%, and 78% for AA amyloidosis, and 98%, 93% and 93% for AL amyloidosis; median patient survival was 13.1 and 7.9 years respectively. Patient survival in AL and AA amyloidosis was comparable to DN, but poorer than ADPKD (HR 3.12 and 3.09 respectively; $p<0.001$). Death censored allograft survival was comparable between all groups. In AL amyloidosis, mortality was predicted by interventricular septal (IVSd) thickness > 12 mm (HR 26.58; $p=0.03$), whilst survival was predicted by haematologic response (very good partial or complete response; HR 0.07; $p=0.018$). In AA amyloidosis, recurrent amyloid was associated with elevated serum amyloid A concentration but not with outcomes.

Conclusions

Renal transplantation outcomes for selected patients with AA and AL amyloidosis are comparable to those with DN. In AL amyloidosis, IVSd thickness and achievement of deep haematologic response pre-transplant profoundly impact patient survival.

Keywords

AL amyloidosis, AA amyloidosis, amyloidosis, recurrent disease, renal transplantation

What is already known about the subject?

- Outcomes from systemic amyloidosis have improved dramatically over the last decade with improvements in therapy allowing better suppression of the underlying precursor protein concentration. There are increasing numbers of patients with end stage renal disease (ESRD) and a stable amyloid burden who may benefit from renal transplantation.
- Recent studies have shown that patient and allograft survival is improving, and highlighted the importance of haematological response in AL amyloidosis, and reduction in serum amyloid A in AA amyloidosis.

What does this study add?

- This study adds extensive multivariable analysis of patient and transplant related variables associated with outcomes and indicates for the first time, comparable allograft and patient survival between patients with amyloidosis and age matched patients with diabetic nephropathy.
- Among patients with AL amyloidosis, mostly treated with chemotherapy rather than autologous stem cell transplantation, we reaffirm the importance of haematological response as a predictor of survival, and interventricular wall thickness >12mm as a powerful independent predictor of patient mortality.
- We show that recurrent amyloid does not preclude excellent graft survival.

What impact may this study have on practice?

- This study provides evidence to support physicians in the selection of patients with systemic amyloidosis for renal transplantation, and enables improved counselling of patients who may have certain ‘higher risk’ features such as cardiac amyloidosis.

- We reaffirm the importance of cardiac imaging in identifying AL amyloidosis patients at increased risk of mortality.

Introduction

Amyloidosis is responsible for approximately 1% percent of end stage renal disease (ESRD).[1] It is characterised by misfolding, aggregation and deposition of proteins as insoluble fibrils in the interstitial space with resultant disruption of tissue structure and function and eventual organ failure.[2, 3] Amyloidosis is classified according to the fibril protein precursor, which is identified by immunohistochemistry or mass spectrometry in amyloidotic tissue samples.[4]

The commonest cause of amyloid nephropathy is systemic AL amyloidosis resulting from monoclonal production of amyloidogenic immunoglobulin light chains that are deposited as extracellular fibrils in the kidney.[5, 6] Renal involvement occurs in up to 80% of patients with systemic AL amyloidosis, typically causing proteinuria and renal dysfunction.[7, 8] Diagnostic proteinuria of >5g/24 hours and an estimated glomerular filtration rate (eGFR) of <50ml/min/1.73 m^2, predict progression to dialysis in 60-85% at 3 years.[9] Prompt chemotherapy directed at the underlying clonal disorder improves renal outcomes and patient survival.[10, 11] Although patient survival has improved in recent years as a result of effective anti–plasma cell therapies, up to one third of AL amyloidosis patients continue to die within one year of diagnosis, with cardiac involvement, defined according to international amyloidosis consensus criteria by interventricular septal (IVSd) thickness > 12 mm, being the main determinant of early mortality.[12-14]

AA amyloidosis, which arises from the overproduction of the acute phase reactant serum amyloid A (SAA) protein in chronic inflammatory states, is the second most common form of systemic amyloid nephropathy.[15] The incidence of AA amyloidosis is falling and patient and renal outcomes are improving, likely due to effectiveness of biological therapies.[16-18]

Kidney involvement is present at diagnosis of AA amyloidosis in 97% of patients, with renal function being associated with amount of amyloid deposition; cardiac AA amyloidosis is rare.[19, 20] Progression to dialysis is associated with failure to achieve remission of the underlying inflammatory disease, in particular failure to suppress SAA concentration.[19, 21]

More effective amyloid therapy with novel biologics in AA amyloidosis and chemotherapeutic agents in AL amyloidosis allow improved control of the underlying precursor protein in both AA and AL amylodoidosis. This has resulted in increasing numbers of patients with controlled underlying disease and ESRD who may benefit from transplantation. Patient survival on renal replacement therapy (RRT) in systemic amyloidosis has traditionally been poor, with one large study indicating a median survival from commencement of dialysis of only 2.1 years versus 4.5 in other causes of ESRD.[1, 8, 22] Historically, outcomes post renal transplantation have also been comparatively poor in systemic amyloidosis,[1, 23] although more recent studies suggest that transplant outcomes are improving.[24, 25]

The primary aim of this study is to determine the risk of graft loss and patient survival for patients with ESRD secondary to AA and AL amyloidosis, and to compare outcomes to a matched cohort of recipients where the primary renal disease does not recur post-transplantation (ADPKD) and those who are at a relatively higher risk of mortality despite transplantation (DN).[26-28] The secondary aim is to identify recipient and donor factors predictive of patient and allograft survival, to support physicians in identifying patients with systemic amyloidosis who may benefit from transplantation.

Methods and Materials

Study design

Data for this retrospective observational study was obtained from the UK National Amyloidosis Centre (NAC), the only specialist amyloidosis referral centre in the UK. Donor and recipient transplant details were derived from the UK Transplant Registry of the Organ Donation and Transplant Directorate of NHS Blood and Transplant (NHSBT), which records mandatory data for patients on the waiting list, and details of episodes of transplantation performed by all 23 UK adult kidney transplant centres. Histology reports were obtained from local hospitals.

Study Participants

All patients with ESRD due to AL or AA amyloidosis followed up at the NAC who underwent their first renal transplant between 1st January1989 and 30th April 2018 were included. Date of amyloidosis diagnosis was defined as date of biopsy confirming amyloid or date of first review at NAC if unavailable. Diagnosis was confirmed by histology with immunohistochemistry and/or mass spectrometry in 97 patients; the remaining two patients were diagnosed with AA amyloidosis on the basis of unequivocal renal amyloid on SAP scintigraphy in association with a chronically elevated SAA concentration in the absence of a plasma cell dyscrasia or mutation in any of the known hereditary amyloidosis genes. Patients attended the NAC 6 to 24 monthly with biochemical evaluation of renal, cardiac and liver function performed at each visit; echocardiography and SAP scintigraphy were performed when indicated. Patients were followed up until the 12th May 2020. Some of the patients reported in this study were included in a previous publication.[24] All patients were managed in accordance with the declaration of Helsinki and provided informed consent for publication of their anonymised data. The study was approved by the Royal Free Ethics committee (REC reference: 06/Q0501/42).

Assessment and monitoring of circulating fibril precursor protein concentration

In patients with systemic AL amyloidosis, haematological response was assessed at each clinic attendance and one to four monthly in the interim. Haematological response was categorized according to International Amyloidosis Consensus Criteria as complete response (CR), very good partial response (VGPR), partial response (PR) and no response (NR).[10] In patients with AA amyloidosis, serum amyloid A (SAA) concentration was measured at each clinic attendance and one to four monthly in the interim.

Assessment of total body amyloid load by SAP scintigraphy

Visceral amyloid load and organ involvement was evaluated by whole body anterior and posterior scintigraphy after administration of ^{123}I-labelled serum amyloid P component (SAP) using an Elscint Superhelix gamma camera, as previously described.[29] SAP scintigraphy was performed at diagnosis, and at one to three yearly intervals determined by clinical need. Images were interpreted by a panel of physicians with experience of interpreting over 20,000 scans.[30, 31]

Assessment of renal allograft and cardiac function

Renal allograft function was evaluated at each visit by CKD Epidemiology Collaboration (CKD-EPI) eGFR calculation, serum creatinine and 24-hour urinary protein measurement.[32] Recurrent amyloid was defined by allograft histology confirming amyloid, or abnormal uptake of ^{123}I-labelled SAP in the allograft.

Detailed echocardiographic assessment by technicians experienced in cardiac amyloidosis was performed at diagnosis and throughout follow up as indicated. New York Heart Association (NYHA) class and serum NT-proB-type natriuretic peptide (NT-proBNP) concentration were assessed at each attendance.

Transplant details

Human leukocyte antigen (HLA) mismatch level was defined according to UK allocation policy for donor.[33] Calculated reaction frequency (cRF) recipient sensitization was defined as HLA antibody reaction frequency, which is calculated by comparison of unacceptable HLA specificities with HLA types of donors of identical ABO blood group in a pool of 10,000 donors on the UK transplant database. Delayed graft function (DGF) defined as need for dialysis within 7 days post-transplant.

Outcomes

Primary outcome measures were all-cause patient death after transplantation, and death censored allograft survival. Patient survival was defined as time from transplantation until death. Death censored allograft survival was taken as time from transplantation to the earliest of graft nephrectomy, re-transplantation or return to dialysis with censoring for death with a functioning graft or at last follow-up evaluation.

Statistical Analysis

Control groups were generated from National Health Service Blood Transplant (NHSBT) registry data for all UK patients with biopsy proven diabetic nephropathy (DN), or autosomal dominant polycystic kidney disease (ADPKD) who received their first renal allograft between 1st January1995 and 30th April 2018. Propensity score matching by logistic regression, using a nearest neighbour approach was used to produce 4:1 DN and ADPKD controls to both AL and AA amyloidosis patient groups.[34] Separate matched groups were created for the AL and AA patient groups due to significant differences in patient characteristics. Patients were matched on factors known to affect transplant outcomes as independent variables. Based on data availability, recipient age, donor status (live vs deceased), immunological mismatch level, transplant year, and pre-emptive transplantation were used to match 84 amyloidosis patients; recipient age, donor status and transplantation year were used for 14 amyloidosis patients, whilst one patient was not matched. Matching was assessed using independent sample testing and Spearman's analysis, to compare baseline characteristics. Recipient age was higher in DN and CRF higher in ADPKD compared with the AA amyloidosis group, and recipient age was lower in ADPKD than AL amyloidosis; a higher proportion of DN patients were male in both groups. Otherwise groups were well matched for transplant year, donor status, donor age, HLA mismatch level, pre-emptive transplantation, cold ischaemic time and delayed graft function (Tables S1 and S2).

Survival functions were estimated according to the Kaplan-Meier (KM) method, with groups compared using the log-rank test. Cox proportion hazard regression analysis was used to estimate hazard ratios for death and graft loss for patient and donor variables. Unrelated variables significant at the 10% level were included in multivariable analyses; where variables were known to be strongly correlated, the most predictive variable on univariate analysis was used in the multivariable analysis. Results are expressed as hazard ratios with calculated 95% confidence interval (CI). A p value of < 0.05 was considered significant.

Patient characteristics are presented as median (interquartile range) or number (percentage) unless otherwise stated. All data analysis was performed in SPSS (IBM Corp, 2017), with graphs generated in GraphPad Prism Version 5.03.

Results

Baseline characteristics of participants

Ninety-nine patients, 48 with AA and 51 with AL amyloidosis, underwent renal transplantation (Table 1). This cohort comprised 7% and 17% of all ESRD patients due to AL and AA amyloidosis attending the NAC during the study period respectively.

Treatment of underlying condition

In the AL amyloidosis group first line treatment was with a thalidomide regimen in 20 (39%) patients, a bortezomib regimen in 5 (10%), a vincristine regimen in 14 (27%), and with melphalan-dexamethasone followed by ASCT in 5 (10%). At the time of renal transplantation no patients were on maintenance chemotherapy, 27 (53%) had received two or more prior lines of therapy, with 12 (24%) having undergone autologous stem cell transplant (ASCT). In the AA amyloidosis group, 12 (25%) received chlorambucil prior to transplantation, 5 (10%) anakinra, 2 (4%) toculizumab, 3 (6%) infliximab, 5 (10%) etanercept, 5 (10%) another biologic, and 6 (13%) colchicine, whilst 10 (21%) received supportive therapy only.

Patient survival

Median follow up post-transplant among 99 transplant recipients with a primary diagnosis of AA or AL amyloidosis was 6.1 years and at the time of censor, 39 (39%) patients had died (Table 2). One-, 5-, and 10-year unadjusted patient survival from renal transplantation respectively was 96%, 84% and 66% in AA amyloidosis and 96%, 79% and 39% in AL amyloidosis.

In the AL amyloidosis group, two patients died within three months of transplantation, one due to post-operative complications and the other from cardiac failure. Pre-transplantation interventricular septum diameter at end diastole (IVSd), left ventricular posterior wall (LVPWd) thickness, NYHA class, and the presence of a serum paraprotein, predicted mortality on univariate analysis, whilst being in a haematologic CR predicted survival (Figure 1A, 1C, 1D); haematologic VGPR or CR vs PR or NR did not predict survival in univariate analysis (Figure 1B). Pre-transplant IVSd > 12 mm and being in a haematologic CR were independent predictors of mortality and survival respectively (Table 3). When haematologic CR was replaced in the multivariable analysis by haemtologic VGPR or CR, this also predicted survival (HR 0.07 [0.01-0.64]; p=0.018). Of note, serum paraprotein, LVPWd and NYHA, all of which were significant in univariable analyses, were not included in the multivariable analysis due to their strong association with those that were included.

In the AL amyloidosis cohort, patient survival following transplants performed after 2007, when bortezemib was approved for the treatment of multiple myeloma in the UK, was not longer than transplants performed before 2007 (HR 1.63 [0.67-3.95]; p=0.284); the same was found in DN (HR 1.38 [0.73-2.61]; p=0.323) and ADPKD (HR 1.94 [0.79-4.81];p=0.151).

In the AA amyloidosis group there was no significant association between mortality and cause of chronic inflammation, amyloid load by SAP scintigraphy pre transplant, recurrence of amyloid, median SAA in year pre-transplant (10 [5-27] mg/L) or median SAA post-transplant (9 [6-19] mg/L; Table 4).

Renal allograft survival

Overall, there were 31 deaths with a functioning renal allograft and 12 (3 AL, 9 AA) further renal allograft losses among patients with amyloidosis (Table 2). Seven patients (13.7%) had recurrence of AL amyloid in the renal allograft occurring a median of 4.5 years post-transplantation, although recurrent amyloid was the primary cause of renal allograft failure in only one such patient. Pre-transplantation haematologic responses in those seven patients were as follows; three had CR, two VGPR, and two PR. The three patients who were in haematologic CR pre-transplantation all had a haematologic relapse post-transplant; 2 received further chemotherapy; the other patient did not receive chemotherapy in view of a very low level haematologic relapse, a stable eGFR with proteinuria <0.6g, and a poor performance status. Following transplant, a total of 11 patients required further chemotherapy for haematologic relapse, and one patient underwent autologous stem cell transplantation; 4 (33%) of these had amyloid in their allograft. Three of these patients commenced maintenance chemotherapy following transplantation, with regimens including daratumumab, lenalidomide and ixazomib.

In the AA amyloidosis cohort, nine patients (19%) had recurrent amyloid in their allograft occurring at a median of 4.0 years post-transplant. Recurrent amyloid was the primary cause of graft failure in 4 (44%) of these patients, occurring a median of 4.3 years after recurrence. Median (IQR) SAA levels post-transplant were 26 (11-36) mg/L and 9 (6-15) mg/L in those with and without recurrence of amyloid in the renal allograft respectively (Mann Whitney U test, p=0.007); the median SAA from transplant to graft loss in the 4 patients who lost their allograft with recurrence was 21 (9-39) mg/L, whilst their median SAA in the year prior to transplantation was 38 (11-152) mg/L. Of note, recurrence in the renal allograft occurred in 4

(57%) hereditary periodic fever syndrome patients and caused graft loss in 3/4 such cases, a median of 8 years post-transplantation. They also had the highest median SAA post-transplant 20mg/L, compared to 9.5mg/L in inflammatory arthritis patients, 6.5mg/L recurrent infection, 10mg/L cause unknown and 9mg/L in inflammatory bowel disease. Following transplantation 6 (13%) patients received treatment with anakinra, 4 (8%) with toculizumab, 1 (2%) infliximab, 4 (8%) etanercept, 1 (2%) adalimumab, 3 (6%) colchicine, and 1 (2%) chlorambucil, whereas 26 (54%) received no anti-inflammatory therapy other than their standard transplant immunosuppression.

Comparison to matched ADPKD and DN groups

Patient survival following renal transplantation was poorer in AL and AA amyloidosis than in matched ADPKD patients ($p<0.001$), but comparable with matched DN patients (Table 5, Figure 2A and 2C). Death censored allograft survival was comparable between all groups ($p>0.05$, Table 5, Figure 2B and 2D).

Discussion

This study demonstrates that selected patients with ESRD from systemic AA and AL amyloidosis achieve post transplantation patient survival comparable to DN, but inferior to ADPKD, and death censored allograft survival comparable to DN and ADPKD. We also highlight that recurrence of amyloid in the renal allograft does not necessarily preclude lengthy graft survival. Outcomes with renal transplantation in systemic amyloidosis have undoubtedly improved in recent years,[1, 24, 25] likely due to increasingly effective suppression of the amyloid fibril precursor protein with chemotherapy in AL amyloidosis[35] and biologic therapies in AA amyloidosis.[17]

Among those with AL amyloidosis who underwent renal transplantation, the strongest pre-transplantation predictor of mortality was IVSd, and the strongest predictor of survival was a pre-transplant haematologic VGPR or CR. These findings are consistent with multiple studies in AL amyloidosis indicating the prognostic implications of cardiac involvement and haematological response to chemotherapy respectively.[36-38] Cardiac amyloidosis is defined according to international amyloidosis consensus criteria by IVSd > 12 mm and it is interesting that despite its lack of specificity in the context of CKD, when IVSd > 12 mm in the absence of cardiac amyloidosis is not infrequent,[14, 39, 40] it predicted patient survival. In this era of macrocyclic gadolinium-based contrast agents, which appear to be associated with a low risk of nephrogenic systemic fibrosis (NSF),[41] the authors would favour consideration of contrast enhanced cardiac magnetic resonance (CMR) imaging to exclude cardiac AL amyloidosis in patients with IVSd on echocardiography > 12 mm who are being considered for renal transplantation.[42, 43] Achieving a haematologic VGPR/CR pre-transplantation was associated with prolonged patient survival post transplantation in the AL amyloidosis cohort, corroborating the recently published findings of the Boston Amyloidosis Center, in which patients who had achieved a haematologic CR or VGPR fared better with renal transplantation than those in PR/NR.[25] It is interesting to postulate that with a big enough cohort, there might be further separation of renal transplant outcomes according to each category of depth of haematologic response pre-transplant (CR, VGPR, PR and NR), analogous to outcomes in AL amyloidosis generally;[10] a multicentre collaborative study is currently underway in order to specifically investigate this hypothesis.

In our cohort of patients with AL amyloidosis, amyloid recurrence in the renal allograft was a contributor to only one graft loss, despite eleven patients receiving post-transplant chemotherapy for persistence or relapse of the underlying haematologic disease. It is interesting that amyloid recurrence did not predict graft loss in this patient cohort, likely reflecting the gradual nature of amyloid accumulation among patients who remain in a degree of haematologic response albeit not in haematologic CR. Recurrence of amyloid in the renal allograft was more common in AA amyloidosis than in AL amyloidosis and associated with persistent elevation of SAA concentration, most evident among patients with hereditary periodic fever syndromes underlying their AA amyloidosis. Once again however, recurrence of amyloid in the renal allograft did not predict graft loss in our cohort which may reflect a 'threshold effect' in which reasonable, albeit incomplete, suppression of inflammation as evidenced by moderately elevated SAA concentration (median (IQR) 26 mg/L (11-36)) leads to very gradual AA amyloid accumulation, without a rapid decline in allograft function. A larger study population with longer follow up may highlight more subtle implications of amyloid allograft recurrence. Overall, the time course and impact on graft survival of disease recurrence in amyloidosis appear to differ substantially from those reported in other causes of ESRD, although this warrants further study.[26, 44]

We did not find a significant difference in post-transplantation survival between patients with AL amyloidosis transplanted before and after 2007, when bortezemib was approved in the UK. This is in contrast to Angel-Korman et al[25] who found significantly better survival in those transplanted from 2007 onwards. This may reflect smaller patient numbers in our pre-2007 cohort (14 versus 24), or a broadening of patient selection criteria with a higher median age, IVSd, NT-proBNP, and higher proportion with echocardiographic evidence of cardiac amyloidosis among patients transplanted from 2007 onwards.

It is also essential to acknowledge that the amyloidosis cohort represents a carefully selected group of patients who were felt by a multi-disciplinary team to be likely to benefit from renal transplantation, comprising only 7% and 17% of dialysis-dependent AL and AA amyloidosis patients attending our national centre respectively. This highlights the fact that the majority of patients with systemic AA and AL amyloidosis continue to be considered unsuitable for kidney transplantation, usually as a result of severe amyloidotic organ dysfunction, functional disability or, often in the case of AL amyloidosis, age. Our data does indicate the increased likelihood of renal transplantation in AA amyloidosis compared to AL amyloidosis, likely due to both younger age and infrequent presence of cardiac AA amyloidosis.[19]

Limitations of our study include the inherent difficulties associated with retrospective cohort matching. There were significant differences in gender and recipient age, whilst recipient ethnicity and dialysis vintage data were unavailable; all of which are known to affect transplant outcomes. The transplantation date time frame used to select control and amyloidosis patients were different due to limitations in NHSBT data availability and a desire to maximise amyloidosis patient numbers for powered analyses; despite this comparison analysis showed no significant differences in transplantation year between patient groups. A median follow up of 6.1 years in the amyloidosis cohorts also limits our ability to comment on longer term renal transplant outcomes.

In summary, we show here that selected individuals requiring RRT due to AA and AL amyloidosis achieve comparable outcomes with renal transplantation to DN. We confirm previous evidence that IVSd thickness and achieving a deep haematologic response pre-transplant predict mortality and survival respectively in AL amyloidosis. We also reaffirm that suppression of SAA concentration in AA amyloidosis reduces the risk of amyloid recurrence in the renal allograft, although our data indicates that gradual amyloid accumulation post-transplant in association with incomplete suppression of the respective fibril precursor protein does not preclude excellent graft and patient survival.

Article Information

Authors' contributions

SL, RM, and JDG were responsible for conceiving the study, interpreting the results and drafting the manuscript. OCC, HJL, TR, ADW, and PNH were responsible for data collection and interpretation.

Conflict of interests

The authors report no conflict of interests. The results presented in this paper have not been published in whole or part previously.

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Data sharing

All of the individual participant data collected during this study after deidentification will be made available for review on request.

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Table 1. Patient characteristics at diagnosis of AL and AA amyloidosis

		AL Amyloidosis (n=51)	AA amyloidosis (n=48)
Age, years (Median, IQR)		55 (50-59)	38 (27-46)
Male gender, n (%)		28 (55%)	27 (56%)
Caucasian Ancestry, n (%)		48 (94%)	40 (83%)
Year of amyloid diagnosis		1987 - 2015	1988 - 2013
eGFR at diagnosis, n (%)	<15 ml/min	16 (31%)	18 (38%)
	15-30 ml/min	12 (24%)	7 (15%)
	30-60 ml/min	7 (14%)	7 (15%)
	>60 ml/min	16 (31%)	16 (33%)
24hr Urine Protein (g) (Median, IQR)		9.2 (5.8-11.9)	5.35 (2.5-7.1)
Time to eGFR<15mls/min (yr) (Median, IQR)		1.0 (0 -2.9)	1.1 (0-6.4)
Organ amyloid*, n (%)	Liver	26 (51%)	13 (29%)
	Spleen	44 (86%)	45 (100%)
	Heart	11 (22%)	0 (0%)
Amyloid load at Diagnosis, n (%)	Small	20 (39%)	11 (23%)
	Moderate	16 (31%)	27 (56%)
	Large	15 (29%)	10 (21%)
NT-proBNP (ng/L) (Median, IQR)		1158 (389-6596)	
IVSd (mm) (Median, IQR)		11 (10-12)	
LVEF (%) (Median, IQR)		60 (57-63)	
NYHA Class, n (%)	1	22 (54%)	
	2	19 (46%)	
Underlying disease, n (%)			
Inflammatory arthritis			20 (42)
Hereditary periodic fever syndrome			7 (15)
Chronic Infection			7 (15)
Inflammatory bowel disease			5 (10)
Castleman's disease			1 (2)
Unknown			8 (17)

LVEF – left ventricular ejection fraction. *Organ amyloid determined by SAP scintigraphy for liver and spleen, and echocardiography for heart.

Table 2. Transplant details and outcomes in AL and AA amyloidosis

	AL amyloidosis (n=51)	AA amyloidosis (n=48)
Age at Transplantation (yr)	61 (57-65)	44 (34-53)
Follow-up post-transplant (yr) (Median, IQR)	5.9 (3.6-8.0)	6.7 (4.7-12.5)
Immunosuppression regimen*		
CNI / MMF / Steroids	18 (35%)	25 (52%)
CNI / MMF	10 (20%)	6 (13%)
CNI / Steroids	5 (10%)	7 (15%)
CNI / Azathiprine / Steroids	4 (8%)	1 (2%)
MMF / Steroids	0 (0%)	1 (2%)
CNI only	3 (6%)	1 (2%)
Other	4 (8%)	0 (0%)
Unknown	7 (14%)	7 (15%)
Recurrent amyloid (n)	7 (14%)	9 (20%)
Time to Recurrence (yr) (Median, IQR)	4.5 (3.6-6.3)	4.0 (2.3-9.1)
Death (n)	20 (39%)	19 (40%)
Cause of graft loss (n)		
Death with functioning graft	18	13
Recurrent amyloid	1	4
Primary non function	1	
Post-operative complications	1	1
Renal artery thrombosis		1
Acute rejection		1
Chronic allograft nephropathy		1
Multifactorial		1

*Immunosuppression on first visit to the NAC after renal transplantation. If visit occurred over two years following transplantation immunosuppression was recorded as unknown.

Table 3. Cox regression analyses of predictors of patient survival and death censored graft survival following renal transplantation in AL amyloidosis

	Patient Survival				**Graft Survival**	
	Univariable		Multivariable			
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
IVSd >12mm*	6.81 (2.00-23.16)	**0.002**	26.58 (1.46-485)	**0.03**	0.035 (n/a)	0.6
IVSd*	1.41 (1.10-1.81)	**0.006**			0.92 (0.52-1.65)	0.8
LVPW*	1.38 (1.07-1.76)	**0.01**			1.15 (0.65-2.05)	0.6
NYHA*	3.36 (1.02-11.08)	**0.05**			0.70 (0.06-7.79)	0.8
Amyloid echocardiogram	2.45 (0.85-7.03)	0.1			0.035 (n/a)	0.6
LVEF*	0.97 (0.89-1.04)	0.4			0.97 (0.81-1.16)	0.7
NT-proBNP*	1.00 (1.00-1.00)	0.9			1.00 (1.00-1.00)	0.7
CR*	0.33 (0.12-0.91)	**0.03**	0.11 (0.02-0.70)	**0.02**	0.015 (0.00-158)	0.4
CR or VGPR*	0.51 (0.21-1.27)	0.2			0.89 (0.08-9.86)	0.9
>1 treatment line*	0.82 (0.34-2.00)	0.7			57.1 (0.01-6.40x10^{5})	0.4
Urinary BJP*	1.24 (0.35-4.40)	0.7			0.037 (0.00-1.47x10^{8})	0.8
Serum PP*	2.87 (1.04-7.92)	**0.04**			0.028 (0.00-9069)	0.6
ASCT	0.55 (0.18-1.65)	0.3			1.38 (0.13-15.3)	0.8
Amyloid recurrence	0.63 (0.18-2.19)	0.5			2.37 (0.21-26.5)	0.5
Haematological relapse**	1.02 (0.39-2.68)	1.0			0.028 (0.00-976)	0.5
Age at diagnosis	1.05 (0.98-1.13)	0.2			1.05 (0.89-1.25)	0.6
Recipient age	1.04 (0.97-1.11)	0.3	0.92 (0.82-1.04)	0.2	1.08 (0.89-1.31)	0.4
Live donor	0.69 (0.25-1.92)	0.5	2.84 (0.01-601)	0.7	0.02 (0.00-283)	0.4
Donor age	1.00 (0.97-1.03)	0.9	1.02 (0.97-1.07)	0.5	1.08 (0.97-1.20)	0.2
HLA group	1.22 (0.71-2.09)	0.5	1.74 (0.53-5.74)	0.4	2.94 (0.52-16.6)	0.2
cRF	0.98 (0.95-1.01)	0.3	0.97 (0.94-1.00)	0.09	1.01 (0.98-1.05)	0.5
CIT (mins)	1.00 (1.00-1.00)	0.3	1.00 (1.00-1.01)	0.4	1.00 (1.00-1.01)	0.2
DGF	1.32 (0.47-3.76)	0.6	0.71 (0.09-5.63)	0.8	366 (n/a)	0.4
Pre-emptive	2.22 (0.28-17.47)	0.5	0.00 (0.00-n/a)	1.0	0.046 (n/a)	0.8

IVSd - interventricular septum diameter at end diastole; LVPW - left-ventricular posterior wall; CR - complete haematologic response; VGPR - very good partial haematologic response; ASCT - autologous stem cell transplant; cRF - Calculated reaction frequency;CIT – cold ischaemic time; DGF – delayed graft function. *Evaluated pre-renal transplantation. **Haematological relapse after transplantation requiring treatment. When 'CR' is replaced by 'CR or VGPR' in the multivariable it predicts survival (HR 0.07 [0.01-0.64]; p=0.018).

Table 4. Univariable Cox regression analyses of predictors of patient survival and death censored graft survival following renal transplantation in AA amyloidosis.

	Patient Survival		**Death Censored Graft Survival**	
	HR	p-value	HR	p-value
Cause of Inflammation				
Inflammatory arthritis	1		1	
Recurrent infection	1.81 (0.47-6.97)	0.4	1.00 (0.12-8.27)	1.0
Unknown	1.51 (0.38-5.96)	0.6	1.00 (0.13-7.97)	1.0
Inflammatory bowel disease	0.58 (0.071-4.65)	0.6	1.00 (0.12-8.26)	1.0
Periodic fever syndrome	0.70 (0.19-2.60)	0.6	1.00 (0.15-6.52)	1.0
Large amyloid load	0.57 (0.073-4.47)	0.6	1.02 (0.12-8.53)	1.0
SAA year pre-transplant (mg/L)	0.99 (0.97-1.01)	0.2	1.01 (1.00-1.02)	0.07
Recurrence	1.10 (0.38-3.22)	0.9	2.08 (0.55-7.89)	0.3
SAA post-transplant (mg/L)	1.01 (0.99-1.04)	0.3	0.99 (0.95-1.04)	0.8

SAA - Serum amyloid A protein; SAA > 10 mg/L pre-transplant represents median SAA concentration in year prior to renal transplantation; SAA post-transplant represents median concentration from renal transplantation to censor.

Table 5. Patient and death-censored renal allograft survival from renal transplantation in AL amyloidosis compared to matched patients with DN and ADPKD.

	Patient survival post transplantation			**Renal allograft survival**		
	Years (95% CI)	HR (95% CI)	p-value	Years (95% CI)	HR (95% CI)	p-value
AL amyloidosis	7.92 (5.52-10.32)	1		Unable	1	
Diabetic nephropathy[1]	11.01 (8.70-13.32)	0.85 (0.50-1.44)	0.5	12.89 (12.25-13.53)	3.09 (0.93-10.26)	0.07
ADPKD[1]	Unable	0.32 (0.17-0.59)	**<0.001**	Unable	1.79 (0.53-6.05)	0.4
AA amyloidosis	13.06 (10.48-45.65)	1		Unable	1	
Diabetic nephropathy[2]	11.35 (8.50-14.20)	1.14 (0.67-1.92)	0.6	14.72 (11.33-18.11)	1.47 (0.71-3.04)	0.3
ADPKD[2]	Unable	0.32 (0.18-0.60)	**<0.001**	Unable	0.74 (0.35-1.57)	0.4

[1]Diabetic nephropathy and ADPKD groups matched to AL amyloidosis group (Supplementary Table 2). [2]Diabetic nephropathy and ADPKD groups matched to AA amyloidosis group (Supplementary Table 1). Unable – unable to estimate due to low number of events

Figure Legends

Figure 1: Patient survival post-transplant in AL amyloidosis stratified by: A) Pre-transplant haemtalogic response divided into very good partial response (VGPR) or complete response (CR) versus partial response (PR) or no response (NR; p=0.12), B) CR vs VGPR, PR, or NR (p=0.03), C) Pre-transplant IVSd wall thickness (p=0.002), D) Pre-transplant NYHA heart failure class ($p<0.05$).

Figure 2: Kaplan-Meier estimates of patient and death censored allograft survival following transplantation for AL (A and B) and AA (C and D) amyloidosis compared to matched diabetic nephropathy and ADPKD patients

Figure 1

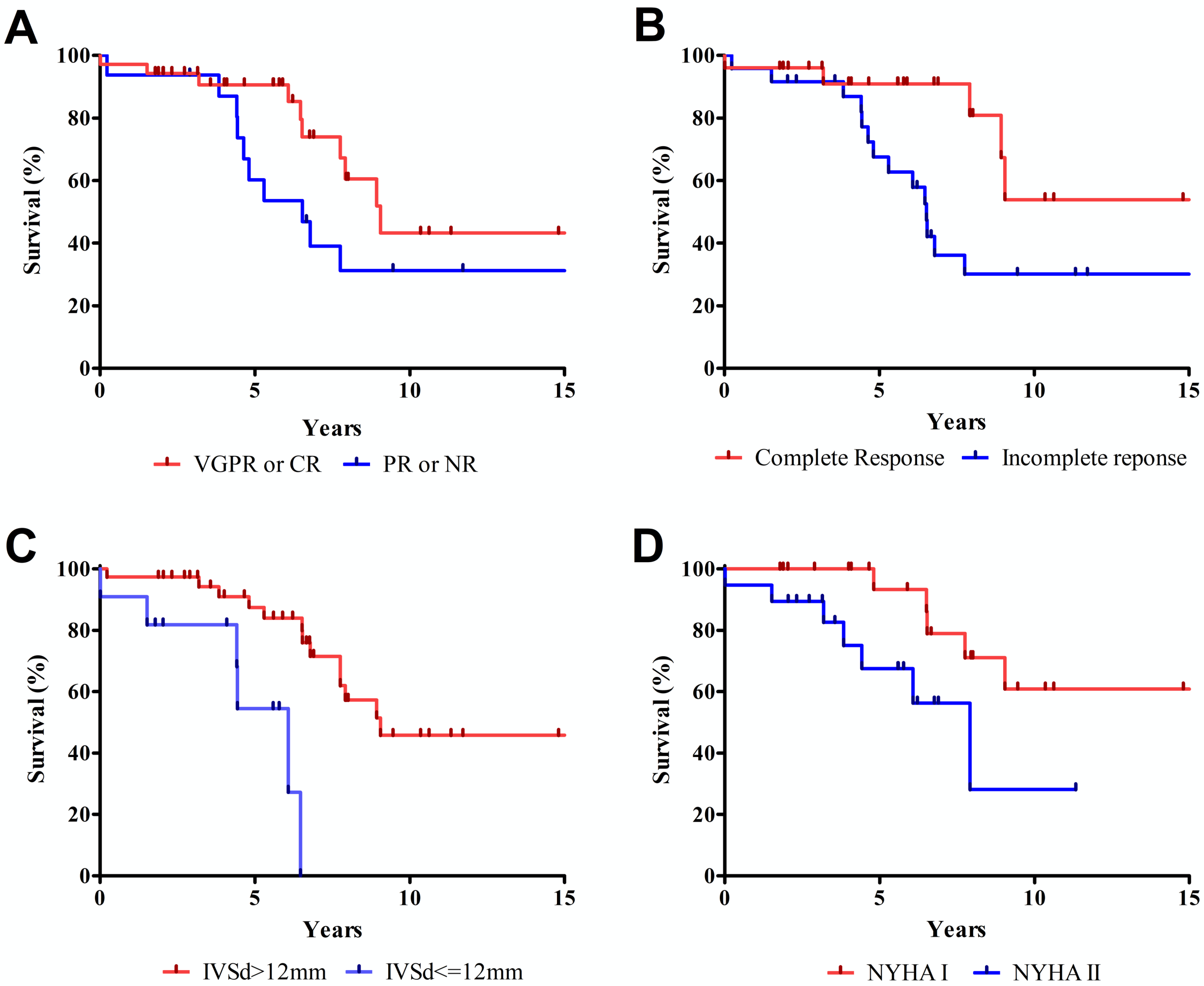
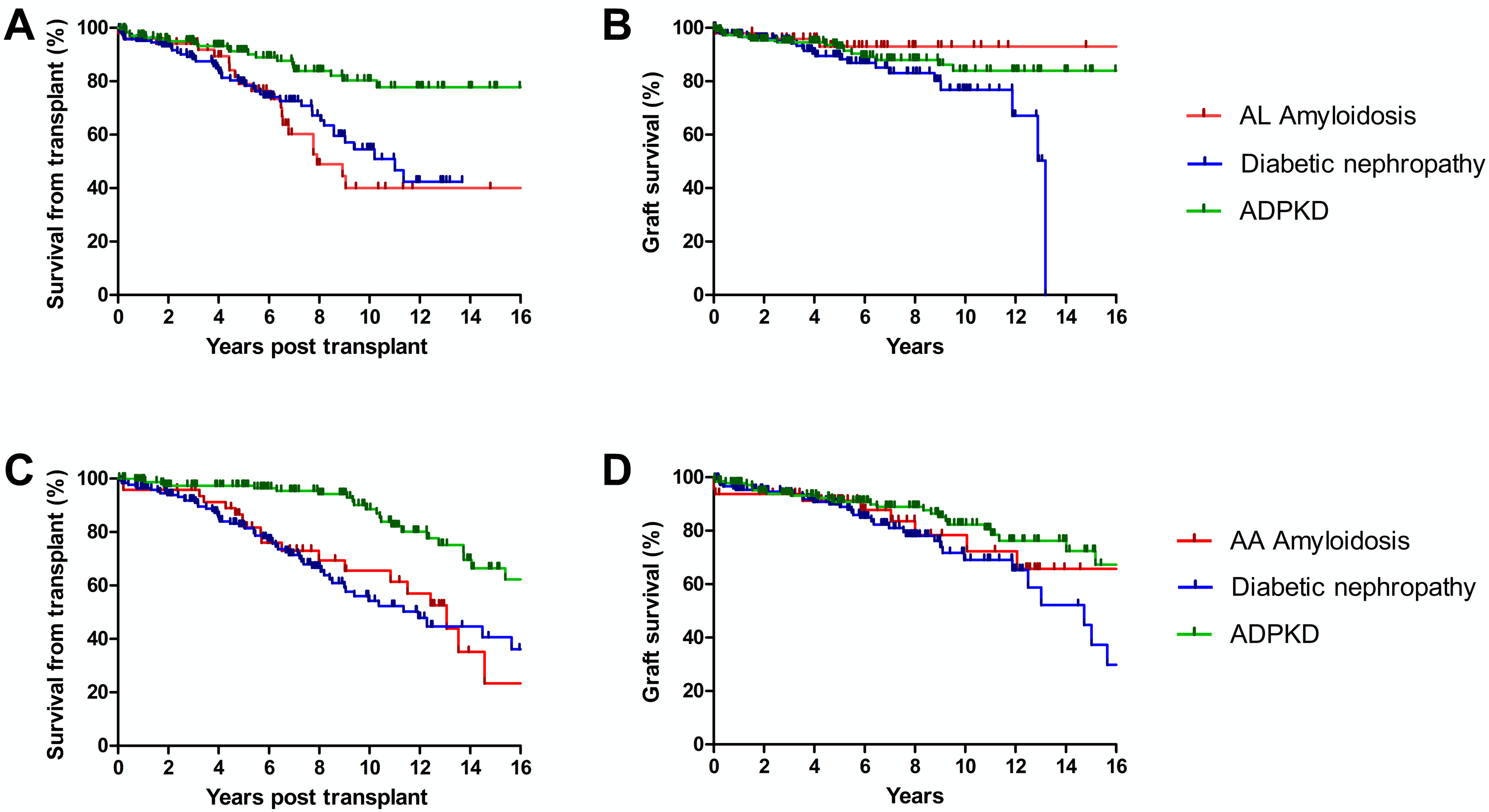


Figure 2


A
Survival from transplant (%)
100
80
60
40
20
0
0 2 4 6 8 10 12 14 16
Years post transplant
B
Graft survival (%)
Years
AL Amyloidosis
Diabetic nephropathy
ADPKD
C
Survival from transplant (%)
Years post transplant
D
Graft survival (%)
Years
AA Amyloidosis
Diabetic nephropathy
ADPKD

1

Supplementary Tables

Table 1. Donor and recipient characteristics of renal transplant patients with primary diagnosis of AA amyloidosis compared to matched diabetic nephropathy and adult polycystic kidney disease patients.

		AA Amyloidosis (n=48)	**Diabetic Nephropathy (n=188)**	**ADPKD (n=188)**
Recipient age		44 (33-54)	56 (47-62)*	49 (42-59)
Male		27 (56%)	138 (73%)*	107 (57%)
Transplant year		1989-2017	1995-2018	1995-2018
Donor status	Live	18 (38)	88 (47)	88 (47)
	Cadaveric	29 (62)	100 (53)	100 (53)
Donor age		41 (30-57)	51 (40-61)	51 (43-59)
HLA mismatch	1	5 (11)	11 (6)	27 (14)
	2	9 (20)	43 (23)	42 (22)
	3	24 (53)	89 (47)	82 (44)
	4	7 (16)	45 (24)	37 (20)
Pre-emptive	Yes	5 (12)	22 (13)	27 (16)
	No	37 (88)	146 (87)	140 (84)
%cRF		0 (0-0)	0 (0-0)	0 (0-21)*
Cold ischaemic time (mins)		710 (180-960)	469 (180-955)	380 (140-848)
Delayed graft function	Yes	3 (8)	26 (19)	23 (16)
	No	33 (92)	113 (81)	118 (84)

* $p<0.05$ when compared to AA amyloidosis group on pairwise testing.

Table 2. Donor and recipient characteristics of renal transplant patients with primary diagnosis of AL amyloidosis compared to matched diabetic nephropathy and adult polycystic kidney disease groups.

		AL amyloidosis (n=51)	**Diabetic Nephropathy (n=204)**	**ADPKD (n=204)**
Recipient age		61 (57-65)	58 (50-64)	55 (49-62)*
Male		28 (55%)	158 (78%)*	108 (53%)
Transplant year		1999-2018	1998-2018	1999-2018
Donor status	Yes	21 (41)	82 (40)	91 (45)
	No	30 (59)	122 (60)	113 (55)
Donor age		56 (40-64)	51 (38-60)	52 (44-60)
HLA mismatch	1	4 (9)	21 (10)	19 (9)
	2	11 (25)	37 (18)	40 (20)
	3	22 (50)	98 (48)	94 (46)
	4	7 (16)	48 (24)	51 (25)
Pre-emptive	Yes	3 (6)	17 (8)	23 (11)
	No	47 (94)	187 (92)	181 (89)
%cRF		0 (0-0)	0 (0-0)	0 (0-28)
Cold ischaemic time (mins)		757 (187-1142)	664 (250-980)	581 (197-954)
Delayed graft function	Yes	10 (29)	43 (25)	41 (24)
	No	25 (71)	128 (75)	128 (76)

* $p<0.05$ when compared to AL amyloidosis group on pairwise testing.