ORIGINAL ARTICLE

Chronic kidney disease after heart transplantation: a single-centre retrospective study at Skåne University Hospital in Lund 1988–2010

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SUMMARY

We aimed to study the incidence, predictors and outcome of chronic kidney disease (CKD) after heart transplantation (HT). All our HT patients 1988–2010 were considered for inclusion. Of these, 134 came for annual follow-ups including evaluation of glomerular filtration rate (GFR) using iohexol clearance measurements, and the CKD-EPI (adults) or Schwartz (children) formulae. Median GFR (Q1–Q3) (ml/min/1.73 m^2) declined from 67.0 (50.0–82.0) during transplant assessment (TA) to 56.0 (45.0–69.0) at year 1, 53.0 (41.0–68.0) at year 5 and 44.5 (25.0–57.3) at year 10. The cumulative incidence of CKD ≥ stage 4 was 25% at 5 years and 41% at 10 years after transplantation. Proteinuria the first year post-HT was the only predictor related ($P < 0.05$) to a higher rate of GFR decline (HR 5.15, 95% CI 1.23–21.55). GFR ≥60 as compared to <60 before HT, or a first-year GFR decline <30% as compared to >30%, was moreover associated ($P < 0.05$) with a lower risk of death (HR 0.30, 95% CI 0.12–0.76 and HR 0.35, 95% CI 0.13–0.90, respectively). Notably, the CKD-EPI and Schwartz formulae overestimated GFR by 28 ± 29% and 26 ± 33%, respectively. In conclusion, CKD in HT patients is common and associated with worse outcome. To avoid diagnostic delay, GFR estimating equations' validity in HT patients needs further study.

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Introduction

Over the last decades, survival after heart transplantation (HT) has steadily improved. According to the latest report from ISHLT (International Society for Heart and Lung Transplantation), based on data submitted on more than 104 000 HT patients from more than 400 HT centres worldwide, the 10-year survival rate after HT has increased from 44% for patients who underwent HT 1982–1991 to 52% for patients transplanted 1992–2001 and 57% for patients transplanted 2002–2005 [1,2]. However, with this improvement in survival, several long-term complications have become evident. Chronic kidney disease (CKD) is of particular importance, contributing substantially to both morbidity and mortality [3].

The development of CKD in HT patients depends on pre-, peri- and postoperative factors. Common causes

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of CKD such as hypertension and diabetes are seen both before and after HT [4]. However, other causes that are more specific for each of the different time periods also exist, such as (i) preoperative renal hypoperfusion due to advanced heart failure with haemodynamic compromise, (ii) perioperative acute renal injury due to complications leading to reduction in renal blood flow, and (iii) postoperative use of the calcineurin inhibitors (CNIs) cyclosporine (CSA) or tacrolimus (TAC), which are important cornerstones in the immunosuppressive regimen that is given to prevent rejection of the donor heart [4].

It is of great importance to diagnose CKD in patients that are awaiting or have undergone HT. Today, most centres rely on creatinine-based equations to estimate glomerular filtration rate (GFR). Although KDIGO (Kidney Disease: Improving Global Outcomes) in their latest guidelines recommends the CKD-EPI (patients >18 years) [5] and Schwartz (patients <18 years) [6] formulae [7] (Table 1), the validity of these (and other) estimating equations in HT patients has not been fully studied [8]. This issue, together with the lack of consensus and the significant variation in the definition of CKD, makes previous studies on renal function in HT patients somewhat difficult to interpret and compare.

Since the beginning of our HT program in 1988, HT patients at our centre have come for annual follow-ups, including iohexol clearance measurements to monitor renal function. To describe our experience and compare it to previously published studies, we aimed to conduct an in-depth analysis of the incidence, predictors and outcome of CKD after HT in our HT population. We also aimed to use our data from iohexol clearance measurements to evaluate the accuracy of the CKD-EPI and Schwartz formulae in the estimation of GFR in adult and paediatric HT patients.

Table 1. The CKD-EPI and Schwartz formulae.

CKD-EPI

$$GFR\ [ml/min/1.73\ m^2] = 141 * \min(S\text{-}cr\ [mg/dl])/\kappa, 1)^{\alpha} * \max(S\text{-}cr\ [mg/dl])/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018\ [if\ female] * 1.159\ [if\ black]$$

Schwartz ("Bedside Schwartz")

$$GFR\ [ml/min/1.73\ m^2] = 0.413 * (height\ [cm]/S\text{-}cr\ [mg/dl])$$

GFR, Glomerular filtration rate; cr, creatinine.

$\kappa = 0.7$ for females and 0.9 for males; $\alpha = -0.329$ for females and -0.411 for males; min indicates the minimum of S-cr [mg/dl])/κ or 1; max indicates the maximum of S-cr [mg/dl])/κ or 1; 1 μmol/l = 0.0113 mg/dl and 1 mg/dl = 88.4.

Patients and methods

Patients and study population characteristics

All 215 patients who underwent HT at our centre 1988–2010 were considered for inclusion. A total of 81 (38%) patients were excluded as our centre is and has been a national referral centre primarily for the HT itself, but not for the long-term follow-up which sometimes has been managed elsewhere. After exclusion, 134 patients in whom 137 HTs (3 re-HTs) had been made, remained for analysis. Of the 137 HTs, 30% involved female patients and 24% involved paediatric patients (<18 years). Study population characteristics, including recipient and donor age and gender, age difference between recipient and donor, sex-matching, AB0-matching, cytomegalovirus (CMV) constellation, recipient diagnosis, waiting time, ischaemic time and immunosuppression, are shown in Table 2. Of all 134 patients, 1 (0.7%) patient underwent a simultaneous heart and kidney transplantation.

The study was performed with approval from the local ethics board in Lund (Approval nos. 2011/777, 2011/368 and 2010/114) and in accordance with the declarations of Helsinki and Istanbul.

Down-titration of maintenance immunosuppression

In general, cyclosporine and tacrolimus trough (C0) levels were monitored once a week, months 0–6; and every other week, months 6–12. C0 levels were generally targeted, respectively, to; 250–300 and 12–15 μg/l, months 0–2; 200–275 and 10–14 μg/l, months 2–4; 150–225 and 8–12 μg/l, months 4–6; 100–175 and 6–10 μg/l, months 6–12; as well as 80–130 and 5–8 μg/l, after the first year. Adult patients generally received a daily corticosteroid dose of 20 mg, months 0–2; 15 mg, months 2–4; 7.5–12.5 mg, months 4–6; 5.0–7.5 mg, months 6–12, as well as 2.5–5.0 mg, after the first year post-HT. In contrast, paediatric patients were given 10 mg/m^2/day, months 0–2; 7.5 mg/m^2/day, months 2–3; 5.0 mg/m^2/day, months 3–4; 2.5 mg/m^2/day, months 4–5; as well as 2.5 mg/m^2 every 2nd day, months 5–6. Thereafter, paediatric patients without severe rejections were usually weaned off corticosteroids.

Yearly follow-ups and measurement of GFR

Each year post-transplant, patients followed at our centre came for extensive follow-ups, including GFR measurements based on the plasma clearance of the

Table 2. Study population characteristics before and after exclusion of patients followed at other centres

Characteristics	Entire cohort (219 HTs)				After exclusion (137 HTs)				
	Mean	SD ±	n	%	Mean	SD ±	n	%	*P*
Age of recipient (years) =	**44.6**	17.2	219		**44.4**	18.3	137		0.88
Paediatric recipients (below 18 years of age)			32	**14.6**			24	**17.5**	0.56
Adult recipients (18 years or older)			187	**85.4**			113	**82.5**	0.56
Age of donor (years) =	**40.1**	15.7	219		**39.2**	16.7	137		0.60
Paediatric donors (below 18 years of age)			17	**7.8**			14	**10.2**	0.54
Adult donors (18 years or older)			202	**92.2**			123	**89.8**	0.54
Difference in age between recipient and donor (years ±)	**12.4**	10.8	219		**12.9**	11.4	137		0.64
0–11			127	**58.0**			77	**56.2**	0.83
12–22			49	**22.4**			31	**22.6**	0.94
23–33			32	**14.6**			19	**13.9**	0.97
34–45			11	**5.0**			10	**7.3**	0.51
Gender of recipient			219				137		
Male			149	**68.0**			96	**70.0**	0.78
Female			70	**32.0**			41	**30.0**	0.78
Gender of donor			219				137		
Male			137	**62.6**			83	**60.6**	0.79
Female			82	**37.4**			54	**39.4**	0.79
Sex matching between recipient and donor			219				137		
Sex matched			161	**73.5**			96	**70.1**	0.56
Sex mismatched			58	**26.5**			41	**29.9**	0.56
AB0 matching between recipient and donor			219				137		
AB0-identical			184	**84.0**			113	**82.5**	0.82
AB0-compatible			32	**14.6**			22	**16.1**	0.83
AB0-incompatible			3	**1.4**			2	**1.5**	0.70
CMV-constellation			204				131		
Donor +/Recipient +			107	**52.5**			72	**55.0**	0.74
Donor −/Recipient −			20	**9.8**			15	**11.5**	0.77
Donor +/Recipient −			28	**13.7**			16	**12.2**	0.82
Donor −/Recipient +			49	**24.0**			28	**21.4**	0.67
Recipient diagnosis			219				137		
Dilated cardiomyopathy			113	**51.6**			74	**54.0**	0.74
Ischaemic cardiomyopathy			59	**26.9**			32	**23.4**	0.53
Other heart disease			47	**21.4**			31	**22.6**	0.90
Waiting time (days)	**150.4**	200.7	219		**144.1**	181.5	137		0.77
0–322			192	**87.7**			120	**87.6**	0.89
323–644			19	**8.7**			14	**10.2**	0.76
645–966			6	**2.7**			2	**1.5**	0.67
967–1289			2	**0.9**			1	**0.7**	0.68
Ischaemic time (minutes)	**185.0**	63.5	216		**183.2**	61.9	135		0.80
46–126			48	**22.2**			30	**22.2**	0.90
127–207			84	**38.9**			56	**41.5**	0.71
208–288			78	**36.1**			45	**33.3**	0.68
289–369			6	**2.8**			4	**3.0**	0.82
Induction immunosuppression			214				134		
Antithymocyte globulin			201	**93.9**			124	**92.5**	0.78
Daclizumab			8	**3.7**			7	**5.2**	0.69
No induction			5	**2.3**			3	**2.2**	0.76
Maintenance immunosuppression in patients alive at discharge			204				129		
Cyclosporine + Azathioprine + Corticosteroids			99	**48.5**			56	**43.4**	0.42
Cyclosporine + MMF/MPA + Corticosteroids			80	**39.2**			50	**38.8**	0.52
Tacrolimus + MMF/MPA + Corticosteroids			13	**6.4**			12	**9.3**	0.44
Other combinations			12	**5.9**			11	**8.5**	0.48

EMB, endomyocardial biopsy; ACR, acute cellular rejection; SD, standard deviation; n, number of heart transplantations in each group; MMF, mycophenolate mofetil; MPA, mycophenolic acid; CMV, cytomegalovirus. *P* – Comparison of bold values.

filtration marker iohexol [9,10]. As this nonionic contrast medium almost exclusively is eliminated through the kidneys [9,10], its use enables accurate determination of GFR, as compared to GFR estimating equations [11]. Before the measurements, estimated GFR was calculated to obtain the optimal sampling schemes. Patients were then administered a dose adjusted solution of iohexol (Omnipaque®, GE Healthcare), whereupon single or multiple plasma sampling was performed depending on patient morphometrics – usually a single sample after four hours or, in patients with atypical body constitution, two samples with the first sample taken after four hours and the second sample taken at least one hour thereafter. In patients with poor renal function, plasma sampling sometimes had to be delayed up to 72 h. High-performance liquid chromatography was thereafter used to determine iohexol concentrations.

Data collection

Iohexol clearance measurements, together with data on S-creatinine, S-urea, blood pressure, height, weight and Hba1c, were collected from transplant assessments and yearly follow-ups. Data were also obtained on survival, potential pre-HT risk factors, and other relevant post-HT variables such as treatment, proteinuria and acute cellular rejection (ACR) on endomyocardial biopsies (EMBs) that had been graded according to the 1990 working formulation from the ISHLT [12]. Data collected after a patient had received a renal transplant were excluded from further analysis.

Data processing

To increase the amount of data available for analysis, we applied GFR estimating equations when iohexol clearance measurements were lacking, but when S-creatinine values were available. Based on the latest guidelines from KDIGO (Kidney Disease: Improving Global Outomes) [7], the CKD-EPI [5] and Schwartz [6] formulae were used in adults and children, respectively (Table 1). Iohexol clearance measurements, nonetheless, constituted the primary source of all the GFR data, representing 90.4% of all 923 data points in adults and 88.1% of all 101 data points in children.

Statistics

For statistical analysis, SIGMASTAT/SIGMAPLOT version 11.2.0.5 (Systat Software Inc, San Jose, CA, USA) was used. A significance level of 0.05 was used throughout all analyses performed. Study population characteristics before and after exclusion were compared using either the chi-square test or Fischer's Exact test (in case of categorical data), or the *t*-test or the rank-sum test (in case of continuous parametric and nonparametric variables, respectively).

To investigate the incidence of CKD, a Kaplan–Meier estimation curve was constructed, showing the proportion of patients that were free from different stages of CKD before and after HT. Data on renal function and associated parameters were also plotted, whereupon values at year 1 were compared to values at transplant assessment, year 5 and year 10 in order to study changes over time. For these comparisons, the *t*-test (parametric data) or rank-sum test (nonparametric data) was used.

Pre-HT risk factors were analysed in uni- and multivariate Cox regression models. Time to >50% reduction in GFR was defined as the end-point in order to study risk factors associated with a higher rate of GFR decline. Previously well-identified risk factors for CKD after HT (age, sex, systolic blood pressure, diastolic blood pressure and Hba1c) were included in the multivariate model. In a separate analysis, other relevant post-HT variables (treatment, proteinuria and ACR) were studied. Here, adjustments were also made for age, sex, systolic blood pressure, diastolic blood pressure and Hba1c-levels in the multivariate model.

To investigate the outcome of CKD, survival was compared in those with GFR <60 vs. ≥60 at transplant assessment and year 1, as well as in those with a first-year GFR decline >30% vs. <30%. The Kaplan–Meier method was used to estimate survival and comparisons between different groups were made using multivariate Cox regression models after adjustment for age and sex.

To determine the accuracy of the CKD-EPI and Schwartz formulae, their estimates were compared with corresponding iohexol clearance measurements using the paired *t*-test. In a subanalysis, the Modification of Diet in Renal Disease (MDRD) formula [13] was also validated among the adults. Bland–Altman plots were then created to illustrate estimation differences across different GFR levels.

Finally, to validate the method of adding estimated GFR values where measured GFR values were missing, sensitivity analyses were performed on the analyses of predictors and outcomes, using GFR data from the iohexol clearance measurements only.

Results

Mortality, dialysis and renal transplantation

During a mean follow-up of 8.3 ± 5.7 (0.0–24.2) years, 34% (n = 46) of the patients died. In two (1%) of those deaths (which occurred 2 and 14 years following the transplantation, respectively), acute on chronic renal failure was one of the most important contributing factors to the death. About 29% (n = 39) of all patients reached CKD ≥ stage 4 (GFR<30; median = 3, min = 0, max = 12 years) and 10% (n = 14) of all patients reached CKD stage 5 (GFR<15; median = 9, min = 0, max = 17 years). About 7% (n = 10) of the patients required dialysis and 2% (n = 3) of the patients required a renal transplant. The renal transplantations were performed 10, 13 and 20 years following the initial HTs.

CKD and GFR

Figure 1a shows Kaplan–Meier estimates of freedom from different CKD stages over time. As seen, a large proportion of the patients had a significant renal function impairment prior to HT (CKD ≥ stage 2 in 79%, CKD ≥ stage 3 in 44%, CKD ≥ stage 4 in 4% and CKD stage 5 in 1%). In the first year after HT, a seemingly larger proportion of the patients progressed above CKD stage 2 and 3 (79 to 97% and 44 to 77%, respectively) than 4 and 5 (4 to 11% and 1 to 2%, respectively). In the years thereafter, the proportion of patients with different stages of CKD steadily increased. By year 10, 100% had progressed to ≥ stage 2, 85% had progressed to ≥ stage 3, 41% had progressed to ≥ stage 4, and 12% had progressed to stage 5.

Figure 1b shows GFR during transplant assessment and over the 10 first years after HT. As illustrated, GFR (ml/min/1.73 m^2) declined from 67.0 (50.0–82.0) during transplant assessment to 56.0 (45.0–69.0) after 1 year, 53.0 (41.0–68.0) after 5 years and 44.5 (25.0–57.3) after 10 years. One year after HT, GFR was significantly lower (P < 0.05) compared with during transplant assessment. It thereafter declined at a slower, yet steady rate, to significantly lower (P < 0.05) levels after 10 years.

Mean yearly GFR change during the whole follow-up was −2.2 ± 14.6 ml/min/1.73 m^2, as compared to −11.9 ± 25.8 ml/min/1.73 m^2 during the first year alone.

Associated parameters

Figure 2a–h shows measured GFR, estimated GFR, S-creatinine, S-urea, blood pressure, body mass index and Hba1c, during transplant assessment and over the 10 first years after HT. As seen, S-creatinine and S-urea increased over time and reached slightly higher (P < 0.05) levels at year 10 post-HT compared with year 1 post-HT (127.0 vs. 104.0 g/l and 9.8 vs. 9.0 g/l, respectively). A clear increase (P < 0.05) was also seen in systolic and diastolic blood pressure during the first year (100 and 66 mmHg at transplant assessment versus 131 and 80 mmHg at 1 year after transplantation). However, neither systolic nor diastolic blood pressure changed much in the years thereafter (P = NS). Similarly, body mass index and Hba1c remained relatively stable following transplantation (P = NS), although an increase in body mass index (23.6 to 25.2 m^2/kg) and a decrease in Hba1c (5.1 to 4.8%) was found when transplant assessment values were compared with values obtained at year 1 (P < 0.05).

Potential pre-HT risk factors and relevant post-HT variables

Worsening in renal function in relation to potential pre-HT risk factors and relevant post-HT variables is

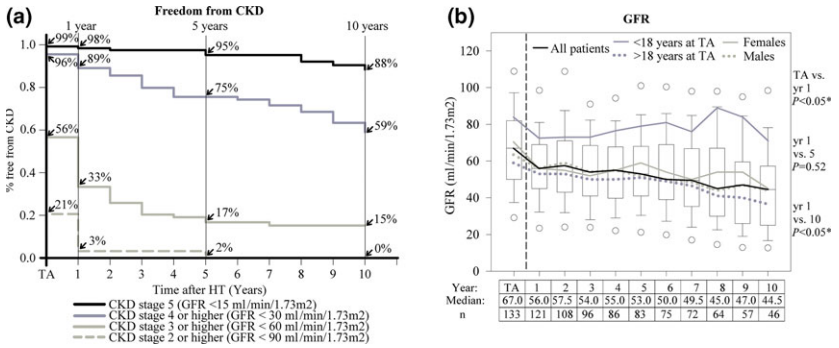

Figure 1 Freedom from different stages of CKD (a), and GFR (b), during TA as well as over the 10 first years after HT. * indicates statistical significance (P < 0.05). Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; HT, heart transplantation; TA, transplant assessment. Percentiles, P values and tabulated values in (b) are all related to 'All patients'.

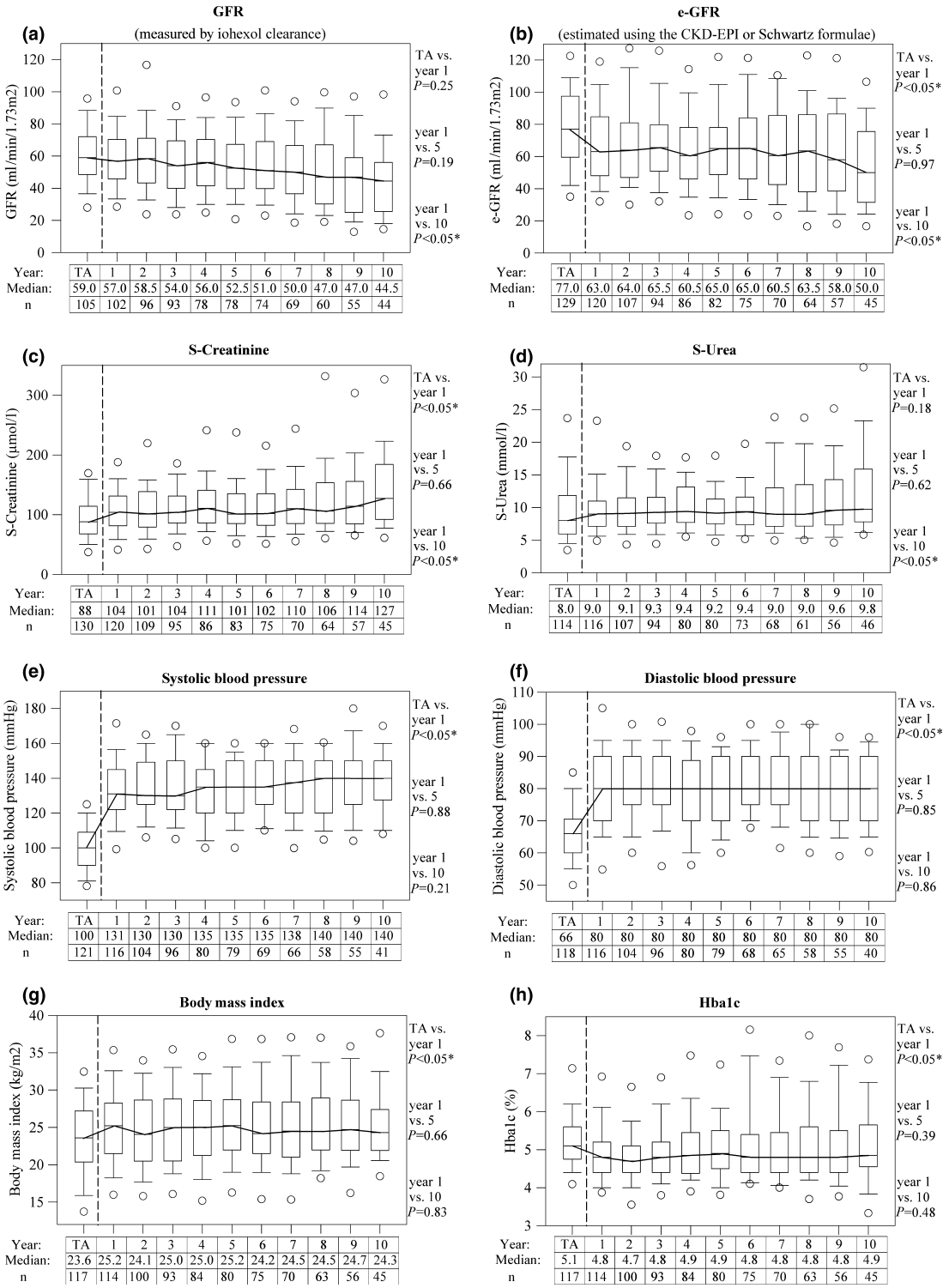

Figure 2 Measured GFR (a), estimated GFR (b), S-creatinine (c), S-urea (d), blood pressure (e–f) body mass index (g) and Hba1c (h), during TA as well as over the 10 first years after HT. * indicates statistical significance ($P < 0.05$). Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; e-GFR, estimated glomerular filtration rate; GFR, measured glomerular filtration rate; HT, heart transplantation; TA, transplant assessment.

shown in Tables 3 and 4, respectively. As seen, proteinuria during the first year after HT was the only predictor significantly ($P < 0.05$) related to a higher rate of GFR decline, with hazard ratio (95% confidence interval) of 2.46 (1.04–5.82) and 5.15 (1.23–21.55) in the univariate and multivariate analysis, respectively.

Outcome

Figure 3a–c shows survival during the 10 first years after HT in relation to GFR during transplant assessment, GFR at 1 year after HT, and in relation to first-year change in GFR. As seen, the risk of death was lower ($P < 0.05$) in patients with GFR ≥60 as compared to <60 during transplant assessment (hazard ratio 0.30, 95% confidence interval 0.12–0.76) and in patients with a first-year decrease in GFR of <30% as compared to >30% (hazard ratio 0.35, 95% confidence interval 0.13–0.90).

Accuracy of creatinine-based GFR equations

Compared with measured GFR, mean GFR (ml/min/1.73 m^2) was higher ($P < 0.05$) using the CKD-EPI (62.1 ± 24.8 vs. 50.0 ± 20.1) ($n = 818$) or Schwartz (94.5 ± 22.6 vs. 79.0 ± 24.4) ($n = 88$) formulae. On average, CKD-EPI overestimated measured GFR by 12.2 ± 13.2 ml/min/1.73 m^2 (or 27.9 ± 28.7%) and misclassified 44% of all cases to a more advanced CKD stage (vs. only 2% to a less advanced stage). Similarly, the Schwartz formula overestimated measured GFR by 15.5 ± 19.6 ml/min/1.73 m^2 (or 25.9 ± 32.7%) and misclassified 44% of all cases to a more advanced CKD stage (vs. only 3% to a less advanced stage). Notably, only 59.2% of the estimations using the CKD-EPI and 59.1% of the estimations using the Schwartz formula were within ± 30% of measured GFR.

In the subanalysis of the MDRD equation, mean GFR was also higher ($P < 0.05$) than measured GFR (61.9 ± 25.4 vs. 50.0 ± 20.1 ml/min/1.73 m^2) ($n = 818$). Mean bias was + 12.0 ± 15.4 ml/min/1.73 m^2 (28.2 ± 31.6%), there was a 43% 'overclassification' versus a 2% 'underclassification' of CKD stages, and only 59.2% of all estimations were within ± 30% of true GFR.

In Fig. 4a–c, the estimation errors for the three formulae across different GFR levels are illustrated in Bland–Altman plots.

Table 3. Cox-regression analysis on the deterioration in renal function in relation to potential pre-HT risk factors.

	Univariate analysis			Multivariate analysis		
Potential risk factor	HR	95% CI	*P*	HR	95% CI	*P*
Age (years)	1.01	(0.99–1.03)	0.24	1.00	(0.97–1.04)	0.96
Gender (female)	1.09	(0.57–2.09)	0.80	1.86	(0.68–5.05)	0.23
Diagnosis (ICM)	0.97	(0.48–1.98)	0.94	0.71	(0.24–2.08)	0.53
Systolic blood pressure (mmHg)	1.02	(0.99–1.04)	0.08	1.02	(0.99–1.05)	0.17
Diastolic blood pressure (mmHg)	1.03	(0.99–1.07)	0.09	1.00	(0.94–1.05)	0.91
BMI (kg/m^2)	1.03	(0.96–1.10)	0.44	0.97	(0.86–1.10)	0.61
Hba1c (%)	0.79	(0.47–1.31)	0.36	0.80	(0.47–1.37)	0.42

HT, heart transplantation; HR, hazard ratio; CI, confidence interval; ICM, ischaemic cardiomyopathy.

Table 4. Cox-regression analysis on the deterioration in renal function in relation to relevant post-HT variables.

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
Initiation of TAC as compared to CSA by year 1†	1.07	(0.41–2.78)	0.89	0.42	(0.05–3.58)	0.43
Initiation of ACEI or ARB by year 1	1.24	(0.68–2.28)	0.49	0.99	(0.43–2.30)	0.98
Presence of proteinuria during year 1	2.46	(1.04–5.82)	<0.05*	5.15	(1.23–21.55)	<0.05*
Presence of one or more ACRs ≥ grade 3A/3B during year 1‡	1.30	(0.71–2.36)	0.40	1.58	(0.68–3.65)	0.29

*Indicates statistical significance ($P < 0.05$). HT, heart transplantation; HR, hazard ratio; CI, confidence interval; TAC, tacrolimus; CSA, cyclosporine; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ACR, acute cellular rejection.

†After exclusion of patients also treated with everolimus, and those receiving both CSA and TAC.

‡After exclusion of patients who did not undergo endomyocardial biopsy during year 1.

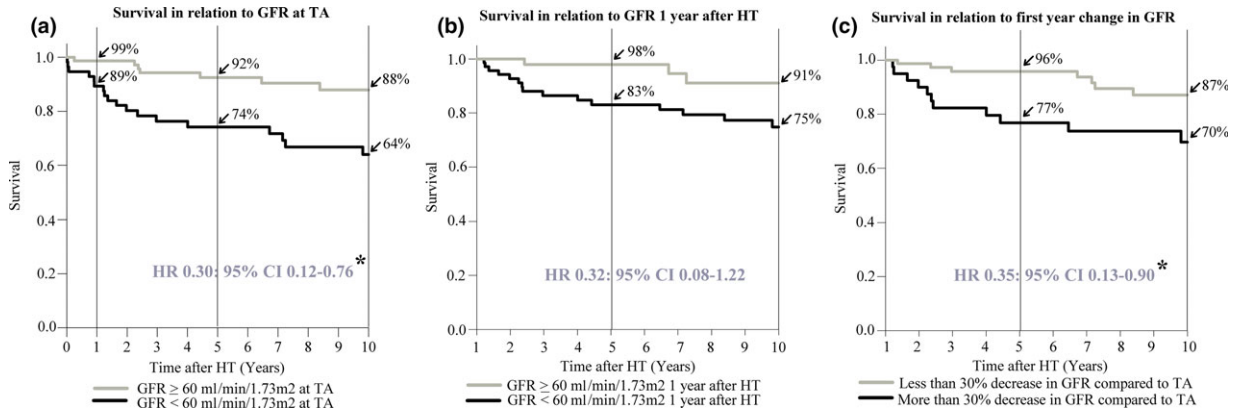

Figure 3 Survival during the 10 first years after HT in relation to; GFR during TA (a), GFR at 1 year after HT (b), and in relation to first-year change in GFR (c). * indicates statistical significance ($P < 0.05$). Abbreviations: HR, hazard ratio; CI, confidence interval; GFR, glomerular filtration rate; HT, heart transplantation; TA, transplant assessment.

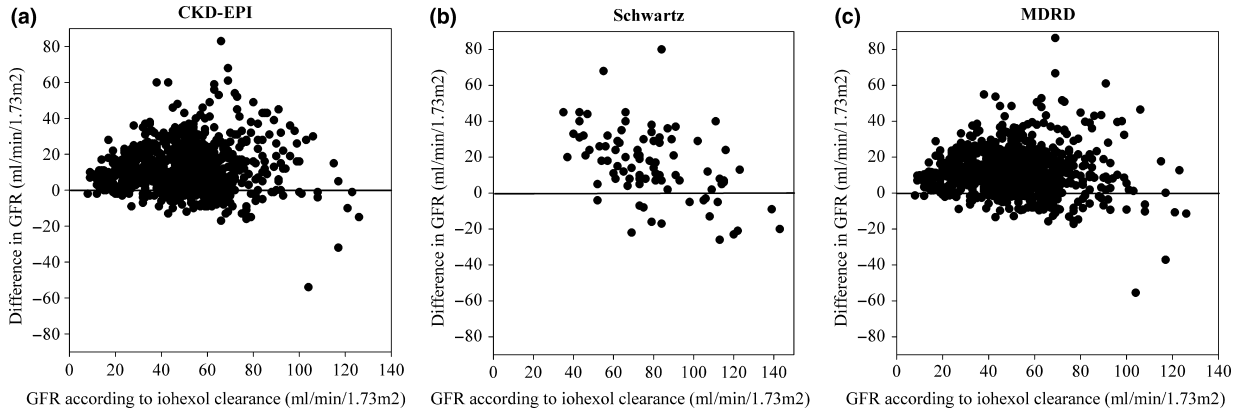

Figure 4 Bland–Altman plots showing the estimation errors for the CKD-EPI (a), Schwartz (b) and MDRD (c) formulae across different GFR levels as compared to iohexol clearance measurements. As seen, the positive estimation errors appear to be relatively persistent at all GFR levels (possibly more pronounced at higher GFR levels for CKD-EPI and MDRD). Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

Sensitivity analyses

The sensitivity analyses performed confirmed the findings on predictors and outcomes. However, when using GFR data from iohexol clearance measurements only, female gender was found to be significantly related ($P < 0.05$) to a more rapid GFR decline in the multivariate analysis. Moreover, the findings on proteinuria and GFR ≥60 vs. <60 before HT were insignificant ($P = 0.06$ and 0.07 in the univariate and multivariate analysis on proteinuria, respectively, and 0.09 in the comparison of survival between patients with GFR ≥60 vs. <60 during transplant assessment).

Discussion

In the present single-centre retrospective study including HT patients at our centre 1988–2010, we conducted an in-depth analysis of the incidence, predictors and outcome of CKD following HT. We furthermore used our data from iohexol clearance measurements to evaluate the accuracy of the CKD-EPI and Schwartz formulae in the estimation of GFR in adult and paediatric HT patients. Our results indicated (i) that quite a large proportion of the patients developed severe stages of CKD, (ii) that the presence of proteinuria early after HT was associated with a higher rate of GFR decline, (iii) that patients with early renal dysfunction had lower survival in the long-term, and (iv) that the CKD-EPI and Schwartz formulae were inaccurate in estimating GFR in HT patients.

In the present study, quite a large proportion of the patients developed severe stages of CKD. Five and 10 years after HT, the cumulative incidence of CKD ≥ stage 4 was 25% and 41%, respectively. This is slightly higher than what was found in two of the largest

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long-term studies on CKD after HT, where the corresponding rates were 11% and 13% after 5 years and 18% and 22% after 10 years [3,14]. This is somewhat surprising since we recently observed excellent outcomes in our HT population, with a ten-year survival rate of around 74% compared with around 57% in the ISHLT registry [1, 15]. However, contrary to our study where GFR in ~90% of the cases was measured with the iohexol clearance method, the US [3] and UK [14] cohort studies mentioned above reported data on GFR estimated with the MDRD formula [13], which in a recent systematic review was found to overestimate GFR among HT patients by 8.8% [16]. A tendency towards overestimation of GFR with the MDRD formula was also found in this study, and it is therefore possible that earlier studies have underestimated the true incidence of CKD after HT.

The rate of GFR decline depends on several factors, but longitudinal studies from the US have reported rates at about -0.75 ml/min/1.73^2/year in healthy subjects >30 years of age [17,18]. In the present study, we observed a yearly rate more than twice as high (-2.2 ± 14.6 ml/min/1.73 m^2). The steepest decline occurred during the first year following transplant (-11.9 ± 25.8 ml/min/1.73 m^2), which is in accordance with earlier studies [14, 19–27]. We believe this, in large part, may be attributed to the higher CNI levels patients generally receive during this time period.

Finding ways of minimizing the use of CNIs has been the focus of several recent studies where induction therapy [28,29] and m-TOR inhibitors [30,31] have shown to be particularly useful. In the present study, we were unable to analyse the effects of different CNI minimization strategies because almost all patients received induction therapy and because very few received m-TOR inhibitors. We were, however, able to evaluate different CNI regimens and the use of renoprotective agents, but none of those treatment modalities were associated with a higher or lower rate of GFR decline.

In other studies, older age [3,14,19,20], female sex [3,14,19,20], hypertension [3] and diabetes [3,14,20] have been associated with an increased risk of renal dysfunction following HT. In our analysis of potential pre-HT risk factors and relevant post-HT variables, the only parameter associated with a higher rate of GFR decline was the presence of proteinuria early after HT. This is an important finding which merits further investigation. Proteinuria has earlier been identified as a marker or GFR decline in the general population [32] as well as in kidney transplant patients [33]. To our knowledge, however, little is known on its potential in predicting GFR decline in HT patients.

Another important finding of the present study was the association between early renal dysfunction and lower survival rates, which confirms data from earlier studies [3,14,19,20].

Also of significant importance, our study indicated that the CKD-EPI and Schwartz formulae were relatively unreliable in terms of estimating GFR among adult and paediatric HT patients. Of notice, only 59.2% and 59.1% of all estimations, respectively, were within $\pm$30% of 'true' GFR. There was also a tendency towards positive bias (12.2 ± 13.2 and 15.5 ± 19.6 ml/min/1.73 m^2). Compared with the few earlier studies that have evaluated the two equations in HT patients [16, 34], our results indicated slightly lower 'P30-values', and slightly higher positive bias, for both formulae. Nonetheless, it still appears as if both estimating equations tend to overestimate GFR in HT patients. The reason for this remains unclear, however, muscle atrophy secondary to long-term corticosteroid use, with lower levels of circulating creatinine resulting in higher estimates of GFR, may contribute. Until further studied, it appears as if both equations should be used cautiously in this population to avoid diagnostic delay.

The present study benefits from the high proportion of GFR data that was obtained from measurements of iohexol clearance (~90%), as compared to less accurate GFR estimating equations. There are, however, a couple of limitations that are necessary to clarify and important to have in mind. First of all, this was a retrospective study including quite a small cohort of patients. Data regarding potential pre-HT risk factors and relevant post-HT variables should therefore be interpreted cautiously. Moreover, although our data indicated that the CKD-EPI and Schwartz formulae had low accuracies, they were used in this study to estimate GFR when iohexol clearance measurements were lacking. Such data, however, only represented 10% of the total data and the sensitivity analyses showed good agreement between the results based on 'measured' GFR and the results based on 'combined' GFR.

In conclusion, CKD in HT patients is common and associated with worse outcome. It is the opinion of the authors that special attention should be given to the patients with previously identified risk factors (older age, female sex, hypertension and diabetes) and to patients with early proteinuria on urine test strips as this was associated with a higher rate of GFR decline in the present study. Most importantly, GFR should be closely followed and CNI minimization strategies

(induction therapy and m-TOR inhibitors) should be considered. Based on our results we cannot, however, make any recommendations on the choice of CNI (i.e. TAC versus CSA) or the use of renoprotective agents (i.e. angiotensin converting enzyme inhibitors and angiotensin receptor blockers).

Of special interest, our iohexol clearance measurements indicated a higher incidence of CKD than two of the largest long-term studies on CKD after HT in which GFR was estimated using the MDRD formula. As this formula overestimated GFR in HT patients in our study and in a recent systematic review, we believe it is possible that earlier studies have underestimated the true incidence of CKD after HT. Our data also indicated that the CKD-EPI and Schwartz formula overestimate GFR in HT patients. Thus, the validity of these (and other) GFR estimating equations in HT patients needs further study. Diagnosis of CKD in this already highly vulnerable group of patients could otherwise be delayed.

Authorship

CS: study design, data collection, data analysis and writing of the article. EL: data collection and reviewing the article. JN, ÖR and TH: data acquisition and reviewing the article. GR: study design, data acquisition, data collection, data analysis, writing and reviewing the article.

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Conflicts of interest

The authors have no conflict of interests to disclose with regard to this manuscript.

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