

With regards to recipients who are less than 18 years old, a study by Ishitani *et al.* examined the success of live, related donor transplantation in paediatric recipients using UNOS Registry data.¹¹ When compared with pre-emptive transplantation, there was a relative risk of graft failure of 1.77 in those transplanted after dialysis had commenced. Kennedy *et al.* used ANZDATA to examine graft outcomes in transplanted adolescents, and also reported improved outcomes with pre-emptive transplantation.¹²

Patient survival – comparison between dialysis and transplantation

Wolfe *et al.* compared the survival of those on the waiting list with those for individuals receiving a primary deceased donor transplant.¹³ Standardized mortality ratios were derived from an analysis of 228 552 subjects on dialysis. A total of 46 164 individuals were on the waiting list, of whom 23 275 received a primary deceased donor transplant over a 7-year period of observation. The annual death rate for those on the waiting list was 6.3 per 100 patient-years. By comparison, those transplanted had a long-term annual death rate of 3.8 per 100 patient-years. The improvement in relative risk of mortality was most pronounced for young, white recipients (20–39 years) and for people with diabetes. It should be noted that there was an initial elevation in the relative risk of mortality related to the early transplant period. The mortality risk was equal in the two groups by day 106 of follow-up, and improved in the transplanted group thereafter.

McDonald and Russ have reported similar findings using ANZDATA.¹⁴ An analysis of the period 1991–2000 found an 80% lower long-term risk of mortality between those transplanted and those remaining on the waiting list.

Quality of Life – comparison between dialysis and transplantation

Cameron *et al.* have performed a meta-analysis examining the effect of transplantation on overall quality of life.¹⁵ Successful kidney transplantation was associated with improved general wellbeing and less distress, when compared with continued haemodialysis or peritoneal dialysis. There are several individual studies that have examined quality of life issues in more detail. Evans *et al.* reported that 79.1% of transplant recipients describe near normal physical function, compared with only 50% of dialysis patients.¹⁶ Mental function scores were also higher in transplant recipients. Studies by both Gorlen *et al.*¹⁷ and Laupacis *et al.*¹⁸ found that the quality of life improvements associated with transplantation were sustained long term. However, transplantation continued to affect quality of life relative to normal.¹⁸ This was attributed to the side effects of immunosuppression, comorbid conditions and the stress associated with the possibility of losing graft function.

Cost effectiveness of transplantation

A detailed analysis of the relative costs of dialysis and transplantation has been performed by Kidney Health

Australia.¹⁹ Estimates of the cost of home or satellite-based dialysis (haemodialysis and peritoneal) for an individual are approximately \$45 000–\$60 000 per year. Hospital-based haemodialysis is estimated to cost approximately \$83 000 per year. Although the initial cost of transplanting an individual is estimated to be relatively high (\$62 000 for the first year) the cost falls significantly thereafter (approximately \$11 000 per year for year 2 and onwards). The estimated costs associated with an individual live donor transplant are similar to those for an individual deceased donor transplant.¹⁹ A Canadian report estimated that transplanting an individual would result in savings of CAN\$104 000 over a 20-year period.²⁰

Overall safety for live donors

Only a brief account of the overall safety data will be summarized here. A much more detailed analysis of the literature regarding donor safety will follow in subsequent sections of these Living Kidney Donor guidelines.

By and large, live kidney donation is considered to be safe for the majority of healthy donors. This contention, however, is based predominantly on large retrospective studies, which demonstrate that unilateral nephrectomy in healthy subjects is generally associated with a very low level of long-term risk.^{21–27} A meta-analysis published by Garg *et al.* has examined the development of proteinuria in donors.²⁸ It concluded that there is a small increase in urinary protein excretion; however, glomerular filtration rate (GFR) was well preserved over a 15-year follow-up period. Another meta-analysis, by Boudville *et al.* examined the effect of donation on blood pressure.²⁹ This concluded that donors may have a 5 mmHg increase in blood pressure within 5–10 years of donation.

Ibrahim *et al.* assessed the vital status and lifetime risk of end-stage kidney disease (ESKD), GFR, urinary albumin excretion, prevalence of hypertension, general health status and quality of life in 3698 kidney donors.³⁰ Survival and risk of ESKD was not significantly different to those in the general population. Most donors had a preserved GFR, normal albumin excretion and an excellent quality of life.

It is important to point out that the absence of any large prospective, well-controlled, long-term follow-up studies on live donors is seen as a significant deficiency.^{27,31,32} Furthermore, long-term studies regarding live donors with isolated abnormalities (e.g. hyperlipidaemia, mild hypertension, obesity) are also lacking, and the long-term risks in these subjects remain particularly ill defined. It is hoped that the recently established ANZDATA Live Donor Registry will help in further clarifying the true long-term donor outcomes in Australia and New Zealand.

With regards to the short-term risks, these are predominantly related to the surgical procedure. The risk of perioperative mortality is generally regarded as being approximately 1 in 3000 – a figure derived from large American surveys³³ and several single centre reports. Although Australian and New Zealand registry data are currently lacking, of approximately 5000 live kidney donations that

have occurred in Australia and New Zealand to date, the transplant community is currently aware of two perioperative deaths (anecdotal reports).

The risk of non-fatal major perioperative complication is also generally felt to be low, approximating 2–4% in most published series (see later subtopics for a detailed account of the supporting literature). The majority of these complications have been haemorrhagic episodes, although a variety of other events have been reported including bowel obstruction, bowel injury, thromboembolic events, pneumothoraces, hernia development and rhabdomyolysis.

Prasad *et al.* performed an observational cohort study of 58 living donors to 6 months post-donation for changes in 24 h ambulatory blood pressure profile, kidney function, urine protein excretion, body mass index, glucose intolerance and fasting lipid profiles.³⁴ No significant changes in blood pressure, protein excretion, body mass index, glucose and lipids were found. Estimated glomerular filtration rate declined significantly ($P < 0.0001$).

SUMMARY OF THE EVIDENCE

Most of the data presented here comes from Registries and from large retrospective cohort studies. There is a lack of prospective long-term data regarding live donor safety, particularly in relation to consequences of donation in certain donor subgroups.

To summarize this guideline topic:

- Live kidney donation is currently justifiable in Australia and New Zealand based on:
 - i) the current overall success of kidney transplantation;
 - ii) the demand for donor organs, which far outweighs the supply from deceased donors;
 - iii) the detrimental effects of waiting on dialysis for several years; and
 - iv) the apparent low level of risk to the majority of healthy donors.
- It is acknowledged that there is a need for more precise information regarding long-term risks faced by donors. This would ideally be obtained from prospectively collected live donor registry data.

WHAT DO THE OTHER GUIDELINES SAY?

National Health & Medical Research Council (Australia):

Two recently published documents cover various aspects of the information presented here.^{31,35} The first document – for health professionals – outlines important ethical principles, and details the rights and responsibilities of donors, health professionals and institutions.³¹ The second document – for potential donors – provides information regarding the assessment, a discussion of the risks and also outlines important ethical issues.³⁵ Both discuss the rationale behind live kidney donation. These are available at: www.nhmrc.gov.au/publications/subjects/organ.htm

British Transplant Society/British Renal Association:

An extensive, 100-page document has been produced outlining similar issues to those discussed here.³⁶ The full version of these British Live Donor Guidelines is available at: www.bts.org.uk and at www.renal.org

The Canadian Council for Donation and Transplantation:

A 70-page document has been produced outlining similar issues to those discussed here.³⁷ A full version of these guidelines is available at: www.ccdt.ca

The Amsterdam Forum:

An International Forum on the Care of the Live Kidney Donor, comprising 100 experts from 40 countries, produced a short manuscript outlining similar issues to those discussed here.³⁸

SUGGESTIONS FOR FUTURE RESEARCH

1. Assess long-term donor risks: medical and psychosocial. Prospective studies are required. The risks in various donor subgroups need to be better assessed (e.g. those with isolated abnormalities such as mild hypertension, obesity, etc.).
2. Survey Australian and New Zealand transplant centres regarding live donor outcomes to date. Known major adverse events to be collated and reported.
3. Examine the barriers to donation for live donors in Australia and New Zealand (e.g. financial, social, community attitudes, awareness).
4. Assess cost-effectiveness of kidney transplantation in Australia/New Zealand.
5. Examine Australian and New Zealand transplant centre practice regarding live donor assessment (handling of ethical issues, informed consent process).

CONFLICT OF INTEREST

John Kanellis has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDIX

Table 1 Characteristics of included studies

Study ID	n	Study methods	Data sources	Results	Main findings
Fehrman-Ekholm <i>et al.</i> 1997 ²²	430	Donor survival (Kaplan–Meier analysis)	1964–1994, national registry, Sweden	Survival after >20 years: donors 85%, expected survival (Hakulinens method) 66%	No long term risk to live kidney donors (better survival likely due to health of persons accepted for donation)
Gjertson and Cecka 2000 ⁵	117, 239	Survival analysis (Kaplan–Meier analysis)	1970–1998, UNOS Renal Transplant Registry	5-year graft survival: spouse donor 75%, LURD 72%, parent donor 77%, cadaver 62%	Living unrelated kidney donors provide excellent long-term results
Goldfarb <i>et al.</i> 2001 ²⁶	70	Donor renal outcome – cross sectional (tests for urinary creatinine, protein and albumin; serum creatinine; blood pressure; eGFR and medical questionnaire)	1963–1975, single centre, US	Mean 24 h creatinine clearance was 72% of pre-nephrectomy value. 19% of subjects had 24 hr protein excretion >0.15 g/24 h	Renal function well preserved after donor nephrectomy
Kasiske <i>et al.</i> 2002 ¹⁰	38 836	Analysis of cadaver and living donor transplants (χ^2 , logistic regression, Kaplan–Meier analysis)	1995–1998, United States Renal Data System Registry, US	Pre-emptive transplantation associated with a lower rate of delayed graft function compared with non pre-emptive transplantation: cadaver (8.4 vs 25.6%) and living donor (2.6 vs 6.1%)	Pre-emptive transplantation is associated with improved patient and graft survival
Mandal <i>et al.</i> 2003 ⁶	31 900	Cox proportional hazards model to approximate risk associated with CRT, LRT	1995–1998, United States Renal Data System Registry, US	Cadaveric <i>versus</i> live donor (younger patients): graft failure uncensored for death RR 1.49 (95% CI: 1.41–1.61), risk of death 1.64 (95% CI: 1.49, 1.82) Cadaveric <i>versus</i> live donor (elderly patients): graft failure uncensored for death RR 1.64 (95% CI: 1.41–1.89), risk of death 1.72 (95% CI: 1.45, 2.04)	Elderly recipients with an imminent LRT should not be offered CRT. CRT may be preferable in younger recipients
Matas <i>et al.</i> 2003 ³³	10 828	Survey sent to transplant centres listed with UNOS	1991–2001, 171/234 UNOS-listed kidney transplant programs	Death from surgical complications 0.02%, mortality rate 0.03%	Morbidity and mortality for living kidney donor nephrectomy is low
Najarian <i>et al.</i> 1992 ²¹	57	Comparison of donors and their siblings	20 years, single centre, USA	Hypertension drugs: donors 32%, siblings 44% Proteinuria: donors 23%, siblings 22%	Perioperative mortality after living donor nephrectomy is low

Table 1 Continued

Study ID	n	Study methods	Data sources	Results	Main findings
Ramcharan <i>et al.</i> 2002 ³² and Matas <i>et al.</i> 2003 ³³	464	Living donor outcomes – cross sectional	1963–1979, single centre, USA	Survival 89.9%, normal kidney function in surviving donors 99.2%	Most kidney donors have normal renal function at >20 years follow up
Rizvi <i>et al.</i> 2005 ²⁵	736	Retrospective analysis of living related kidney donation	2000–2004, single centre, Pakistan	Creatinine clearance: 87% of pre-nephrectomy value, hypertension 10.3%, proteinuria > 150 mg/24 h 24.3%, ESKD in one donor.	Donor nephrectomy has minimal adverse effect on overall health status
Simforoosh <i>et al.</i> 2006 ⁴	2155	Survival analysis (Kaplan–Meier analysis)	1984–2004 transplant data, single centre, Iran	15-year graft survival: LRD 85.4%, LURD 53.7%, 15-year patient survival: LRD 73.9%, LURD 76.4%	Long term results for living unrelated kidney transplantation comparable with living related kidney transplantation
Terasaki <i>et al.</i> 1995 ²	47 206	Graft survival rates (Kaplan–Meier analysis)	UNOS Renal Transplant Registry	3-year survival rate: spouse donor 85%, living unrelated 81%, parents 82%, cadaveric 70%	High rate of graft survival in kidney donations from spouses and parents
Voiculescu <i>et al.</i> 2003 ³	62	Transplant data (Fisher's exact test, Mann–Whitney <i>U</i> -test)	Transplant data, single centre, Germany	Acute rejection: LRD 52.2%, LURD 54.2%; delayed graft function: LRD 15.8%, LURD 4.2%; number of patients with rejection: LRD 52.5%, LURD 54.2%	Kidney transplantation from emotionally related living donors is a valuable option

CI, confidence interval; CRT, cadaveric donor renal transplantation; ESKD, end-stage kidney disease; LRD, living related donor; LRT, live donor renal transplantation; LURD, living unrelated donor; RR, relative risk; UNOS, United Network for Organ Sharing.