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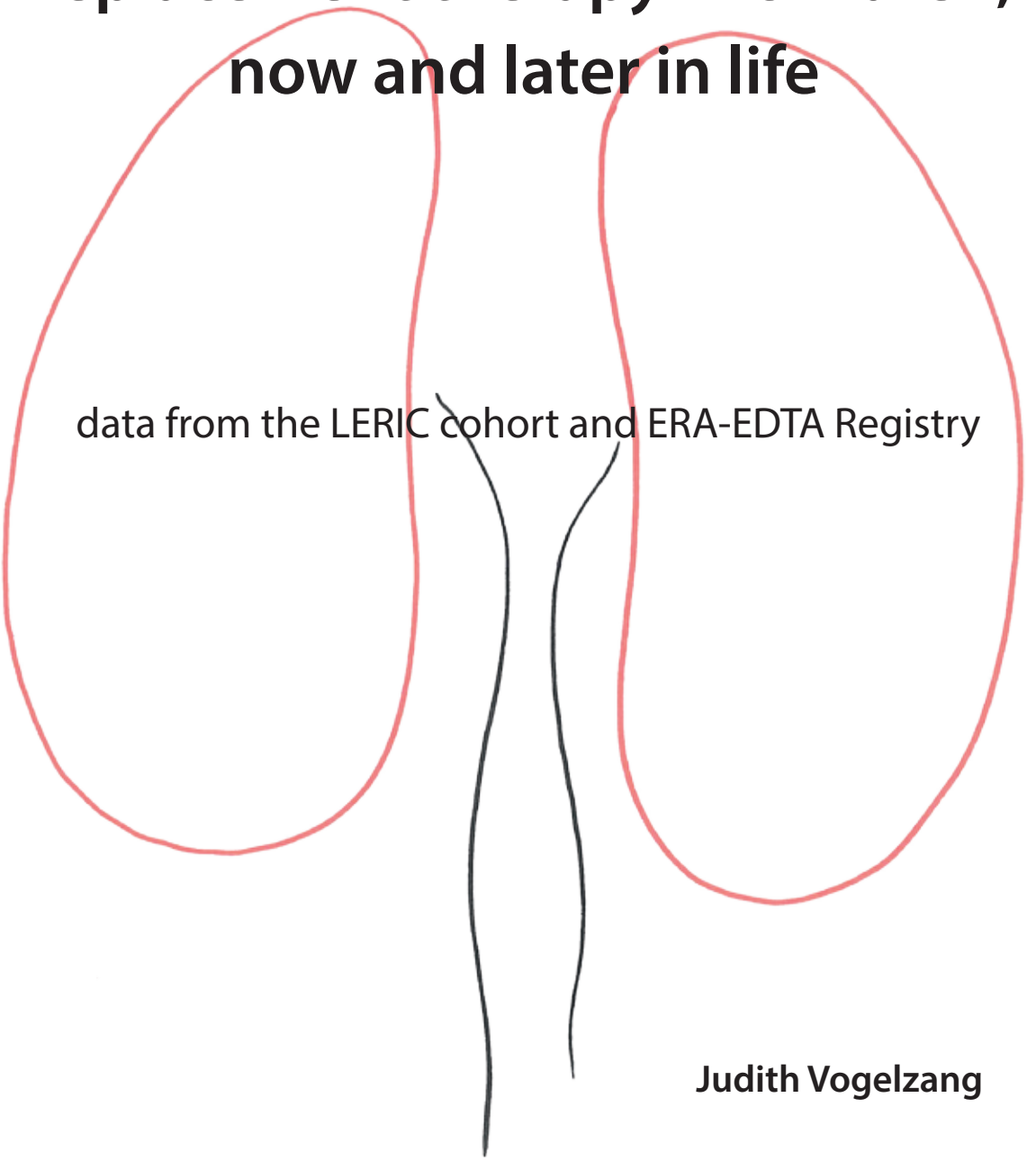

data from the LERIC cohort and ERA-EDTA Registry

Judith Vogelzang

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Effects of initiating chronic renal replacement therapy in children, now and later in life

Data from the LERIC cohort and ERA-EDTA Registry

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General introduction, aim and outline of thesis

INTRODUCTION

End-stage renal disease (ESRD) in children is a rare but serious and life-threatening disorder. [1] In the Western world, the yearly incidence of ESRD in patients <19 years of age is estimated between 6 to 8 per million of the age-related population. For a population of 3.9 million people below the age of 20 years in the Netherlands, this implies about 30 new patients per year. [2]

End-stage renal disease in children was a lethal condition until the 1960s. In the late sixties, the first experimental hemodialysis treatments in children in the Netherlands were performed by pediatricians in Utrecht, Amsterdam, Rotterdam and later on also in Nijmegen, all in close collaboration with internist-nephrologists. In 1972, the first official Dutch center for dialysis in children opened its doors in Utrecht, soon followed by the other 3 centers and in 1973 the first child in the Netherlands received a renal graft. From that moment, renal replacement therapy (RRT) for children with ESRD rapidly became routine therapy. In 1978, the Academic Medical Center (AMC) in Amsterdam was one of the first sites in the world providing chronic peritoneal dialysis to children. Soon peritoneal dialysis would become the preferred mode of dialysis in children, at least in small children.

During the first 20 years of chronic RRT in children, the prospects of these children improved dramatically. As a result of these successes, a new generation of young adults with ESRD since childhood had gradually emerged at the turn of the millennium. As the problem of acute mortality of childhood RRT had diminished, patients and caretakers shifted their attention to its implications for life after childhood. Up to 2000 there was hardly any information on the somatic, social and psychological outcomes of ESRD since childhood at adult age. Therefore, in 2000, the Late Effects of Renal Insufficiency (LERIC) study was conducted. This was a comprehensive study to evaluate the late effects of renal insufficiency in all Dutch children who had started chronic renal replacement therapy (RRT) between 1972 and 1992 at an age less than 15 years and who were born before 1979.

Data collection started in 1998 so, consequently, at time of the study the patients who participated had reached adulthood, defined as aged 18 years or older, and received RRT for at least 6 years.

The study revealed important findings, such as the extreme impact of cardiovascular disease, and of mineral bone disease on daily life and on psychosocial outcomes. Below is a summary of the most important findings:

Mortality and causes of death. The studies in the LERIC cohort with follow-up up to 2000, revealed that the mortality rate was 31 times higher than that in the aged-matched general population. [1] Cardiovascular disease was by far the most important cause of death among both the dialysis patients and transplant recipients, accounting for 41% of all deaths. [1;3] Later, these mortality figures were confirmed by German and Australian studies. [4;5] LERIC revealed a high prevalence of cardiovascular disease among the survivors: 49% of male patients and 39% of females had apparent left ventricular hypertrophy, 19% had aortic valve calcifications and, on average, patients had significantly increased stiffening of the arterial walls. [3;6] These surrogate outcomes were all independently and strongly associated with an increased risk for acute death, as has been shown in older adult ESRD patients, and indicated a higher prevalence of cardiovascular disease that was extremely uncommon for their age and therefore unexpected at that time. Later, other studies confirmed the high prevalence of cardiovascular disease in young adults with childhood ESRD. [7-10]

Infections and malignancies. Infections and malignancies were the second and third most important causes of death of patients of the LERIC cohort in 20001. There are indications that these comorbidities might become even more important than cardiovascular complications in the coming years. The UK Renal Registry data, for instance, shows a marked decrease in cardiovascular mortality in the first decade of the 2000s (from 34% in 2000 to 22% in 2011), while mortality rates due to infections and malignancies seem to remain unchanged. [7;11] Infection is one of the major causes of mortality and morbidity in patients with ESRD, accounting for 15–23% of deaths in the prevalent RRT population. [12-14] Various factors contribute to the high rate of life threatening infections in ESRD patients including the overall impaired immune function [15;16] as a result of decreased renal function, the open connection of the peritoneal cavity in patients on peritoneal dialysis and of the central venous system in hemodialysis patients, [17-19] and the use of immunosuppressive therapy in transplanted patients. [20] The role of other determinants, such as gender, primary disease or age was inconclusive up to the publication of this work. Previous studies found an increased mortality due to non-cardiovascular causes in women treated with chronic dialysis treatment compared with men. This was especially pronounced among women treated with peritoneal dialysis. [7;21]

Infection is furthermore one of the most frequent causes of hospitalization in ESRD patients. [1;22-26] In adults it has been associated with a 10% death rate within 30 days following admission, [14] which underscores its importance. In contrast to what might be expected in view of these figures, there is still paucity of studies reporting on the burden of severe non-fatal infections in long term RRT.

Malignancies in organ transplant recipients have been strongly linked to the use of immunosuppressive agents, as such agents may cause DNA damage and interfere with normal DNA repair mechanisms. They may also impair immune surveillance of neoplastic cells. [27] Patients with pediatric onset of Renal Replacement Therapy disease are, theoretically, particularly at risk for cancer as they have a relatively long exposure of carcinogenic factors. Indeed, we found a probability of 17% for developing a malignancy among adult patients aged 20–40 years. This corresponds to a 10 fold increase in the incidence of de novo malignancy compared to the general population, and were in line with other studies. [28-32]

Quality of Life. There was particular concern about the implications following a nearly lifelong renal replacement therapy starting in childhood for the Quality of Life (QoL) in adult life. QoL is an important marker of disease burden and can also be used to assess treatment effectiveness and predict risk for adverse outcomes. [33] In adult ESRD patients, studies report substantial effects on the patient's QoL by negatively affecting their social, financial and psychological well-being. [34-36] Low QoL scores are associated with hospitalization, graft failure and long term mortality. [37-39] Determinants of impaired QoL in the ESRD population include both medical and socio demographic factors. [40-42] However, despite the major interest of young patients and their families, only few data exist on the effect of intensive, chronic therapy since childhood on physical and social development in adulthood. In 2000, in the LERIC cohort, we found close-to-normal QoL in patients who underwent transplantation, and significantly impaired physical but normal mental QoL in patients receiving dialysis. [43] The relatively high mental scores in both dialysis and transplantation

came as a surprise as they sharply contrasted with scores found among Dutch dialysis patients of the same age but with adult onset of disease. [44-47] The latter group scored significantly lower, which suggests that patients with pediatric onset of disease appear to have found effective ways of coping with their disease over time. These outcomes made us curious about the follow up. To what extent would these patients keep their positive view on mental health after another 10 more years of renal replacement therapy?

AIMS AND RESEARCH QUESTIONS OF THE THESIS

The overall aim of this thesis is to comprehensively describe the effect of more than 25 years of renal replacement therapy in children on somatic and psychosocial status. We therefore extended the LERIC study by 10 years and collected data on mortality and morbidity over these years. We also collected data on medication, mode of RRT and other potential determinants over this period. We approached patients of the cohort for data on QoL and social outcome by sending questionnaires and if necessary by contacting them by telephone.

Since there were indications in the literature that infections and malignancies were becoming more important over the last decades as comorbidity of and cause of death in ESRD, we broadened our study by using data from the European Renal Association – European Dialysis and Transplantation Association (ERA-EDTA). The ERA-EDTA collects data on RRT patients via national and regional renal registries in Europe

Our first aim was to describe the effects of RRT in children on the very long run (>25 years following the initiation of RRT). Our second aim was to investigate the relationship between clinical characteristics and outcomes in order to present recommendations for improvement of treatment for patients with ESRD.

To achieve these aims we addressed the following series of research questions:

1. *Mortality and causes of death after 25 years of renal replacement therapy.* Given the high prevalence of cardiovascular disease among the survivors of RRT since childhood in the LERIC study and a possible further increase thereof due to advancing age, we expected cardiovascular death to become an even more pronounced problem after 2000. We investigated the actual trend in long-term mortality and causes of death after 2000 and aimed to investigate whether there was a change in the prevalence of cardiovascular risk factors potentially relating to changes in cardio protective treatment over the past decade.
2. *The impact of infections and malignancies in ESRD.* Infections and malignancies are the most common non-cardiovascular causes of death in patients on RRT. However, information on the interaction of sex, age and primary renal disease with infection- and malignancy-related mortality in RRT patients is lacking. We used data from the ERA-EDTA Registry to analyse these interactions and to investigate the occurrence of the most common non-cardiovascular causes of death (infections and malignancies) in patients treated with dialysis or living with a kidney transplant compared to the general population.

3. *The impact of infections and malignancies in ESRD children after 25 years of renal replacement therapy*. Infections and malignancies were the second and third most important causes of death of patients of the LERIC cohort in 2000. Our aim was to evaluate the total burden of severe infections in patients with a long history of RRT and to analyze the change in burden of severe infections over time.
   As most malignancies occurred at the end of the follow-up period in 2000, we conjectured that with ageing of our cohort the risk of malignancies might dramatically increase. We described the prevalence and risk factors of cancer after very long term follow-up in patients who started RRT in childhood, and investigated which malignancies can be held responsible for the increased prevalence.
4. *Quality of Life*. Few data exist on the effect of intensive, chronic therapy since childhood on physical and social development in adulthood. In 2000, in the LERIC cohort, we found close-to-normal Quality of Life (QoL) in patients who underwent transplantation, and significantly impaired physical but normal mental QoL in patients receiving dialysis. We hypothesized that in 2010 the meanwhile longer period on RRT would affect their physical condition and that aging would negatively influence their QoL and social status.

OUTLINE

Part I consists of chapters 2 and 3 and focuses on mortality, change of pattern over time in causes of death and on potential determinants for this pattern. Chapter 2 describes the results of the extended follow-up study of the LERIC cohort on (transitions in) causes of death in patients with RRT since childhood over time. Because this study showed a decrease in cardiovascular disease as cause of death over time, we consequently investigated in chapter 3 whether there was a simultaneous trend in non-lethal cardiovascular disease. We also explored whether this trend was in line with a decrease of cardiovascular risk factors as a result of adjustment of cardio-protective treatment over this period in our cohort.

PART II consists of chapters 4, 5 and 6 and focuses on the prevalence of infections and malignancies as important comorbidities in pediatric and adult ESRD in relation to RRT exposure as well as era of onset of RRT. In chapter 4, we describe the mortality risk attributed to infection and malignancies in RRT patients as compared, by treatment modality, with the general population by age group and sex. To this end, we use data from the ERA-EDTA Registry. Chapter 5 describes the total burden and the change in burden over time of severe infections in patients of the LERIC cohort with a long history of RRT. Chapter 6 describes the prevalence and risk factors of cancer in patients with pediatric onset of ESRD after very long-term follow-up in the LERIC cohort.

Part III consists of chapter 7. In this chapter, the results of the quality of life after 30 years of RRT and the determinants (both medical and socio-demographic) associated with impaired QoL are presented.

Finally, a General Discussion of all findings in this thesis is presented in Chapter 8. This chapter addresses implications for clinical practice and delineates directions for future research.

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Part I

Cardiovascular disease

02

Trend from cardiovascular to non-cardiovascular late mortality in patients with renal replacement therapy since childhood

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ABSTRACT

Background: To evaluate transitions in causes of death in patients with renal replacement therapy (RRT) since childhood over time, we performed a 10-year extension of the Late Effects of Renal Insufficiency in Children (LERIC) study.

Methods: The LERIC cohort consisted of all 249 Dutch patients, who were born before 1979 and started RRT <15 years of age between 1972 and 1992. We collected data on mortality and causes of death over the period 2000–10 and compared them with the previously gathered data over the period 1972–99.

Results: The median duration of follow-up from the start of RRT was 25.5 (range 0.3–39.0 years). Overall, 97 patients died of whom 34 in 2000–10. The overall mortality rate and mortality rate ratios (MRRs) stabilized over time. The MRR for cardiovascular death decreased from 660 in 1972–89 to 70 in 1990–99 and to 20 in 2000–10. Conversely, the MRR for infectious death showed a U-shape; it decreased from 503 in 1972–89 to 102 in 1990–99 and increased again to 350 in 2000–10. In 2000–10, infections became the most prevalent cause of death (44%). In 2000–10, the cardiovascular mortality had decreased with 91% since 1972–89 [adjusted hazard ratio (HR): 0.09, 95% confidence interval (95% CI): 0.02–0.45, P = 0.003], while infectious mortality had doubled over time, although not significantly (adjusted HR: 2.12, 95% CI: 0.88–5.11, P = 0.09).

Conclusions: Over the last decade, we found a substantial shift from cardiovascular disease to infections as the main cause of death at long-term follow-up in patients with chronic kidney disease since childhood and who were born before 1979.

INTRODUCTION

Few data exist on the very long-term outcome of patients with chronic kidney disease (CKD). Between 1998 and 2000, we conducted a comprehensive study to evaluate the Late Effects of Renal Insufficiency (LERIC) in all Dutch children who had started chronic renal replacement therapy (RRT) at <15 years of age between 1972 and 1992. Previous analyses of this cohort including data up to the year 2000 showed that, in this age category, patients with CKD had a 31-fold increased risk of mortality when compared with the general population [1], and that cardiovascular disease was by far the most important cause of death among both the dialysis patients and transplant recipients, accounting for 41% of all deaths. [1;2]

Our findings were confirmed by McDonald and Craig, [3] who found a similar mortality risk in patients from Australia and New Zealand who started RRT before the age of 20 years between 1962 and 2000. They found the equally high percentage of 45% of all deaths being contributed to cardiovascular disease. [3] Among the survivors in the LERIC cohort in 1999, we also found a high prevalence of cardiovascular disease, which was reflected by an overall increased mean arterial wall stiffness, left ventricular hypertrophy in 40% and aortic calcifications on ultrasound in 19% of patients. [2] In 2002, Oh *et al*. [4] showed similar cardiovascular abnormalities in young adults with chronic renal failure since childhood and treated with RRT, including a high prevalence of calcifying arteriopathy. Coronary calcifications were observed in 92% of patients, and carotid intimae media thickness was significantly increased compared with matched controls. [4]

Given this high prevalence of cardiovascular disease among the survivors of RRT since childhood and a possible further increase due to advancing age, we expected cardiovascular death to become an even more pronounced problem after 2000. We conducted an extended follow-up study of this cohort to investigate the actual trend in long-term mortality and causes of death after 2000.

SUBJECTS AND METHODS

Study design

The LERIC cohort comprised all Dutch patients who had started chronic RRT at <15 years of age between 1972 and 1992, and who were born before 1979. In 1998 and 2000, the first follow-up study of these 249 patients was conducted, which was described in detail previously. [1] In 2010, a second follow-up study was conducted covering the period from the last chart review in 1999 until the last chart review in 2010–11 or the patient's death. In this paper, we analysed data on mortality and causes of death in the total cohort from 1972 until 2010 and compared two time periods, 1990 until 1999 and 2000 until 2010, with the time period 1972 until 1989. We obtained permission from the medical ethical committee and informed consent from all patients who were alive in 2000.

Data collection

For the second follow-up period, we reviewed medical charts from all patients between 1 June 2010 and 1 February 2011. We attempted to localize all emigrated patients. Among others, we

collected data on the cause of death, total duration of hemodialysis (HD), peritoneal dialysis (PD) and transplantation (Tx), age at death and modality of RRT at the time of death. In living patients, the day of review was considered as the end of the observation period for that particular patient.

Categorization of causes of death

Causes of death were categorized independently by three reviewers (J.L.V., J.W.G. and K.J.J.), using detailed description of all available data around the patient's time of death. After assessment of interobserver variability, consensus was achieved by discussion. When after discussion the patient's cause of death was still unclear, the patient's nephrologist was contacted to obtain information on the cause of death. As a reference, mortality data from the Dutch general population were used, which were obtained from the Dutch Office of Death Statistics. [5]

Statistical analysis

The mortality rate (MR) was calculated as the number of deaths per 100 patient years (pys) on RRT with a 95% confidence interval (95% CI). The mortality rate ratios (MRRs) were calculated to compare mortality in RRT patients with that in the general population. The MRR was defined as the MR for a certain cause of death in RRT patients divided by the MR in the Dutch general population for the same cause of death thereby adjusting for age and time period. We used the Cox proportional hazards model (adjusted for age and gender-related general population mortality: background mortality) to analyse whether the risk of death for overall, cardiovascular and infectious mortalities changed over the time periods 1990–99 and 2000–10 when compared with the time period 1972–89.

RESULTS

Study population

The total cohort consisted of 249 patients (Table 1). Only 3 of the 249 patients (1.2%) were lost to follow-up. The median age at the start of RRT was 11.2 (range 1.9–15.0 years) and 54.6% were males (Table 1). The median age of survivors was 28.9 (range 21.0–40.9 years) in 1999 and 40.0 (range 31.6–50.8 years) in 2010. The median total follow-up time was 25.5 (range 0.3–39.9 years), time on hemodialysis 2.3 (range 0.03–36.5 years), time on peritoneal dialysis 2.4 (range 0.01–18.6 years) and time living with a renal graft 19.7 (range 0.0.1–39.3 years; Table 1). Among the 231 (93%) transplant recipients, 71 (31%) lived with a single transplant – not necessarily their first – for more than 20 consecutive years and up to 37.2 years (Table 1).

Ninety-two patients received only a single renal allograft (39.8%). Transplantation was performed two times in 84 (36.4%) patients, three times in 43 (18.6%), four times in 8 (3.5%), five times in 1 (0.4%) and six times in 3 (1.3%). Patients changed treatment modality between 1 and 11 times during the study period. Of the 249 patients, only 2 (0.8%) patients lived on a functioning graft during their entire follow-up (median survival 25.3 years) and 18 (7.2%) only received dialysis (median survival 3.7 years).

Of the 186 patients who were still alive in 2000, 79% had a functioning renal graft, similar to the proportion of the 152 patients who were still alive in 2010 (80%).

Mortality and causes of death

Of all 249 patients, 42 died between 1972 and 1989, 21 between 1990 and 1999 and 34 between 2000 and 2010. The overall (1972–2010) MR was 1.69/100 patient-years. The median age at the time of death was 22.8 (range 4.2–46.24 years). In the last decade, 12 of the patients died from cardiovascular disease, 44 from infections, 20.5 from malignancies, 20.5 from other causes and 3% (1 case) from unknown cause. Most patients died while on dialysis (53%; Supplementary material, Appendix 1). Of those who died of cardiovascular disease, 75% received dialysis at the time of death; of those who died of infections, this was 60%. Of those who died of infections in the last decade, one-third died of PD-related peritonitis.

Table 1 | Main characteristics of the cohort between 1972 – 2010

1972 – 2010	N	Median (range) in years	Treatment duration in years Median (range)
Male (%)	136 (54.6%)		
Age at start of RRT	249	11.2 (1.9 – 15.0)	
Total follow-up time on RRT	249		25.5 (0.3 – 39.9)
HD: patients with at least 1 period of HD	236		2.3 (0.03 – 36.5)
HD: patients who had HD for more than 10 years	33		12.9 (10.2 – 36.5)
PD: patients with at least 1 period of PD	101		2.4 (0.01 – 18.6)
PD: patients who had PD for more than 10 years	5		11.2 (10.1 – 18.6)
Tx: patients with at least 1 period of Tx*	231		19.7 (0.01 – 39.3)
Tx: patients who had Tx for more than 20 years (combined)	114		26.1 (20.0 – 39.3)
Tx: patients who had one Tx for more than 20 consecutive years	71		25.6 (20.1 – 37.2)

* Number of renal transplants per patient: median (range) 2 (0–6)

Changes in the patterns of the cause of death

Table 2 presents the MRs and the MRRs for the overall causes of death in the periods 1972–89, 1990–99 and 2000–10, divided into five categories: cardiovascular, infections, malignancies, other and unknown. The all-cause crude MR did not significantly change over time. The cardiovascular MR decreased significantly from 0.97/100 per py (95% CI: 0.58–1.51) in 1972–89 to 0.22/100 py (95% CI: 0.06–0.56) in 2000–10. In contrast, the infection-associated MR did not significantly change over time from 0.51/100 py in 1972–89 (95% CI: 0.24–0.94) to 0.82/100 py (95% CI: 0.46–1.35) in 2000–10. The MR for malignancies, other and unknown causes of death did not change over time (Table 2). We

saw the same trends in MR for the different causes of death when we calculated the MR for dialysis patients and transplant recipients separately.

Table 2 | Mortality rates (deaths/100 patient years) and mortality rate ratio (mortality rate in patients/ mortality rate in age and gender related general population) over three time periods

Mortality rate	1972–1989 (95% CI)	1990–1999 (95% CI)	2000–2010 (95% CI)
All causes	2.14/100 py (1.54–2.89)	1.11/100 py (0.69–1.70)	1.86/100 py (1.29–2.60)
Cardiovascular	0.97/100 py (0.58–1.51)	0.37/100 py (0.15–0.76)	0.22/100 py (0.06–0.56)*
Infection	0.51/100 py (0.24–0.94)	0.32/100 py (0.12–0.70)	0.82/100 py (0.46–1.35)
Malignancy	0.20/100 py (0.05–0.51)	0.11/100 py (0.01–0.40)	0.38/100 py (0.15–0.78)
Other	0.41/100 py (0.18–0.81)	0.32/100 py (0.12–0.70)	0.38/100 py (0.15–0.78)
Unknown	0.05/100 py (0.00–0.28)	0/100 py (0.00–0.00)	0.05/100 py (0.00–0.28)

* P<0.05 compared to 1972–1989

Mortality rate ratio	1972–1989 (95% CI)	1990–1999 (95% CI)	2000-2010 (95% CI)
All causes	53.0 (36.9–69.1)	19.7 (10.8–28.6)	26.8 (17.8–35.8)
Cardiovascular	660.3 (368.1–952.5)	70.0 (14.0–126.0)	19.6 (0.5–38.7)
Infections	502.5 (177.5–827.5)	101.8 (14.1–189.5)	352.6 (174.0–531.2)
Malignancies	29.2 (12.3–46.1)	18.8 (8.0–29.6)	18.5 (11.5–25.5)
Other	17.1 (5.9 - 28.2)	8.6 (1.0–16.2)	12.8 (3.4–22.2)
Unknown	19.9 (0.9–38.9)	0 (0.0–0.0)	10.5 (0.3–20.7)

When we compared the mortality of RRT patients with that in the general population, the age-adjusted MRR for all causes of death decreased from 53.0 in 1972–89 to 19.7 in 1990–99, but increased again to 26.8 in the last decade (Table 2). However, the trends over time in the MRR were different for various causes of death: the MRR for cardiovascular disease decreased significantly from 660 in 1972–89 to 70 in 1990–99 and decreased further to 20 in 2000–10. Conversely, the MRR trend for infections showed a U-shape; it decreased from 503 in 1972–89 to 102 in 1990–99 and increased again to 353 in 2000–10. The age-adjusted MRR for malignancies did not change over time. In addition, we saw the same trends in MRR for the causes of death when we calculated the MRRs for dialysis patients and transplant recipients separately.

Figure 1a shows the change in the pattern of causes of death per 10-year age category and per time period. It shows a shift from cardiovascular mortality in the younger age categories (Figure 1b) towards infectious mortality in the older age categories over time (Figure 1c and 1d).

A Cox-regression analysis adjusted for background mortality confirmed this change in the pattern. We found a 50% reduction in the risk of overall mortality for 1990–99 when compared with 1972–89 [hazard ratio (HR): 0.50, 95% CI: 0.29–0.86, P = 0.01], but no reduction in overall mortality risk for 2000–10 when compared with 1972–89 (HR: 0.75, 95% CI: 0.47–1.20, P = 0.2; Table 3). After

adjustment for expected cardiovascular background mortality, the risk of cardiovascular mortality was 74% lower in 1990–99 than in 1972–89 (HR: 0.26, 95% CI: 0.10–0.66, P = 0.005) and in 2000–10, and it was 91% lower than in 1972–89 (HR: 0.09, 95% CI: 0.02–0.45, P = 0.003; Table 3).

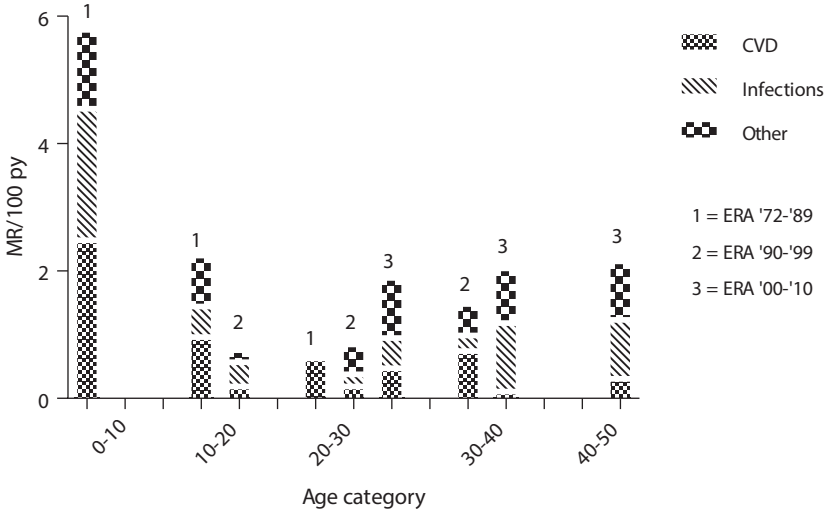

Figure 1 | Mortality rate/100 person years per age category per ERA

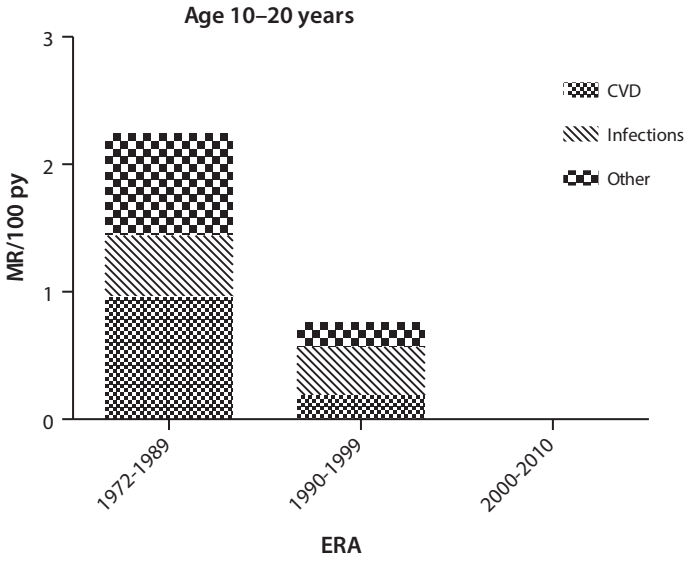

Figure 1a | Mortality rate/100 person years per era in age category 10–20 years

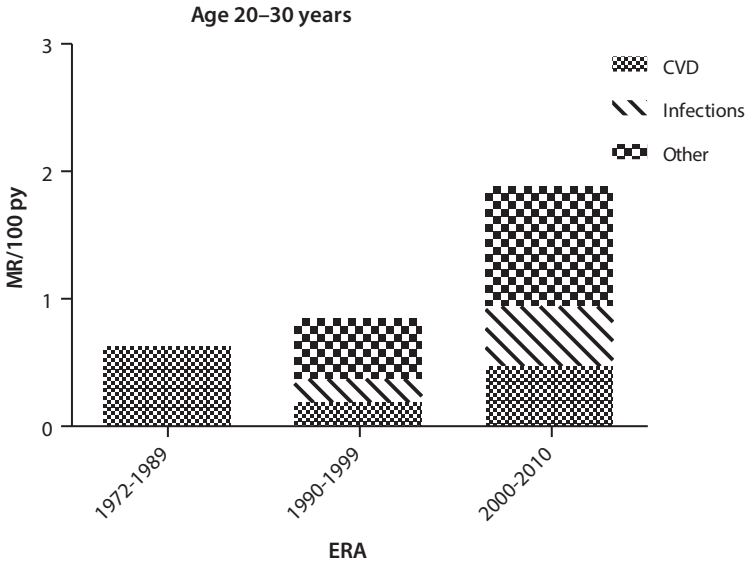

Figure 1b | Mortality rate/100 person years per era in age category 20–30 years

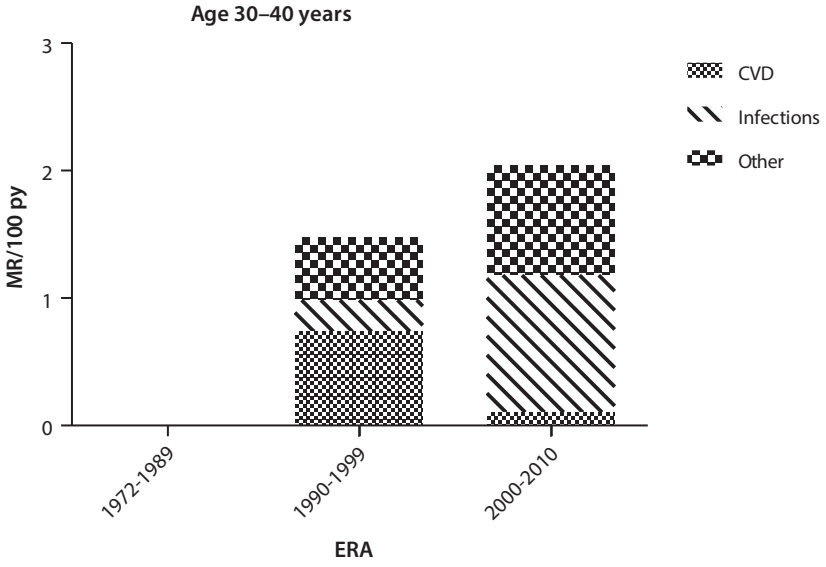

Figure 1c | Mortality rate/100 person years per era in age category 30–40 year

Table 3 | Risk of death for overall, cardiovascular and infectious mortality in the time period 1990–1999 and 2000–2010 compared to mortality in the period 1972–1989

	1990–1999 HR (95% CI, p value)	2000–2010 HR (95% CI, p value)
All causes of death		
– unadjusted	0.48 (0.28–0.81, p = 0.006)	0.79 (0.50–1.26, p = 0.3)
– adjusted for all causes of death general population	0.50 (0.29–0.86, p = 0.01)	0.75 (0.47–1.20, p = 0.2)
Cardiovascular mortality		
– unadjusted	0.30 (0.12–0.77, p = 0.01)	0.21 (0.07–0.61, p = 0.004)
– adjusted for cardiovascular mortality general population	0.26 (0.10–0.66, p = 0.005)	0.09 (0.02–0.45, p = 0.003)
Infectious mortality		
– unadjusted	0.43 (0.15–1.27, p = 0.1)	1.59 (0.72–3.52, p = 0.3)
– adjusted for infectious mortality general population	0.59 (0.19–1.86, p = 0.4)	2.12 (0.88–5.11, p = 0.09)

After adjustment for the expected infectious background mortality, there was a borderline significant trend suggesting an increased risk of death by infections in the last decade 2000–10 when compared with 1972–89 (HR: 2.12, 95% CI: 0.88–5.11, P = 0.09; Table 3). The trend was, however, statistically significant when we compared infectious mortality in 2000–10 with that in 1990–99: the risk of death from infections in the last decade was more than thrice the risk in 1990–99 (HR: 3.22, 95% CI: 1.16–8.99, P = 0.03).

DISCUSSION

In contrast to our expectations, we found a substantial shift from cardiovascular disease to non-cardiovascular disease as the cause of death over the last 10 years in a long-term nationwide follow-up study of patients with pediatric CKD. This occurred while the overall mortality had stabilized over time.

This study is unique in its length of follow-up of patients who started RRT in childhood. Our specific interest in the long-term follow-up of young patients unfortunately hampers the comparison with registry data that are usually presented for overall groups or older age categories with a relatively short follow-up. In addition, time may have affected mortality and causes of death in our cohort in three different fashions. First, there may be an effect of calendar time, as both mortality and causes of death may have changed over time among RRT patients as well as within the general population. Time has also led to a selection of survivors in our cohort and finally, our patients have grown older. We will discuss our results with respect to cardiovascular and infectious death in comparison with other studies, taking these three time dimensions into consideration.

Cardiovascular mortality

Trends over calendar time

As cardiovascular disease turned out to be the most important cause of death in young end stage renal disease (ESRD) patients during the 1990s, several authors have highlighted the huge impact of ESRD and RRT on cardiovascular integrity and function. [1;6–10] Yet, there are more recent data that confirm a trend of infections gradually replacing cardiovascular disease as the most important cause of death over the last decade. The United States Renal Data System (USRDS) data show a declining burden of cardiovascular mortality among the dialysis patients of all ages over the last years (MR 120/1000 per py) in 2001 to (MR 83/1000 py in 2008) [11] without changes in other causes of death over time (MR 100/1000 py in 1998, 2001 and 2008). [12] This trend was similar in patients, aged 20–44 years, with a cardiovascular MR declining from 40.5/1000 py in 2001 to 31.3/1000 py in 2008. [11] Australian and New Zealand Dialysis and Transplantation Registry (ANZDATA) also showed decreasing cardiovascular MRs for all dialysis patients (MR 9.0/100 py in 1992 to 6.4/100 py in 2005), but not among the younger patients aged 35–54 years. [13] In our study, among patients who started RRT at very young age, the decline in cardiovascular deaths over time was far more pronounced than in both the USRDS and ANZDATA studies. This difference may partially be explained by the lack of patients with diabetes mellitus in our cohort, whereas the prevalence of this disease in the RRT population with adult onset of RRT has significantly increased according to both the USRDS and ANZDATA over time. According to the USRDS data, the prevalence of diabetes mellitus as primary disease in the specific age group of our patients increased from 32.5 in 1996 to 42% in 2005, whereas the percentage of diabetes patients aged <55 years in the ANZDATA database even doubled over time from 21.9 in 1992 to 43.3% in 2005. [13;14] The absence of increase in cardiovascular deaths in ANZDATA cohort over time with such a concomitant substantial increase in the proportion of diabetic patients with a related severe cardiovascular burden also indicates a change in cardiovascular outcome in dialysis patients.

A possible explanation for the trend of decreased cardiovascular mortality over the last decade could be an increased awareness of the burden of cardiovascular disease in renal patients among physicians and those that may have resulted in better treatment and consequently better survival. If this would be true for our patients, it would also mean that a more aggressive treatment of cardiovascular disease and the prevention of risk factors may be beneficial even in patients who are already on dialysis or living with a functioning graft for a long time. Previous studies have shown that optimized treatment for cardiovascular comorbidity, for example, with Angiotensin-converting-enzyme inhibitors, β-blockers and angiotensin receptor blockers in patients receiving hemodialysis may indeed induce a reduction in both left ventricular hypertrophy and hypertension. [15;16]

The decline in cardiovascular death in our population partly reflects the trend in the western general population. However, according to the MRR, the decline in our RRT patients was much more pronounced than in the general population.

Long-term follow-up and ageing

Long-term outcome data on patients with ESRD are sparse. Most studies exist on transplanted patients. Previous studies in transplanted patients showed a decrease in cardiovascular death at

longer follow-up. [17;18] The USRDS data have been analysed for all-cause, cardiovascular and infectious mortality in patients who received their first transplant at <21 years of age, between 1983 and 2006, and with a follow-up until 2006. [17] This study showed a significant decrease in cardiovascular mortality in young transplant recipients over time. [17;18] The risk of all-cause death decreased yearly by 1% after the end of the first year of the first transplant. This decrease in risk was most pronounced for cardiovascular death (16% per year) after the end of the first year of the first transplant. [17] Using the same data, Meier-Kriesche *et al*. showed a progressive decrease in cardiovascular death rates in transplant recipients >18 years by renal transplant vintage. The MR decreased from 20.8/1000 py 0–3 months after transplantation to 2.8/1000 py 60+ months after transplantation. [18] These findings suggest that transplantation may halt or even reverse the progression of cardiovascular disease. Most of our patients were transplanted, so this certainly will have contributed to a decrease in cardiovascular death in our study. However, we found the same trend in reduction of cardiovascular death among dialysis patients and therefore transplantation cannot be solely responsible for the reduction of cardiovascular death. Moreover, the prevalence of risk factors for cardiovascular death, such as increased vascular stiffness, left ventricular hypertrophy and aortic valve calcification, was high among our patients in 1999, despite the fact that most of them had a long-time lasting functioning graft at that time.

In 2010, all our patients were between 30 and 50 years old. In line with what can be expected in ageing patients, the overall mortality increased over the last decade. However in contrast to that, the cardiovascular disease induced MR decreased with advancing age over the last decade. This could of course have been the result of a selection process and hence of a survivor bias; the sickest patients with cardiovascular comorbidity may have died already before 2000 of cardiovascular disease, leaving the strongest patients for the observation period after 1999. However, as mentioned before, among these survivors, there was a high prevalence of risk factors for cardiac death in 1999. [2] Furthermore, this trend was only observed over the last decade, whereas cardiovascular mortality did increase with age in our patients, in line with the general population between 1990 and 1999.

Infectious mortality

Trends over calendar time

We found a trend in infectious mortality in three different time periods that suggests an increased risk of death by infections in 2000–10 when compared with 1972–89 and 1990–99.

Infections have for a long time been found to be the second cause of death in patients with ESRD. [12] In line with our data, McDonald and Craig [3] showed a decrease of infectious mortality in patients with pediatric onset of ESRD from 39 between 1963 and 1972 to 16% between 1993 and 2002.

In contrast to our findings, the USRDS data showed a decline of infectious mortality between 1989 and 2010 in ESRD patients, aged 20–44 years. This was accompanied by a similar decline in overall mortality. [22] At the same time, there are data that confirm a more recent tendency towards increase of life-threatening infections in patients with ESRD. The USRDS showed a significant increase in hospitalization due to infection in dialysis patients from 1993 to 2005, [19] as well as in transplanted patients between 1991 and 1998. [20] The latter may be caused by a more intensive anti-rejection

therapy of the last two decades, leading to a more impaired immunity including defective phagocytic function of granulocytes. [21] According to the UK Renal Registry, the number of deaths caused by infections in all patients on RRT has stabilized around 20% between 2000 and 2010. In contrast, the percentage of cardiac deaths decreased from 34 to 22% in this period. [22] The USRDS MRs by infection have also stabilized between 1998 and 2007 for both dialysis and transplanted patients. [14] However, all these reports have the limitation of relatively short follow-up periods.

In dialysis patients, the USRDS reported both an increase in catheter-related infections over time and in catheter-related septicaemia and an overall increasing use of catheters between 1998 and 2007. [23;23] In both hemodialysis and peritoneal dialysis patients, catheter-related infections are considered to be the main source of life-threatening infections, leading to peritonitis in peritoneal dialysis and to central venous line-induced septicaemia in hemodialysis.

Our data could not be explained by the trend in the general population, in which infection plays a minor, and over time even a decreasing, role in the cause of death, at least in the western world. [5; 14]

Long-term follow-up and ageing

The USRDS data showed that infectious MR in patients who received their first transplant <21 years of age, between 1983 and 2006 and with a follow-up until 2006, did not change at follow-up, [17] suggesting that the risk was the same in the first year, as in the years thereafter. This implies, that the relative contribution of infectious death has increased over time. Recurrent needle sticks of arteriovenous fistulas or grafts have also been associated with an increased risk of infections. [21] Jean *et al*. [24] found that a high incidence of catheter-related bacteraemia, and bacteraemic catheters were more often observed in patients with longer catheter survival time.

There are no data that support the becoming of age of our patients as a potential factor for an increased risk of fatal infections. Previously, it had been found that, in transplanted patients, very young as well as very old patients were particularly prone to dying of infections. [20] The oldest patient of our cohort was 50 years old in 2010, and very few children have been transplanted at a very young age. This may explain why we found that the risk of infectious death was constant across all age groups.

LIMITATIONS

The establishment of the exact cause of death in patients with a complicated course of disease, as was often the case in our patients, can be difficult. In order to cope with this problem, three observers independently determined the cause of death based on detailed descriptions of all available chart information covering the period around the patient's time of death. After assessment of interobserver variability, consensus was achieved by discussion.

CONCLUSION

In conclusion, we show that there is a substantial shift in causes of death after long-term RRT since childhood. Cardiovascular mortality decreased significantly in the last 10 years compared with the period 1972–99, and infectious mortality increased (although not significantly). A possible reason for the significant decreased risk of cardiovascular mortality could be the awareness of the cardiovascular burden in these patients that urged a strict cardiovascular management of these patients. Physicians should on the other hand be aware of the emerging burden of potentially fatal infections in these patients and take precautions for prevention.

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03

Simultaneous reversal of risk factors for cardiac death and intensified therapy in long-term survivors of pediatric end-stage renal disease over the last 10 years

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ABSTRACT

Background: In an extended long-term follow-up of patients on chronic renal replacement therapy (RRT) since childhood (LERIC study), we observed a substantial reduction in cardiovascular (CV) death over the last decade. In this study, we investigated the contemporaneous changes in risk factors for CV death and cardioprotective therapy.

Methods: The cohort consisted of 140 Dutch patients, who were born before 1979 and started RRT before 15 years of age between 1972 and 1992. We compared the prevalence of various factors in 2000 and 2010 by calculating matched odds ratios ($OR_{matched}$).

Results: Median age of patients was 38.5 years (range 23.2–50.8) in 2010, after a median time on RRT of 28 years. The prevalence of CV risk factors decreased from 41.3% in 2000 to 18.8% in 2010. The $OR_{matched}$ in 2010 compared with 2000 for left ventricular hypertrophy, hypertension and hypercholesterolaemia were 0.26 (95% CI 0.09–0.66), 0.22 (95% CI 0.01–0.59) and 0.04 (95% CI 0.01–0.25), respectively. The rate of nonfatal CV events dropped, although not significantly, from 1.75/100 (95% CI 1.3–2.4) per patient year (py) in 1972–2000 to 0.95/100 (95% CI 0.5–1.7) py in 2000–2010. ACE inhibitors/angiotensin receptor blockers and cholesterol lowering medication were prescribed significantly more often in the period 2000–10 [$OR_{matched}$ = 7.40 (95% CI 2.90–24.10) and 11.5 (95% CI 4.20–43.90)]. Trends were similar among those who survived and those who did not survive the last decade.

Conclusions: We observed a decrease in clinical cardiovascular disease synchronous to intensified antihypertensive and antidyslipidaemic therapy in long-term survivors of pediatric renal failure. This advocates a vigorous cardioprotective management in these patients.

INTRODUCTION

For decades, cardiovascular (CV) disease has been recognized as the major cause of death in patients with end-stage renal disease (ESRD). This accounts especially for young patients. [1-5] Between 1998 and 2000, we conducted a comprehensive study to evaluate the Late Effects of Renal Insufficiency (LERIC) in all Dutch children who had started chronic renal replacement therapy (RRT) between 1972 and 1992 below 15 years of age. In the period before 2000, CV disease had been the most important cause of death both in dialysis and transplant patients, even after a long time period of living with a renal graft. [6] Other studies confirmed the extreme impact of CV disease in young patients with ESRD. [2;7] Among the patients who had survived the LERIC study up to 2000, we found a high prevalence of CV comorbidity, compared with age- and gender-matched controls, reflected by an overall increased mean arterial wall stiffness, left ventricular hypertrophy (LVH) in 40% and by aortic calcifications in 19% of patients. [7;8] In 2002, Oh *et al*. [9] reported similar CV abnormalities in young adults with chronic renal failure since childhood, including a 92% prevalence of calcifying arteriopathy and a significantly increased carotid intima media thickness compared with matched controls.

Given this high prevalence of CV disease among the survivors of our cohort in 2000, we expected CV death to become an even more pronounced problem after 2000, as ageing would become an additional risk factor. To our surprise, however, we found that in the period 2000–10 CV mortality had dramatically decreased when compared with the period 1972–99 [MR 0.22 (95% CI 0.06–0.56) versus 0.67/100 per year (95% CI 0.44–0.98)]. [10] Although other recent studies have also reported a trend towards a decline in CV mortality in patients on RRT over the last years. [6;11;12] the size of the reduction in CV mortality in our study group was unexpected. Based on this finding, we hypothesized that increasing awareness of the CV burden of ESRD in the late nineties may have urged physicians to intensify cardioprotective management to reduce CV risk factors. In this study, we therefore aimed to investigate whether there was a decrease in the prevalence of CV risk factors potentially relating to changes in cardioprotective treatment over the past decade.

METHODS

Study design

The LERIC cohort comprised all Dutch patients who had started chronic RRT between 1972 and 1992 at less than 15 years of age and who were born before 1979. In 1999–2000, the first follow-up study of these 249 patients was conducted. [2;7] In addition, we performed an assessment of CV status including CV risk factors and intermediate outcomes like blood pressure and cardiac abnormalities at ultrasound. Of all 186 patients still alive at that time, 140 participated in this assessment. Participants (N = 140) and nonparticipants (N = 46) were similar in terms of age, disease severity, comorbidity, duration of RRT and therapy characteristics. In this article, we refer to these measurements as the 2000 measurements.

In 2009–2010, an extension of the follow-up study was conducted covering the period from the last chart review in 1999–2000 until the last chart review or the patient's death. These measurements will be referred to as the 2010 measurements. We attempted to localize all emigrated patients. In patients who were alive the day of review, and in patients were lost to follow-up or who had died the day of last seen or death was considered as the end of the observation period for that particular patient. For this study, we obtained permission from the medical ethical committee and informed consent from all patients.

Data collection

In 2000, assessment of cardiac abnormalities by ultrasound included B- and M-mode echo measurements on both the right and the left common carotid artery, according to the guidelines of the American Society of Echocardiography. [13] Left ventricular end-diastolic diameter, interventricular wall thickness during diastole and posterior wall thickness during diastole were measured by the same experienced cardiac sonographer. [8]

In 2000 and 2010, we collected, among others, data on potential risk factors for CV death and CV events. We considered obesity, hypertension, high cholesterol level, smoking habit, LVH and cardioprotective therapy, i.e. antihypertensive medication and cholesterol lowering medication, as potential positive or negative risk factors for CV death. We defined CV events as the occurrence of cerebrovascular accident (CVA), transient ischaemic attack (TIA) or myocardial infarction (MI). All information was derived from the medical charts of the patients. Hypercholesterolemia was defined as: increased total cholesterol levels in combination with increased low-density lipoprotein (LDL) cholesterol levels. Blood pressure was scored as the mean blood pressure of all documented blood pressures over 6 months before the last day of chart review. Among hemodialysis patients, we used the mean of the pre- and postdialysis blood pressures. If no blood pressures were available in this period, the last documented blood pressure within 1 year from the study visit was used. Hypertension was defined as having both a systolic blood pressure ≥140 mmHg and a diastolic blood pressure ≥90 mmHg.

Statistical analysis

The prevalence of CV risk factors and cardioprotective medication was calculated for 2000 and 2010, both for living and deceased patients. To adjust for the fact that the measurements were correlated as they took place within the same individual we calculated matched odds ratios ($OR_{matched}$).

RESULTS

Study population

In 2000, in 140 patients CV risk factors and outcomes were assessed. At that time, their median age was 28.7 years (range 20.6–40.9, Table 1). In 2010, the median total follow-up time from the start of RRT was 27.8 years (range 10.6–38.9). Between 2000 and 2010, out of 140 patients 22 died, two (1.4%) were lost to follow-up, while one patient (0.7%) had avoided medical care since 2007.

Of the 116 patients still alive in 2010, 22 (18.6%) were treated with dialysis and 96 (81.4%) lived on a functioning graft. Of these transplanted patients, 28 (29.2%) received kidneys from a living and 68 (70.8%) from a deceased donor. This treatment distribution was very similar to the one in 2000 (Table 1).

Table 1 | Demographics and cardiovascular assessment LERIC participants in 2000 (*N* = 140)

	N	At onset of observation (2000)
Male (N (%))	140	75 (53.6)
Age in years (median (range))	140	28.7 (20.6–40.9)
History of cardiovascular events* (N (%))	138	57 (41.3)
– Prevalence of only MI, CVA or TIA (N (%))		18 (13.0)
Tx recipients (N (%))	138	108 (78.3)
Systolic blood pressure (mean (5^{th}–95^{th} percentile))	136	130 mmHg (100–170)
Diastolic blood pressure (mean (5^{th}–95^{th} percentile))	136	86 mmHg (64–110)
Pulse pressure (mean (5^{th}–95^{th} percentile))	136	40 mmHg (30–70)
Hypertension** (N (%))	136	36 (26.5)
Systolic hypertension (N (%))	136	42 (30.9)
Left ventricular hypertrophy (N (%))	140	60 (42.9)
Hypercholesterolemia*** (N (%))	136	62 (45.6)
Body Mass Index (mean (5^{th}–95^{th} percentile))	140	23.7 (18.3–33.7)
Smoking (N (%))	137	42 (30.7)
Antihypertensive medication (N (%))	136	77 (56.7)
1–2 antihypertensive medication	136	65 (47.8)
>2 antihypertensive medication	136	12 (8.8)
Cholesterol lowering medication (N (%))	136	17 (12.5)

* Cardiovascular event = cerebrovascular accident (CVA), transient ischemic attack (TIA), myocardial infarction (MI), dyspnoea, orthopnoea, intermittent claudication, angina pectoris and cardiac intervention.

** Hypertension = bloodpressure ≥140/90 mmHg

*** Hypercholesterolemia = increased cholesterol total and increased LDL-cholesterol

Cardiovascular outcomes

Between 2000 and 2010, of the 138 patients 22 (15.9%) patients died after a median follow-up on RRT of 24.0 years (range 10.7–32.3). Only 1 (0.7%) died due to CV disease (CVA), 9 (6.5%) patients died of an infection, 5 (3.6%) patients died due to a malignancy, 6 (4.3%) had another cause of death and for 1 (0.7%) patient the cause of death was unknown. Of the 138 patients, 11 (8.0%) experienced a CV event (MI, CVA or TIA) over the period 2000–10 resulting in an event rate of 0.95/100 py (95% CI 0.5–1.7), which was lower, although not statistically significant, than in the period 1972–2000 (1.75/100 py, 95% CI 1.3–2.4).

Main cardiovascular risk factors

We obtained information on recent echocardiographic data of 114 patients who were alive in 2010 and of 21 deceased patients within 1 year before death. Tables 2 and 3 show the change in CV risk factors and in cardioprotective therapy in the period 2000–10 of patients surviving up until 2010. In 2010, the prevalence of LVH among those survivors was significantly lower than in 2000 [$OR_{matched}$ = 0.26 (95% CI 0.09–0.66), P<0.01]. There was also an important decrease in the prevalence of hypertension [$OR_{matched}$ = 0.22 (95% CI 0.01–0.59), P<0.01] and of hypercholesterolemia [$OR_{matched}$ = 0.04 (95% CI 0.01–0.25), P<0.01] (Table 2). There was no significantly different trend in the prevalence of smoking [$OR_{matched}$ = 0.60 (95% CI 0.18–1.82), P = 0.4]. BMI increased significantly over the last decade (P<0.01) (Table 2). The prevalence of overweight (BMI 25–30) and obesity (BMI>30) increased during the last decade [$OR_{matched}$ = 8.00 (95% CI 1.88–71.8), P = 0.03 and $OR_{matched}$ = 11.00 (95% CI 1.60–467), P = 0.01, respectively; Table 2].

Similar trends were seen in patients who died between 2000 and 2010, with the exception of BMI that did not change in deceased patients (Table 3). Furthermore, trends were similar in dialysis and transplantation patients.

Cardioprotective therapy

Cholesterol-lowering medication was more often prescribed in 2010 compared with 2000 [$OR_{matched}$ = 11.5 (95% CI 4.20–43.9), P<0.01], whereas the increase of the number of patients using antihypertensive medication was borderline significant [$OR_{matched}$ = 2.09 (95% CI 0.98–4.75), P = 0.06 (Table 2)]. The number of antihypertensive drugs per patient increased each year over the last decade, although not statistically significant [Figure 1a; >2 antihypertensive medication $OR_{matched}$ = 2.14 (0.82–6.21), P = 0.2]. The percentage of patients taking ACE inhibitors/ARBs increased significantly from 18.1% in 2000 to 47.3% in 2010 [$OR_{matched}$ = 7.40 (95% CI 2.90–24.1), P < 0.01, (Table 2)].

Table 2a | Change in risk factors for cardiovascular death and use of cardio-protective medication over the period 2000-2010 of patients surviving up until 2010

	2000 assessment (N=116)	2010 assessment (N=116)	Matched odds ratio (95% CI)	Paired T–test (mean change (95%CI))	P-value
Number of transplant recipients (N (%))	98 (84.5)	96 (81.4%)			
Systolic blood pressure (mean ((95% CI))	128 (118–140)	123 (112–130)		5.6 (1.5–9.6)	p<0.01
Diastolic blood pressure (mean (95% CI))	84 (75–90)	78 (73–85)		5.8 (2.5–9.2)	p<0.01
Hypertension* (N (%))	24 (21.2)	6 (5.3)	0.22 (0.01–0.59)		p<0.01
Systolic hypertension (N (%))	30 (27.0)	16 (13.8)	0.44 (0.20–0.93)		p = 0.01
Left ventricular hypertrophy (N (%))	45 (38.8)	24 (21.1)	0.26 (0.09–0.66)		p<0.01
Hypercholesterolemia** (N (%))	49 (42.6)	2 (5.3)	0.04 (0.01–0.25)		p<0.01
Body Mass Index (mean (95% CI))	23.5 (20.8–24.7)	24.7 (21.4–26.6)		1.2 (0.6–1.8)	p<0.01
- Patients with overweight (BMI>25) (N (%))	26 (23.9)	41 (37.6)	8.00 (1.88–71.8)		p = 0.03
- Patients with obesity (BMI>30) (N (%))	0 (0)	11 (10.1)	11.00 (1.60–467)		p = 0.01
Smoking (current) (N (%))	38 (32.8)	31 (29.2)	0.60 (0.18–1.82)		p = 0.4
Antihypertensive medication (N (%))	61 (52.6)	72 (63.7)	2.09 (0.98–4.75)		p = 0.06
– >2 antihypertensive medication	11 (9.5)	19 (16.8)	2.14 (0.82–6.21)		p = 0.2
– ACE-inhibitors/ARBs	21 (18.1)	53 (47.3)	7.40 (2.90–24.1)		p<0.01
Cholesterol lowering medication (N (%))	14 (12.4)	56 (50.0)	11.5 (4.20–43.9)		p<0.01

* Hypertension = systolic blood pressure ≥140 as well as diastolic blood pressure ≥90 mmHg; ** Hypercholesterolemia = increased cholesterol total and increased LDL-cholesterol (in 2010 78 missing values)

Table 2b | Development of cardiovascular risk factors over the period 2000-2010 in patients who died in the period 2000–2010

	2000 assessment (*N* = 22)	2010 assessment (within one year before death) (*N* = 22)	Matched odds ratio (95% CI)	Paired T-test (mean change (95% CI))	P-value
Number of transplant recipients (N (%))	10 (45.5)	9 (40.9)			
Systolic blood pressure (mean (95% CI))	143 (128–160)	130 (117–150)		10.4 (0.8–21.7)	p = 0.07
Diastolic blood pressure (mean (95% CI))	97 (88–105)	83 (74–98)		13.4 (3.5–23.4)	p = 0.01
Hypertension* (N (%))	12 (57.1)	3 (15.8)	0.25 (0.01–2.53)		p = 0.2
Systolic hypertension (N (%))	12 (57.1)	4 (21.1)	0.33 (0.01–4.15)		p = 0.2
Left ventricular hypertrophy (N (%))	15 (71.4)	10 (47.6)	0.40 (0.04–2.44)		p = 0.2
Hypercholesterolemia** (N (%))	13 (61.9)	No data	No data		
Body Mass Index (mean (95% CI))	23.6 (21.5–25.7)	23.2 (20.8–25.6)		1.0 (0.8–2.5)	p = 0.30
- Patients with overweight (BMI>25) (N (%))	7 (31.8)	4 (18.2)	0.50 (0.01–9.60)		p = 0.3
- Patients with obesity (BMI>30) (N (%))	0 (0)	1 (4.5)	1.00 (0.01–78.1)		p = 1.0
Smoking (current) (N (%))	4 (18.2)	1 (6.7)	0.25 (0.00–2.42)		p = 0.1
Antihypertensive medication (N (%))	16 (76.2)	17 (89.5)	3.00 (0.24–158)		p = 0.6
– >2 antihypertensive medication	1 (4.8)	5 (26.3)	4.00 (0.40–196)		p = 0.3
– ACE-inhibitors/ARBs	6 (27.3)	10 (52.6)	6.00 (0.73–277)		p = 0.4
Cholesterol lowering medication (N (%))	2 (9.5)	2 (10.0)	1.00 (0.01–78.1)		p = 1.0

* Hypertension = blood pressure ≥140/90 mmHg; ** Hypercholesterolemia = increased cholesterol total and increased LDL-cholesterol (in 2010 missing values)

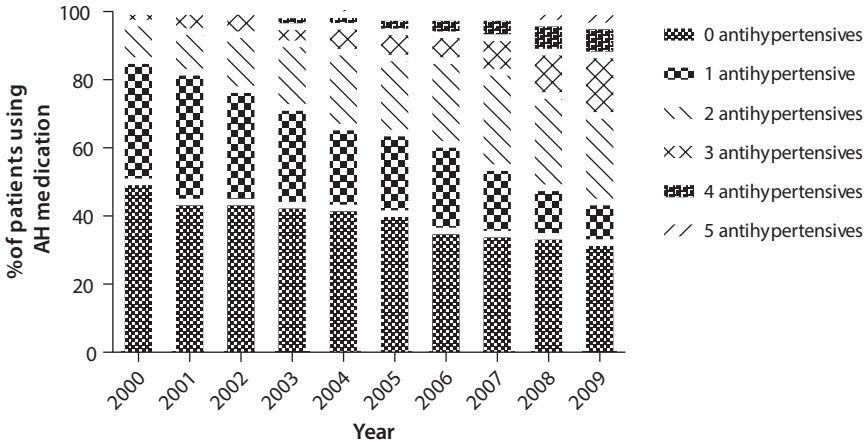

Figure 1a | Number of antihypertensive agents used per patient in each calendar year by the 116 patients still alive in 2010

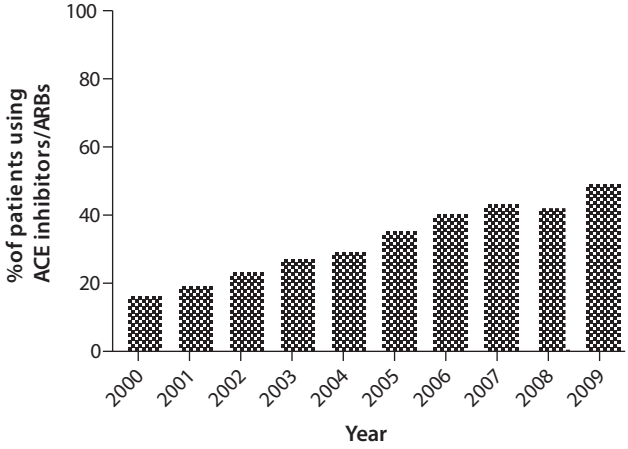

Figure 1b | Percentage of patients using ACE-inhibitors/Angiotensin Receptor Blockers per year in the period 2000–2009 of the 116 patients still alive in 2010

DISCUSSION

In this 10 years extension of a long-term follow-up study in patients with ESRD since childhood, we found a significant decrease in the prevalence of LVH, hypertension and hypercholesterolemia over the last decade. We also found a trend towards a decrease in nonfatal CV events. CVA, TIA and MI decreased over the period 2000–10, compared with 1972–99. This was consistent with the significant decrease in CV death over the same period on which we previously reported. [10] We found a simultaneous significant increase in both cholesterol-lowering medication and antihypertensive medication, especially of ACE inhibitors/ARBs, between 2000 and 2010.

Recent registry reports show that CV disease remains the most important cause of premature death in patients with ESRD. This accounts for all age groups. [1;6] Among dialysis patients over the last decade, 23–30% suffered from ischaemic heart disease, according to the UK Renal Registry data and the USRDS. [14;15] The USRDS reported unchanged rates of acute myocardial infarction (AMI), TIA and CVA between 2000 and 2010. [11] Yet, recent studies also confirm a trend towards a decrease in CV casualties over the last decade and a concordant intensified management of CV disease in patients on RRT. According to the USRDS data, the rate of sudden cardiac death among hemodialysis patients fell from 70/1000 to 50/1000 per year between 2000 and 2010. [11] The same trend was found in peritoneal dialysis patients. The data also show a significant decline of fatal AMI events among all dialysis patients over this period. [11] At the same time, both the use of antihypertensive medication and statins had increased over the last 3 years and most casualties were found in patients receiving no cardioprotective therapy. [11]

Our findings imply that intensified cardioprotective therapy and more optimal control of hypertension, especially by ACE-inhibitors or angiotensin receptor blockers may be effective in reducing LVH, cardiac events and cardiac death even after more than 20 years of RRT. In the late nineties, LVH was recognized as an important and strong independent determinant for decreased survival in ESRD patients and was shown to progress over time in most patients. [16] At the same time, LVH was considered to be more or less irreversible beyond the first years of hemodialysis. [16]

More recent studies however, although often small-sized and uncontrolled, confirm our findings that adequate cardioprotective therapy may indeed lead to reversal of cardiac abnormalities, such as LVH, in ESRD patients, as we found in our study. Optimized heart failure therapy with β-blockers, ACE inhibitors and ARBs, in combination with epoetin β to reach Hb targets has been shown to lead to a significant reduction of LVH, also among HD patients. [17-19] The efficacy of ACE inhibitors/ARBs in reducing LVH in dialysis patients has been confirmed in a systematic review. [19] Ibernon *et al*. [20] found a significant reduction in LVH in adult renal transplant recipients 2 years after transplantation that was closely related to adequate blood pressure control. Ardeleanu *et al*. [21] showed in a small study that a significant reduction in LVH in hemodialysis patients was possible even after a follow-up of 10 years. Other studies, with a follow-up of 3–5 years, showed that ACE inhibitors and use of ARBs have a role in preventing fatal and nonfatal CV events in the general population. [22-25]

The direct impact of the use of ACE inhibitors and angiotensin receptor blockers on CV outcome in dialysis patients has been a matter of debate for a long time. Very recently, a systematic review confirmed the efficacy of angiotensin receptor blockers in reducing LVH in dialysis patients. [26] In transplanted patients, ACE-inhibitors have been found effective in reducing left ventricular mass in a randomized trial. [27] These findings are in line with data from the ESCAPE study in children with CKD, in which the use of ACE-inhibitors was associated with a reduction in the left ventricular mass index as well as with improvement of the myocardial function independent of the LVMI reduction. [28]

These studies and our findings are in contrast with most registry outcomes. Noncompliance with guideline recommendations for prevention of CV disease may be an important reason for the ongoing burden of cardiac disease in RRT patients. In an analysis of the data of European Society of Nephrology/European Renal Association-European Dialysis and Transplant Association (ESPN/ERA-

EDTA) database on the prevalence of hypertension in children on RRT, uncontrolled hypertension was found in 45.5% of all hemodialysis patients and in 35.5% of all PD patients. [29] According to the NAPRTCS data, even nearly 57% of all dialysis patients had uncontrolled hypertension. [30]

In adults, in a large quality intervention study, the MAURO study, only 45% of renal transplanted nonproteinuric patients met the targets for blood pressure control at baseline of the study, despite the fact that 95% received antihypertensive medication. For proteinuric and diabetic patients, normal blood pressures were found in only 14 and 18%, respectively. [31] In our study, using similar criteria, only 6.5% of the patients had hypertension. A better awareness among physicians of this problem and of the potential efficacy of cardioprotective therapy even in patients with a long-lasting burden of CV disease is essential to improve the overall outcome of patients with ESRD.

LIMITATIONS

Although this study is unique in its length of follow-up of patients who started RRT in childhood, our specific interest in long-term follow-up of young patients unfortunately hampers the comparison with registry data, as the latter are usually presented for overall groups or older age categories with and a relatively short follow-up.

In 2000, extra CV data could only be collected in 140 out of 186 patients. However, participants and nonparticipants were similar in terms of disease severity, CV risk factors, duration of RRT and therapy characteristics. [8] In 2000 echocardiography, to investigate LVH, was performed by one and the same experienced cardiac sonographer. [8] In 2010, however, we collected information on LVH from echocardiographic data assessed at the local sites, which may have influenced the detection of LVH. Changes in therapeutic strategies tackling CKD-metabolic bone disease or renal anaemia may also have contributed to the observed effect. Unfortunately, we were not able to collect reliable data on calcium exposure or on haemoglobin, PTH levels and vitamin D exposure; hence, we were not able to detect the influence of these changes in management on outcomes. Also changes in immunosuppressive treatment may have influenced CV outcome. However, we found no significant change in prescription of immunosuppressive therapy over the last 20 years with respect to drugs with an adverse CV profile, e.g. calcineurine inhibitors and steroids. Most patients who were transplanted before 2000 remained on the same regime between 2000 and 2010. Those patients who were transplanted after 2000 all received calcineurine inhibitors, contrary to patients with grafts from the seventies and early eighties only have been relative CV friendly regime with low dose prednisone and azathioprine.

CONCLUSION

We found an unexpected reduction in CV events and risk factors for CV death in patients with pediatric onset of RRT over the last 10 years when compared with the period up to 2000. This was associated with a significant increase in cardioprotective therapy, even after more than 28 years of

RRT. Although a causal relationship between the two cannot be inferred from this study, our data strongly suggest that a strict blood pressure control, especially by ACE-inhibitors or angiotensin receptor blockers and reduction in dyslipidaemia may be effective in reducing cardiac threat in patients with ESRD even after a long lasting burden of CV disease.

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Part II

Infections and malignancies

04

Mortality from infections and malignancies in patients treated with renal replacement therapy: data from the ERA-EDTA Registry

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ABSTRACT

Background: Infections and malignancies are the most common non-cardiovascular causes of death in patients on chronic renal replacement therapy (RRT). Here, we aimed to quantify the mortality risk attributed to infections and malignancies in dialysis patients and kidney transplant recipients as compared with the general population by age group and sex.

Methods: We followed 168,156 patients included in the ERA-EDTA Registry who started RRT in 1993-2007 until January 1st 2012. Age- and cause-specific mortality rates per 1,000 person years and mortality rate ratios compared with the European general population (WHO) were calculated. To identify risk factors we used Cox regression.

Results: Infection-related mortality was increased 82-fold in dialysis patients and 32-fold in transplant recipients compared with the general population. Female sex, diabetes, cancer and multisystem disease were associated with an increased risk of infection-related mortality. The sex difference was most pronounced for dialysis patients aged 0-39 years, with women having a 32% (adjusted HR 1.32 95%CI 1.09–1.60) higher risk of infection related mortality than men. Mortality from malignancies was 2.9 times higher in dialysis patients and 1.7 times higher in transplant recipients than in the general population. Cancer and multisystem disease as primary causes of end-stage renal disease were associated with higher mortality from malignancies.

Conclusion: Infection-related mortality is highly increased in dialysis and kidney transplant patients, while the risk of malignancy-related death is moderately increased. Young women on dialysis may deserve special attention because of their high excess risk of infection-related mortality. Further research into the mechanisms, prevention and optimal treatment of infections in this vulnerable population is required.

INTRODUCTION

Death rates in patients treated with chronic renal replacement therapy (RRT) are substantially higher than in the general population. [1] Cardiovascular diseases have been recognized as the main cause of death in both dialysis and transplanted patients. Nevertheless, most patients die from non-cardiovascular causes, with infections and cancer being the most common ones. [1]

As compared with the general population, dialysis patients have been reported to have an up to 100-fold increase in age-adjusted risk of mortality due to infections associated with sepsis, as well as a 10-fold increased risk of death due to pulmonary infections. These risks were 20 and 2-fold increased respectively among transplant recipients. [2;3] Furthermore, many studies have shown that transplanted patients have a 3 to 4-fold increased risk of fatal and especially non-fatal cancer, while in dialysis patients the risk of non-fatal cancer is only marginally increased. [4;5]

The UK Renal Registry data have shown that over the last decade there has been an important decrease in cardiovascular mortality (from 34% in 2000 to 22% in 2011), [6] but similar trends have not been observed for death due to infections and malignancies (stable around 18 and 10% respectively). [6;7] In a previous study we found an increased mortality due to non-cardiovascular causes in women treated with chronic dialysis treatment compared with men, especially among women treated with peritoneal dialysis. [7;8] We therefore hypothesized that infection rates might be higher in females than in males. However, to date, information on the interaction of sex, age and primary renal disease with infection- and malignancy-related mortality in RRT patients is lacking.

In this study we therefore aimed (1) to quantify the occurrence of the most common non-cardiovascular causes of death, infections and malignancies, in patients treated with dialysis or living with a kidney transplant, (2) to compare rates of these fatal events with those in the general population and (3) to assess the role of age, sex and primary renal disease as determinants of mortality due to infections and malignancies in these patients.

SUBJECTS AND METHODS

Data collection and study population

The European Renal Association – European Dialysis and Transplantation Association (ERA-EDTA) Registry collects data on RRT patients via national and regional renal registries in Europe. These data include the date of birth, sex, primary renal disease, date of start of first RRT for end-stage renal disease, changes in treatment modality, and date and cause of death. We included data from registries providing sufficiently complete data on cause of death, i.e. less than 25% missing or unknown. Patients starting RRT between January 1st 1993 and December 31st 2007 were followed until January 1st 2012. In total, 20 registries participated in the study, including the national registries of Austria, Denmark, Finland, Greece, Iceland, The Netherlands, Norway and Sweden, and the regional registries of Dutch- and French-speaking Belgium, Calabria (Italy), Andalusia (Spain), Aragon (Spain), Asturias (Spain), Basque Country (Spain), Catalonia (Spain), Castilla-la Mancha (Spain), Canary Islands (Spain), Extremadura (Spain) and Scotland (United Kingdom). All renal registries had 100%

coverage of the population in their corresponding region. RRT patients were defined as dialysis patients (hemodialysis and peritoneal dialysis patients combined) and renal transplant recipients. Some patients who were transplanted during the study period also had periods on dialysis, either before or after the kidney transplantation, and they fell into both categories. We defined two non-cardiovascular mortality groups using the ERA-EDTA coding system for causes of death. [48] Death due to infections included codes 31–39, 41, 42 and 100–102, whereas death due to malignancies comprised codes 66–68. Of the infection-related codes, number 35 represented septicaemia and 31–33 and 36 pulmonary infections. We did not evaluate other specific causes of non-cardiovascular mortality. Primary renal disease was categorized as glomerulonephritis / clerosis, pyelonephritis, polycystic kidneys adult type, diabetes mellitus, hypertension / renal vascular disease, multisystem disease, cancer, miscellaneous and unknown / missing. The category cancer included those primary renal diseases coded as kidney tumour (95) or myelomatosis / light chain deposit disease (82), while the category multisystem disease included granulomatosis with polyangiitis (Wegener's granulomatosis, 74), renal vascular disease due to polyarteritis (73), glomerulonephritis related to liver cirrhosis (76), cryoglobulinaemic glomerulonephritis (78), amyloid (83), lupus erythematosus (84), Henoch-Schönlein purpura (85), Goodpasture's syndrome (86), systemic sclerosis (scleroderma; 87) and other multisystem diseases (89).

As a reference, mortality data from the general population of the same 20 countries and regions for the same period were obtained from the World Health Organization (WHO) (www.who.int). WHO provides cause-specific mortality data, classified by International Statistical Classification of Diseases, 10th Revision (ICD-10) codes, stratified by 5-year age categories and sex. [10] Infections were classified according to codes A00-B99, J10-J11 and J12-J18, while malignancies were classified according to codes C00-D48. [10]

Data analyses

Patients were classified by age (into 10-year age categories) and sex. For dialysis patients, the person-time on dialysis was calculated using both naive and post-transplant dialysis periods. As there were no differences in mortality between these types of dialysis periods, we report results for total time on dialysis only. For dialysis patients, follow-up time was measured until recovery of renal function, kidney transplantation, loss to follow-up and end of the follow-up period, whichever came first. For transplanted patients we used the person-time of the first functioning graft; the event studied was death while living with a kidney transplant or death within 60 days after return to dialysis. The follow-up time for these patients was measured until the end of the first 60 days on dialysis, loss to follow-up or end of the follow-up period.

Age-specific mortality rates (per 1,000 person-years; py) were calculated by dividing the total number of deaths due to infections or malignancies by the total person-time lived in that age stratum, according to treatment modality (in the RRT population) and sex (in both the RRT population and the general population). Excess mortality risk was calculated in two ways. Firstly, Mortality Rate Ratios (MRRs), adjusted for 5-year age groups and sex, were calculated to compare mortality in RRT patients with that in the general population. Confidence intervals were calculated according to the Poisson Exact method using MedCalc Statistical Software version 13.1.1. We also calculated the MRRs for

malignancy as cause of death excluding patients with malignancies as cause of primary renal disease (ERA-EDTA code 95). For the calculation of MRRs we used direct standardisation. The mortality rates in both transplant recipients and dialysis patients were weighted by the age distribution of the general population. Secondly, to study the effect of primary renal disease, and study the effects of age and gender in more detail, we performed survival analysis among the dialysis patients and transplant recipients. We performed Cox regression models to calculate adjusted hazard ratios (HRs) with 95% Confidence Intervals (95% CI). In these Cox regression analysis we applied four main groups of primary renal disease; glomerulonephritis, diabetes mellitus, cancer and multisystem disease. Patients in other primary renal disease groups were included in the analyses; however, their results are not presented.

RESULTS

Study population

Between 1993 and 2007, 168,156 patients started RRT in the included registries (Table 1). Median age at start was 66.0 years and 61.2% of the patients were men. Of all patients, 82.0% started RRT with hemodialysis, 16.0% with peritoneal dialysis and 2.1% received a pre-emptive renal transplant.

The median follow-up time in dialysis patients was 2.4 (interquartile range [IQR] 0.9–4.7) years. Median follow-up time for the 44,540 patients who received a transplant was 5.2 years (IQR 2.4–8.8).

A total of 112,653 patients died; 36.4% due to cardiovascular causes and 48.2% due to non-cardiovascular causes. In 15.5% of the patients the cause of death was unknown. Of the non-cardiovascular deaths, 18,273 (16.2% of the total number of deceased patients) died from infections and 8,744 (7.8%) from malignancies. Other non-cardiovascular causes accounted for 24.2% of deaths of which haemorrhages (2.7%), cachexia (3.2%) and withdrawal (7.9%) were the most common causes. The general population in the corresponding subgroups of age- and sex in the different countries covered 1,5 billion person years (py) over the observation period and 49.2% were men. Of the general population 9.6% died during follow-up, and among the deceased persons 39.8% died of cardiovascular causes, 58.1% died of non-cardiovascular causes and 2.1% from unknown causes. Of all deaths, 3.6% were due to infections and 25.8% due to malignancies.

Infection-related mortality

Dialysis patients

Among dialysis patients, the mortality rate from infections was 30.5 per 1,000 py (95%CI 30.0–31.0, Table 2). Of these, the mortality rates for septicaemia, pulmonary infections and other infections were 20.2, 7.0 and 4.4 per 1,000 py, respectively. Among patients in whom the causative agent was known (87.4%), 95.9% died from bacterial infections, 2.6% from viral infections and 1.4% from other types of infections (fungal, protozoal or parasitic).

Table 1 | Baseline characteristics of patients starting renal replacement therapy according to age categories

Characteristics	All (n = 168 156)	0–19 years	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years	>80 years
Age, median (IQR), years	66.0 (53.1–74.4)	14.0 (7.6–17.5)	25.9 (23.2–28.1)	35.6 (33.0–37.9)	45.8 (43.1–48.0)	55.6 (52.9–57.8)	65.6 (63.0–67.9)	74.7 (72.4–77.1.2)	82.7 (81.2–84.9)
– Sex (%)									
– Men	61.2	58.8	61.8	62.3	62.8	64.0	62.0	59.5	57.9
Follow-up, median (IQR), years									
– All patients	3.7 (1.3–6.8)	8.3 (4.6–12.6)	8.8 (5.1–12.8)	7.7 (4.4–11.7)	6.6 (3.7–10.6)	5.0 (2.5–8.6)	3.5 (1.3–6.1)	2.4 (0.8–4.4)	1.5 (0.5–3.3)
– Dialysis patients	2.4 (0.9–4.7)	1.5 (0.6–3.6)	1.7 (0.7–3.5)	1.6 (0.7–3.1)	2.2 (0.9–4.2)	2.3 (1.0–4.2)	2.4 (1.0–4.4)	1.8 (0.8–3.4)	1.7 (0.6–3.4)
– Transplant recipients	5.2 (2.4–8.8)	8.2 (5.7–11.1)	7.7 (5.1–10.6)	7.3 (4.8–9.9)	6.6 (4.2–9.5)	6.0 (3.7–8.8)	5.3 (3.2–7.9)	4.8 (2.8–6.5)	4.4 (0.1–9.2)

Table 2 | Mortality rates from infections and malignancies per 1,000 person-years in the European RRT population and in the general population, segregated by age and sex (men, M; women, W)

Characteristic		All	0–19 years	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years	>80 years
Infection-related mortality										
– Dialysis patients										
	M	29.5	9.3	5.3	7.1	12.5	18.5	28.5	40.3	54.0
	W	32.0	5.5	5.6	11.6	12.7	19.5	31.9	41.7	52.5
	Total	*30.4*	7.6	5.4	8.8	12.5	18.9	29.8	40.9	53.4
– Transplant recipients										
	M	6.7	2.2	2.1	1.8	3.0	5.9	11.0	18.9	38.7
	W	6.9	3.0	1.6	3.6	3.9	6.5	10.6	14.7	34.9
	Total	*6.8*	2.6	1.9	2.5	3.4	6.2	10.9	17.4	37.4
– General population										
	M	0.3	0.02	0.01	0.06	0.1	0.1	0.3	1.2	6.5
	W	0.4	0.01	0.01	0.02	0.04	0.06	0.2	0.7	5.3
	Total	*0.4*	0.02	0.01	0.04	0.07	0.1	0.2	1.0	5.7
Malignancy-related mortality										
– Dialysis patients										
	M	15.9	1.2	1.2	1.9	4.1	10.3	17.2	22.2	26.1
	W	11.2	3.9	0.9	1.9	5.5	9.2	12.4	14.1	14.0
	Total	*14.0*	2.3	1.1	1.9	4.6	9.9	15.3	18.8	20.9
– Transplant recipients										
	M	5.1	0.9	0.6	0.9	2.3	4.8	8.8	13.8	29.8
	W	3.7	0.8	0.5	1.2	1.6	4.0	5.7	9.4	17.5
	Total	*4.6*	0.9	0.5	1.0	2.1	4.5	7.6	12.2	25.6
– General population										
	M	2.8	0.04	0.07	0.2	0.7	2.6	7.0	15.0	27.9
	W	2.1	0.03	0.06	0.2	0.7	1.9	3.9	7.6	14.5
	Total	*2.5*	0.04	0.06	0.2	0.7	2.3	5.4	10.7	19.0

Abbreviations: y = years; M = men; W = women

Mortality rates due to infections were much higher than in the general population and increased in proportion with aging. Nevertheless, when studying mortality rates stratified by age category, the dialysis patients aged 0–19 years were at higher risk of infection-related death (7.6 per 1,000 py, 95% CI 4.8–11.5) than the oldest members of the general population >80 ears (5.7 per 1,000 py).

After adjustment for age and sex, the infection-related mortality in dialysis patients was highly increased, compared with the general population, with an adjusted MRR of 81.6 (95% CI 79.6–83.6). In contrast to the absolute mortality rates, the age-specific MRRs of infection-related death strongly decreased with age (Figure 1A).

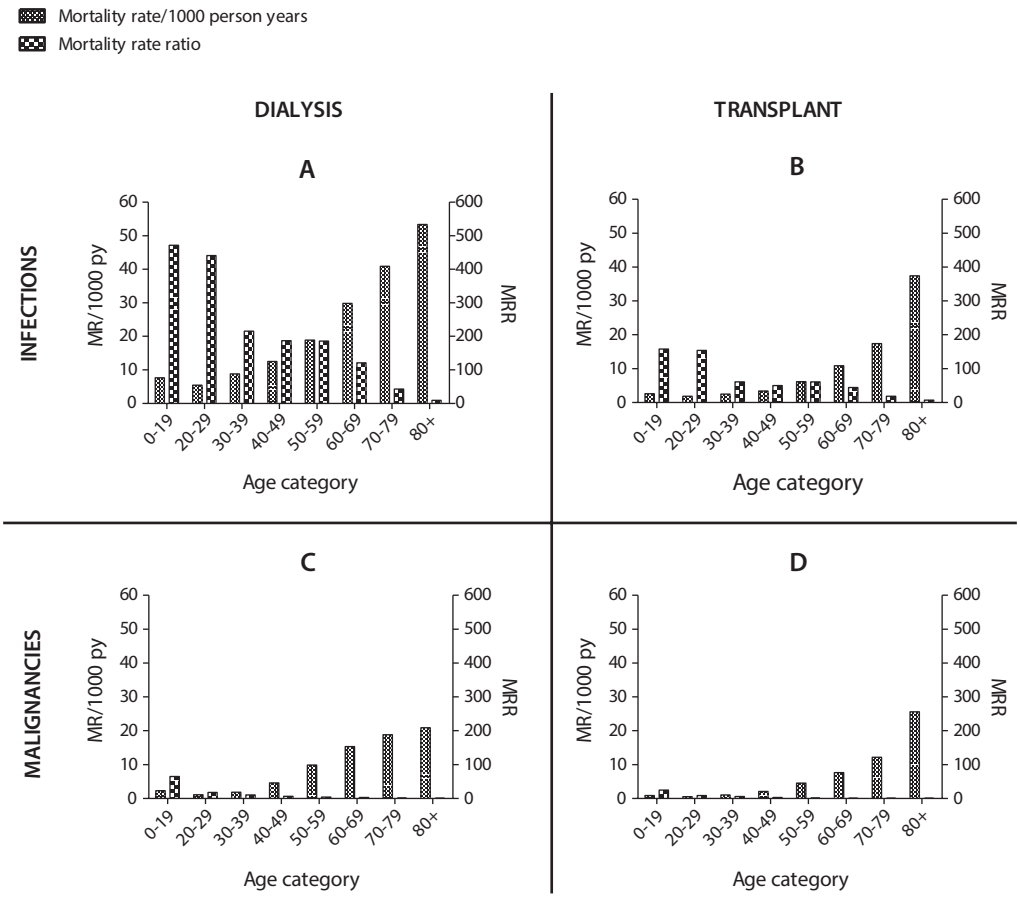

Figure 1 | Differences in mortality rate/1000 person years and mortality rate ratios for infections (**A+B**) and malignancies (**C+D**) among dialysis patients (**A+C**) and transplant recipients (**B+D**). Mortality rate/1000 person years is shown on the left scale and increases with age. Mortality rate ratio is shown on the right scale and decreases with age.

Table 3 | Mortality rate ratios of cause-specific non-cardiovascular mortality by sex and per age category

Characteristic	All	0–19 years	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years	>80 years
Infection-related mortality									
– Dialysis patients									
M adj	67.7	527.3	366.3	122.6	129.3	133.4	88.5	32.8	8.3
W adj	98.8	371.3	565.2	490.2	342.0	302.0	181.2	55.8	10.0
Age- and sex standardized MRR	81.6								
– Transplant recipients									
M adj	25.3	127.6	143.9	31.6	31.9	42.8	34.1	15.4	5.9
W adj	39.1	204.1	156.2	151.6	105.5	100.8	60.4	19.6	6.6
Age- and sex standardized MRR	31.5								
Malignancy-related mortality									
– Dialysis patients									
M adj	2.5 *(1.9)**	28.8	17.9	11.3	5.7	4.0	2.5	1.5	0.9
W adj	3.5 *(2.4)**	125.6	16.4	9.3	7.3	4.7	3.1	1.9	1.0
Age- and sex standardized MRR	2.9 *(2.2)**								
- Transplant recipients									
M adj	1.5 *(1.2)**	23.2	8.3	5.6	3.3	1.9	1.3	0.9	1.0
W adj	1.9 *(1.3)**	26.4	8.5	5.5	2.2	2.1	1.5	1.2	1.2
Age- and sex standardized MRR	1.7 *(1.3)**								

* ( )*The mortality rate ratios (MRR) of mortality from malignancies if we excluded malignancies as cause of primary renal disease;*
Abbreviations: y = years; M = men; W = women; adj = adjusted

Table 4 | Risk factors for cause-specific mortality in dialysis patients and transplant recipients (adjusted Hazard ratios (95% CI))

Infection-related mortality	Total	0–39 y	≥40 y
Incident dialysis patients			
Sex			
– Men	1	1	1
– Women*	1.07 [1.04–1.10]	1.32 [1.09–1.60]	1.06 (1.03–1.09)
Primary renal disease**			
– Glomerulonephritis	1	1	1
– Diabetes Mellitus	1.95 [1.84–2.07]	3.30 [2.36– 4.60]	1.92 (1.80–2.04)
– Cancer	2.19 (1.97–2.43)	2.20 (0.68–7.09)	2.16 (1.95–2.40)
– Multisystem disease	2.26 (2.09–2.45)	3.88 (2.69–5.60)	2.20 (2.02–2.39)
Recipients of a first kidney transplant			
Sex			
– Men	1	1	1
– Women*	[0.92–1.11]	1.54 [1.17–2.04]	0.98 (0.89–1.08)
Primary renal disease**			
– Glomerulonephritis	1	1	1
– Diabetes Mellitus	2.06 [1.77– 2.40]	2.84[1.84–1.38]	1.97 (1.67–2.31)
– Cancer	1.54 (0.87–2.75)	3.25 (0.4–23.9)	1.45 (0.79–2.64)
– Multisystem disease	2.13 (1.73–2.63)	2.10 (1.20–3.68)	2.12 (1.6–2.66)
Malignancy-related mortality	**Total**	**0–39 y**	**≥40 y**
Incident dialysis patients			
Sex			
– Men	1	1	1
– Women*	0.70 [0.67–0.73]	1.07 [0.72–1.60]	0.69(0.66–0.73)
Primary renal disease**			
– Glomerulonephritis	1	1	1
– Diabetes Mellitus	0.79 [0.72–0.88]	1.35 (0.48–3.81)	0.78 (0.71–0.86)
– Cancer	12.4 (11.3–13.6)	89.0 (35.7–222.2)	12.1 (11.0–13.3)
– Multisystem disease	1.45 (1.26–1.67)	2.49 (0.81–7.67)	1.44 (1.25–1.65)
Recipients of a first kidney transplant			
Sex			
– Men	1	1	1
– Women*	0.70 [0.62–0.79]	0.84 [0.56–1.25	0.69 (0.61–0.79)
Primary renal disease**			
– Glomerulonephritis	1	1	1
– Diabetes Mellitus	1.05 [0.863–1.29]	0.67 [0.29–1.56]	1.08 (0.88–1.33)
– Cancer	2.82 (1.70–4.67)	14.08 (3.29–60.2)	2.51 (1.47–4.30)
– Multisystem disease	1.32 0.99–1.75)	1.91 (0.89–4.07)	1.25 (0.92–1.70)

* Adjusted for country and year of start RRT; ** Adjusted for age, sex, year of start RRT and country

Transplant recipients

Among transplant recipients, the mortality rate due to infections was 6.8 per 1,000 py (95% CI 6.5–7.1, Table 2). Septicaemia, pulmonary infections and other infections accounted for 3.2, 1.6 and 0.9 deaths per 1,000 py, respectively. Bacterial infections were less common than in dialysis patients (85.3%), 8.9% died of viral infections and 5.9% of other types of infections. Mortality rates for infection-related death were substantially higher than in the general population, increasing strongly with age. Again MRRs decreased with age (Figure 1B). The age and sex adjusted MRR for infection-related mortality in transplant patients was 31.5 (95% CI 29.6–33.4).

Association of sex, age and primary renal disease to mortality

In both dialysis patients and transplant recipients, mortality rates were comparable for both sexes. In contrast, women had a higher age-adjusted MRR of dying from infections than men: 98.8 (95% CI 95.9–102) vs. 67.7 (95% CI 65.5–69.9) among dialysis patients and 39.2 (95% CI 36.1–42.4) vs. 25.3 (23.1–27.7) among transplant recipients (Table 3). Among dialysis patients, Cox regression analysis with adjustment for age, country and year of start of RRT, revealed a 7% higher risk of infection-related death for women when compared with men (adjusted HR 1.07 95% CI 1.04–1.10) (Table 4). Among the recipients of a first kidney transplant, women on average had a similar risk of infection-related death compared with men (adjusted HR 1.01 95% CI 0.92–1.11).

When stratified by age, women on dialysis aged 0-39 years had an extremely high MRR of infection-related mortality (>500 fold increased). In that age category, women on dialysis had a 32% higher risk of infection-related death compared with similar-aged men. Overall, women with a renal transplant had a 54% higher risk of infection-related death compared with men in the same age category (Table 4). In transplant recipients this differential risk between men and women was more prominent in patients aged 20-40 years while in transplant recipients aged >40 years this sex difference disappeared (Table 4).

All patients on dialysis with multisystem disease as primary cause of renal disease were at excess risk of dying from infections as compared to the general population (14.3 and 16.2 deaths/1,000 py in women and men, respectively). Even within the RRT population they had a two-fold increased risk of death as compared to patients with glomerulonephritis (adjusted HR of 2.26 (95% CI 2.09–2.45) in dialysis and 2.13 (95% CI 1.73–2.63) in transplant patients, table 4). In addition, the prevalence of multisystem disease was two times higher in women than in men, especially in the young age categories (Figure 2). Even after adjustment for primary renal disease and the dialysis modality, young women on dialysis or with a transplant still had a higher risk of infection-related death than men (HR 1.42 95% CI 1.13–1.80 and 1.53 95% CI 1.06–2.22, for dialysis patients and transplant recipients respectively).

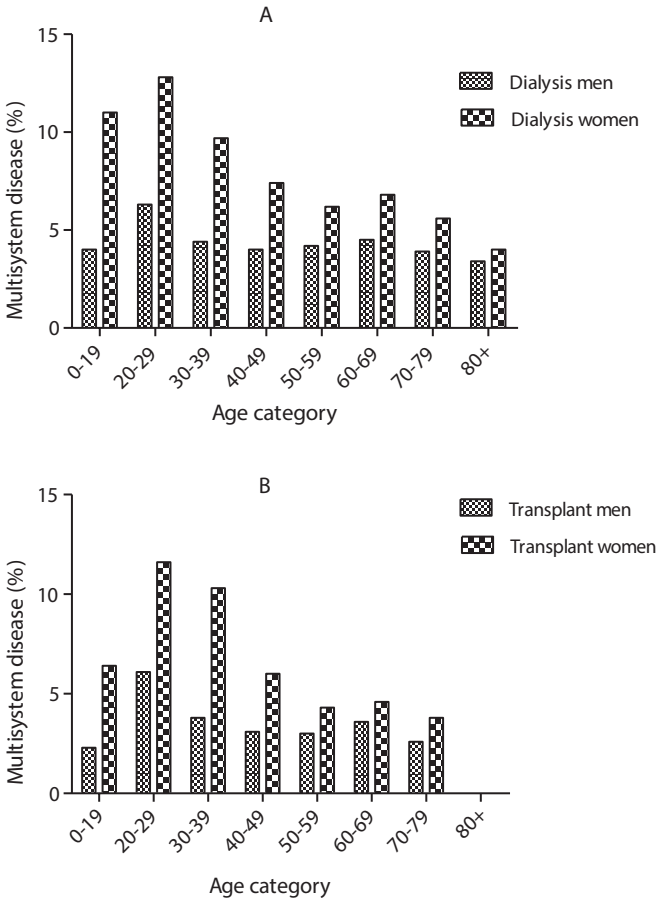

Figure 2 | Differences in sex and age groups for prevalence of multisystem disease in dialysis patients (**A**) and transplant recipients (**B**)

Malignancy-related mortality

Dialysis patients

Among dialysis patients there were 14.0 deaths per 1,000 py (95% CI 13.7–14.4) due to malignancies (Table 2). Mortality rates were almost three times higher than in the general population (age and sex adjusted MRR 2.9 (95% CI 2.8–3.1), Table 2, Figure 1C and Table 3). If patients with malignancies as primary renal disease were excluded, the adjusted MRR was 2.2 (Table 3).

Transplant recipients

Among the transplant recipients there were 4.6 deaths per 1,000 py (95% CI 4.3–4.8) because of malignancies (Table 2). Compared with the general population, the mortality from malignancies was significantly increased with an age and sex-adjusted MRR of 1.7 (95% CI 1.6–1.8). This MRR was

slightly lower after exclusion of patients with malignancies as primary renal disease. The MRRs from malignancies decreased with age (Figure 1D).

Association of sex, age and primary renal disease to mortality

Overall, women on RRT had a lower risk of dying from malignancies than men, which is in line with the trend observed for the general population. However, girls aged 0–19 years on dialysis had a relatively higher risk of dying from malignancies. Consequently, in the age group 0–40 years the female survival advantage observed in the general population was not present in the dialysis group (Table 3).

Conversely, among older patients, female sex was associated with a lower risk of mortality from malignancies, which remained after adjustment for primary renal disease (Table 4). Exclusion of cancer as primary disease did not change these outcomes.

As presented in Table 4, having cancer as primary cause of end-stage renal disease was associated with an almost 2-fold increased risk of cancer related mortality. Both dialysis patients and transplant recipients under 40 years of age were at a markedly increased risk of cancer mortality (2.2 and 3.3 times increased, respectively). To a lesser extent also multisystem disease tended to be associated with a higher risk of dying of malignancies in the dialysis population.

DISCUSSION

Most studies on mortality in end-stage renal disease patients emphasize the importance of cardiovascular disease as the major cause of death. Yet, most of these patients die of non-cardiovascular causes, of which infections and malignancies are most prominent. [12] In this large cohort of RRT patients, we confirmed that infection-related mortality was importantly increased in both dialysis patients and kidney transplant recipients. The risk of malignancy-related death, however, was only mildly increased as compared with the general population. We also identified young women to have a relatively higher risk of premature death by infections as compared with young females from the general population.

Infection-related mortality

We found that dialysis patients were at an 82 times increased risk of death by infection when compared with the general population. Fatal infections concerned bacterial infections in 96% of the cases. These findings are in line with previous studies in dialysis patients, in which bacterial infections were found to be the second leading cause of death, the majority of casualties due to septicaemia. [11] A study based on data from the Unites States Renal data System (USRDS) during the period 1994–1996 showed that patients on dialysis had an up to 100-fold increase in age-adjusted risk of mortality from infections associated with sepsis and a 10-fold increased risk of death from pulmonary infections. [2;3] Similarly, we found that in dialysis patients the mortality rate from infections associated with sepsis was 20.2/1,000 py, but we could not extract a comparable rate

for the general population. Our death rate due to septicaemia and pulmonary infections (27.8 per 1,000 py) in dialysis patients was very similar to that reported in the United States (US, 26/1,000). [11]

We observed important differences in the risk of infection-related deaths between both sexes, especially among dialysis patients. The relative risk as compared with men was markedly increased in younger women, a phenomenon that was partially explained by their higher prevalence of multisystem disease, mainly lupus erythematosus. Patients with multisystem disease are at higher risk of infections, possibly due to an altered immune response or use of immunosuppressive medication. However, after adjustment for multisystem disease, we still found a 1.4 fold (95% CI 1.08–1.91) increased risk among women younger than 40 years, suggesting a role for additional factors. This finding is in line with a recent study in peritoneal dialysis patients from Andalusia, Spain, which showed a two-fold increased risk of infection-related death among women as compared with men. [8] In the general population the risk of death due to infections is extremely low and women have even lower death rates than men. While the high infection-related MRR in young women may be partially explained by the low risk in women in the general population, this finding suggests a loss of the "survival advantage" of women regarding infection-related causes of death. [12]

The fact that the largest differences between men and women in our study occurred at relatively young age may suggest a role of sex hormones on the immune system. [13] In females, phagocyte function of neutrophils is enhanced by estrogen [14] while testosterone has a suppressive effect on immune responses, among others on macrophage function and increases susceptibility to infections. [15] Among women on dialysis, estradiol levels are generally lower than in transplant recipients [16] and the general population, [17] which explains the loss of gender advantage. Subsequently, we speculate that a reduced immune response in young women on dialysis, in addition to a higher prevalence of multisystem disease (further compromising the immune system) may be a potential explanation for this observation.

When patients die of cardiovascular disease they are no longer able to die from infections. Therefore, if males would die more often from cardiovascular related causes, at the cost of infections, this could explain the gender difference for infectious death. However we previously showed that the standardized mortality rates for cardiovascular death were similar between both sexes. [1] Therefore we do not believe that this could explain the gender difference for infectious related death.

Another reason for the reported sex difference may be related to the choice of vascular access. Several studies, including the Dialysis Outcomes and Practice Patterns Study (DOPPS) and Scottish data, have shown that sepsis/infection occurs more often in patients with a central venous catheter than in patients with an AVF or graft. [18-23] According to the USRDS, in 2007 22.9% of women used a catheter, versus 13.3% of men, while 44.3% of women had an arteriovenous fistula (AVF), versus 64.2% of the men. Women also had more often an arteriovenous graft. [18] Similar proportions were observed in a recent study based on data from the ERA-EDTA Registry. Moreover, this study showed that the risk of infectious death was strongly reduced in women with an AVF when compared to women with other vascular access types. [40]

Concerns about smaller vascular diameters and reports of higher failure rates in women may prevent nephrologists and surgeons from considering AVF for female dialysis patients and might justify the preferred utilization of catheters in women. [24] These concerns are questionable, since

Caplin et al. showed that women have as adequate a vasculature for the placement of AVFs as men. [25]

Among transplant recipients, infections were the second leading cause of death (20.8%) after cardiovascular disease (29.3%), similarly to reports from the US [21] and the UK [6]. We showed that in these individuals the mortality rate from infections was 6.8 per 1,000 py, and mortality from infections associated with sepsis was 4.0 per 1,000 py. In transplant patients the risk of dying from infections was 31.5 times higher than in the general population, which is in line with previous reports. [2;3] Possible causes of the high death rate in renal transplant recipients are the use of immunosuppressants and defective phagocytic function of granulocytes. [2]

Malignancy-related mortality

We found an almost 3 times increased risk of death due to malignancies in dialysis patients, similar to previous studies. [26-28] A recent review suggested that the incidence of cancer was increased in patients with chronic kidney disease both before and after the start of RRT, and that dialysis patients had an 1–2 fold increased risk of developing cancer as compared with the general population. [4] Women in the older age groups had a survival advantage with respect to malignancies as cause of death. Previous studies in the general population have shown this survival benefit among older women and this is a well-known phenomenon for anorectal carcinomas as well as for other tumour groups. [29;30] Environmental, behavioural and biological factors have been assumed to contribute to this sex difference, but the exact mechanism has still to be elucidated. [29] In addition we noted that patients with diabetes had a lower risk of death due to malignancies. We have no explanation for this. However as the risk of cardiovascular death is very high in patients with diabetic nephropathy, [39] we could speculate that patients may not survive long enough to develop fatal malignancies. Especially as this hazard is compared with that among the relatively healthy glomerulonephritis patients with a lower risk of cardiovascular death.

As in previous studies, we found in transplant recipients a small, but significantly increased risk of malignancy-related mortality after adjustment for age and sex. [5;31] The highest increased risk was observed among younger patients and was similar to the 10-fold increased risk of cancer among patients who start RRT in childhood age that we found in a previous study. [31] Rates in the elderly were only slightly, if at all, increased, which has been shown before. [32] Interestingly, the MRR was higher on dialysis than on transplantation which could be explained by the potentially increased risk of graft loss among cancer patients due to the use of chemotherapy [33;34] and the reduction of immunosuppressive medication, leading to a subsequent death on dialysis. We tried to avoid this effect by attributing those deaths on dialysis within 60 days after graft-loss due to transplantation, [35] but still this might not be sufficient for malignancies. The death rate due to cancer, was slightly lower as that of the number of new cancer cases [4;5] and also as compared with studies from Australia and New Zealand. [36] This might be explained by the a high prevalence of basal cell skin cancer and squamous cell carcinoma in patients on dialysis and in transplant recipients, which are often not fatal. [4;33] A potentially more dangerous combination of the use of immunosuppressants and the higher sun exposure in Australia and New Zealand could have led to increased risks of fatal malignancies in that area. [26;31]

LIMITATIONS

A few limitations of our study need to be noted for adequate interpretation of our results. First, the cause of death was unknown in approximately 15% of all patients on RRT while it was missing in only 0.16% of the general population. This may have resulted in underestimation of our MRRs. Within the ERA-EDTA Registry only one cause of death can be reported. Therefore there may be have been overlap between patients who had both a malignancy and an infection at death. This may have led to an underestimation of both the IRR of cancer and of infections. This different percentage in the category unknown may be explained by the slightly different method of collecting cause of death data between the patients and the general population. Causes of death among the RRT population were collected by the treating nephrologist and autopsies will have been performed in only very few cases. Causes of death within the general population are commonly recorded by the physician who confirmed the death and thereafter sent to the statistics office, resulting in relatively few missing causes of death. However, it seems unlikely that death due to infection or malignancy was missed by a nephrologist. Second, malignancies contributing to a decision to abandon RRT may have remained unreported. This means that the category "dialysis withdrawal" might also include some patients with malignancies, leading to a slight underestimation of the percentage of patients dying from malignancies. Finally, we combined person-time on dialysis for the first and subsequent dialysis periods. Recent studies suggest that transplant failure patients returning on dialysis have a higher (infection-related) mortality compared with naïve transplant patients. [37;38] Because we investigated prevalent mortality rates, for dialysis patients we included all time on dialysis. Performing a sensitivity analysis including only the first dialysis period did not alter our conclusions.

CONCLUSION

The present study shows that infection-related mortality is highly increased among both dialysis patients and kidney transplant recipients. Young patients on dialysis, especially females with multisystem disease, are at a relatively high risk of infection-related mortality. They deserve special attention because of their excess risk of infection-related death. Physicians must be aware of factors increasing the risk of infection-related death and try to avoid them. Research into the mechanisms, prevention and better treatment of infections deserves a prominent place on the research agenda.

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05

Infection related hospitalizations over 30 years of follow-up in patients starting RRT at pediatric age

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ABSTRACT

Background: Pediatric Renal Replacement Therapy (RRT) patients surviving long time have a 30-times higher mortality risk compared to the age-matched general population. Recently, we demonstrated a transition from cardiovascular disease to infection as main cause of death in a long-term follow-up study of pediatric RRT. Here, we explored the burden of infections requiring hospitalization over 30 years of follow-up on RRT.

Methods: The cohort comprised all 234 Dutch patients on RRT under 15 years of age in 1972-1992. We analyzed infection-related hospitalizations during 1980-2010. We evaluated the rate of Hospital Admission (HAR) per patient-years (py) and the infectious over non-infectious HAR ratio (HARR).

Results: HAR decreased significantly over time for all patients. The rate of HD-related infections decreased between 1980 and 1999, but stabilized in 2000-2010, whereas PD-related infections decreased progressively. Transplantation-related infections did not change, except for urinary tract infections which increased significantly from 3.3/100 py [95% CI 3.2–3.4] in 1980–1989 to 4.4/100 py [4.2–4.5] in 2000–2010 ($p<0.001$). The contribution of infection to hospitalization rate increased significantly in transplanted patients (HARR: 1980–1989: 0.25 [0.2–0.3]; 2000-2010: 1.0 [0.79–1.27], $p<0.001$).

Conclusions: Our findings indicate a relative increase of infections requiring hospitalization over time in patients who started RRT at pediatric age, especially severe urinary tract infections in transplantation. More attention for urological abnormalities in case of recurrent urinary tract infection and tailored adjustment of immunosuppression, might reduce risk in these patients.

INTRODUCTION

Patients starting renal replacement therapy (RRT) at pediatric age and surviving for long time have a mortality risk at least 30-times higher compared to healthy peers. [1-3] Infection is one of the major causes of mortality and morbidity in patients on RRT, accounting for the 15–23% of deaths in this population. [4-6] Various factors may contribute to the high rate of life-threatening infections in these patients, such as an impaired immune function as a result of decreased renal function, the open connection of the peritoneal cavity in patients on peritoneal dialysis and of the central venous system in hemodialysis patients, and, above all, the use of immunosuppressive therapy in transplanted patients. [7-12] It is of major concern that recent reports show an increasing trend in infection-related mortality, both in dialysis and transplanted patients, and not only in incident patients, but also in patients with a long history of RRT, years after transplantation, [13;14] with an infectious mortality rate increasing from 0.51/100 patient-year before 1989 to 0.82/100 patient-year after 2000 in a Dutch cohort. [15] Infection is one of the most frequent causes of hospitalization in RRT patients. [1;7;10;16-21] In adults it has been associated with a 10% death rate within 30 days of admission. [14] Still, studies reporting the burden of severe non-fatal infections in long-term RRT patients are lacking.

Our primary aim was therefore to evaluate the burden of infections requiring hospitalization in patients starting RRT at pediatric age and a 30-year follow-up. Our second aim was to analyze the change in burden of severe infections over time using infection-related hospitalization as a marker. Lastly, as hospitalization patterns in the Netherlands have adopted a higher threshold for admission over the last 30 years, [22] we also analyzed the infection/non-infection admission rate ratio over time in order to correct for this change in admission policy.

SUBJECTS AND METHODS

Data collection

We gathered information on patients from the Late Effects of Renal Insufficiency Cohort (LERIC) study, which comprised all Dutch patients who started chronic RRT between 1972 and 1992 at less than 15 years of age, and who were born before 1979. From the original LERIC cohort, we included all patients alive at the 1st January 1980. Data collection details and results of the first follow-up studies conducted on this cohort between 1998 and 2000 have been described previously. [1,15] In 2000 and 2010, coworkers of the LERIC study visited all 37 hospitals that had been involved in the medical care of the patients during the observation period and collected data on, amongst others, age at RRT start, start and end dates of HD, PD and Tx, date and cause of death, and the cause of each hospital admission. In living patients, the day of review was considered as the end of the observation period. We obtained permission from the medical ethical committee and informed consent from all patients.

Hospital admissions

Information on any hospital admission between 1st January 1980 and the end of the observation period were collected. Causes of hospitalization were classified independently by three reviewers (J.L.V., J.W.G. and K.J.J.), using a detailed description of each patient status around the admission date. Admissions for child birth, dialysis access placement and transplantation were classified as "planned" and excluded from the analyses. Infection-related hospitalizations were classified as either airway infection, gastroenteritis, peritonitis, sepsis, urinary tract infection, vascular access infection and other infections. Other Infections include all infections with unknown origin. Furthermore, bacterial infections were defined as any positive bacterial cultures, abscesses, urinary tract infections, sepsis, tunnel/central venous line infections, PD peritonitis (except when indicated other), sinusitis, segmental pneumonia, bilateral pneumonia with severe disease, pneumonia successfully treated with antibiotics, "fever with chills and antibiotics treatment". Infections defined as viral included all diagnoses due to a specific virus, gastroenteritis except when indicated bacterial, and upper airway infection.

Statistical analysis

In this paper, we compare the rate of hospital admission and infection-related admissions during 2000–2010 with the previous two decades (1980–89 and 1990–99). The Hospital Admission Rate (HAR) was calculated as the number of hospital admissions per 100 patient-years (py) on RRT with a 95% confidence interval (95% CI). Hospital Admission Rate Ratios (HARRs) were calculated to compare infection and non-infection-related admissions. Poisson regression models were used to examine the trends in infection and non-infection HAR with the decade of admission (1980–89, 1990–99 and 2000–2010). In the Poisson model, the natural logarithm of the total patient-years at risk was used as the offset. Data analysis was performed using R (v. 3.0.1, The R Foundation for Statistical Computing). [23]

RESULTS

STUDY COHORT

The total cohort consisted of 234 patients with a median follow up of 25.0 years (range 0.2–31.4). The median age at the start of RRT was 11.2 years (range 1.9–15.0) and 55.6% were female. The patient characteristics for each decade are shown in Table 1. Between 2000 and 2010, two (1.4%) patients were lost to follow-up due to emigration and one patient (0.7%) had avoided medical care since 2007.

All-Cause Hospital Admission Rates

A total of 2563 hospital admissions were recorded, 757 (29.5%) of which were infection-related. 1202 admissions occurred between 1980 and 1989, 877 during 1990–99, and 484 after the turn of the century. Nearly all patients (224/234) experienced at least one unplanned admission during follow-up, with a median of 9 admissions per patient (range 1–100). Over the 30-year period, the average

Table 1 | Characteristics of the study population at specific time points during the 30 years follow-up.

	Total	1–1–1980	1–1–1990	1–1–2000	1–1–2010
Nr. Pts	234	95	199	185	152
Male (%)	104 (44.4%)	39 (41.05%)	88 (44.22%)	83 (44.86%)	71 (46.71%)
Patients age (years)	-	14.53 (3.60–21.88)	19.48 (11.01–31.88)	29.42 (21.01–41.50)	39.30 (31.01–51.50)
CAKUT patients (%)	77 (30.92%)	29 (30.53%)	64 (32.16%)	62 (33.51%)	52 (34.21%)
Age at RRT (years)	11.39 (1.88–21.33)	11.00 (1.88–14.94)	11.25 (1.88–15.87)	11.62 (1.88–21.33)	11.74 (1.88–21.33)
Hemodialysis Time (years) *	2.79 (0.03–36.52)	1.21 (0.13–6.40)	1.82 (0.03–15.63)	2.23 (0.03–25.63)	2.31 (0.03–35.63)
Peritoneal dialysis Time (years) †	2.42 (0.08–18.55)	0.04 (0.02–5)	1.03 (0.01–10.73)	1.62 (0.01–15.36)	2.13 (0.01–10.73)
Transplantation Time (years) ‡	20.20 (0.01–39.65)	2.05 (0.01–9.05)	5.77 (0.01–19.06)	13.93 (0.13–29.05)	23.43 (0.19–39.06)

* = patients with at least one period on HD;† = patients with at least one period on PD; ‡ = patients with at least one period on Tx

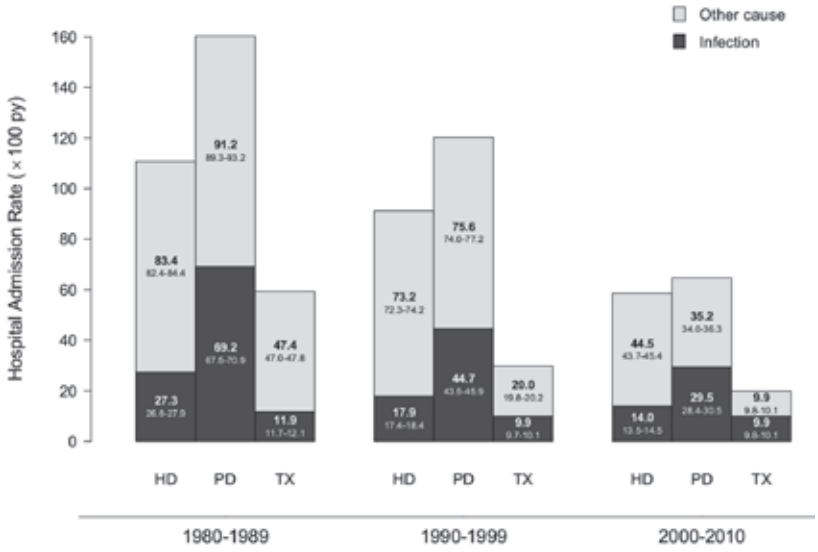

Figure 1 | Hospital admission incidence rate for infection and non infection-related causes by decade and RRT modality. Inside the bars hospital admission incidence rates with 95% CI are presented.

HAR was 48.5/100 py (95% CI 48.3–48.7), so almost once every two years. HAR was significantly higher in the eighties (77.0/100 py, 95%CI 76.6-77.5, p<0.0001) and nineties (44.6/100 py, 44.3–44.9, p<0.0001) compared to 2000-2010 (27.6/100 py, 27.3-27.8). Figure 1 presents the trend in hospital admissions between 1980 and 2010 by decade and RRT modality.

Infection-Related Hospital Admission Rates

Infection-related HAR decreased between 1980–1989 and 1990–1999, but stabilized in 2000–2010. Infection-related HAR in HD patients also decreased from 1980–1989 to 1990–1999, and stabilized after 2000, whereas infection-related HAR in PD patients showed a progressive decrease over time. Conversely, infection-related HAR in transplant patients did not change significantly during the study period, with an almost constant HAR from 11.9 during the eighties to 9.9/100 py during the nineties and 2000s.

During the first year after transplantation, infection-related HAR was consistently more frequent compared to the period after the first year. Furthermore, there was no improvement over time for neither the first-year risk, nor the long-term risk of infection-related admission, with a HAR in the eighties of 30.7 (95% CI 29.8–31.5) for the 1st year vs. 8.5 (95% CI 8.4–8.7, p<0.0001) for later infections and 34.1 (95% CI 32.5–35.8) vs. 9.0 (95% CI 8.9–9.2, p < 0.0001) during the 2000s (Figure 2).

Non-infection vs. Infection-Related Hospital Admission Rate Ratios

Compared to the rate of admissions for non-infectious causes, the rate of infection-related admissions increased significantly over time: the rate ratio over the last decade was 0.73 (95% CI 0.61–0.88) versus 0.32 (95% CI 0.28–0.37, p<0.001) and 0.42 (95% CI 0.36–0.49, p<0.001) for the eighties and nineties, respectively. This rise was entirely due to a proportional increase in infection-related admissions in transplant patients, with an infection/non-infection ratio rising from 0.25 (95% CI 0.20–0.30, p<0.001) between 1980 and 1989, to 0.50 (95% CI 0.41–0.60, p<0.001) between 1990 and 1999, and up to 1 (95% CI 0.79–1.27) during the last decade (Figure 3).

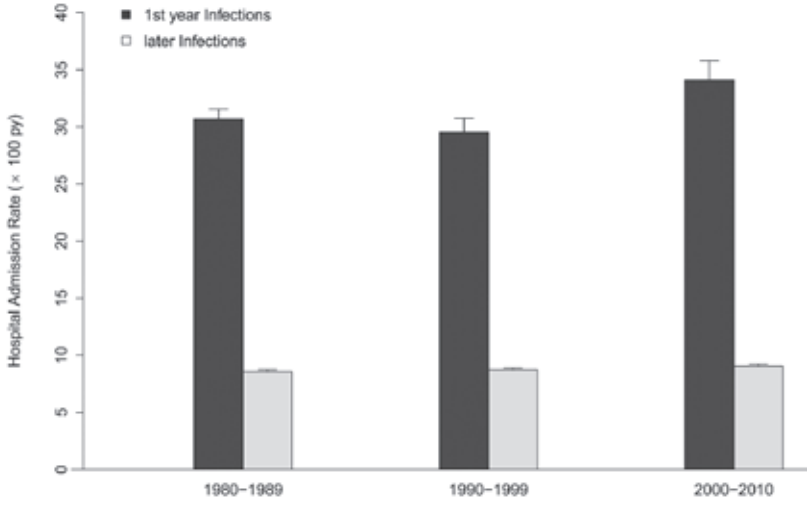

Figure 2 | Hospital admissions incidence rate for infection in the first year and later after renal transplantation. Error bars represent 95% CI.

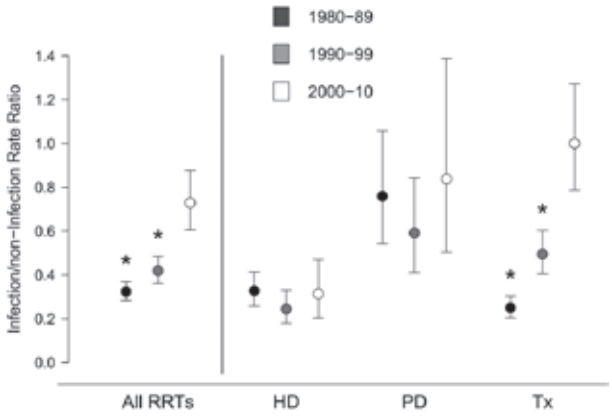

Figure 3 | Infection/non-Infection Hospital Admission Rate Ratio by decade and RRT modality. * p<0.001 vs. 2000–2010 decade. Whiskers represent 95% CI.

Diagnoses-Specific Infection-Related Hospital Admission Rates

We classified infection-related admissions into specific diagnoses categories; Airway Infections (AWI), Gastroenteritis, Peritonitis, Sepsis, Urinary Tract Infections (UTI), Vascular Access Infections (VAI) and Other Infections. Of the 178 HD-related admissions due to infection, 30 (16.8%) were airway infections, 28 (15.7%) sepsis, 26 (14.6%) vascular access infections and 94 other types of infections. Rates of airway infections, sepsis, and other infections did not show any significant trend between 1980 and 2010, however, nearly all vascular access infections (21, 11.8%) occurred during the eighties (Figure 4A).

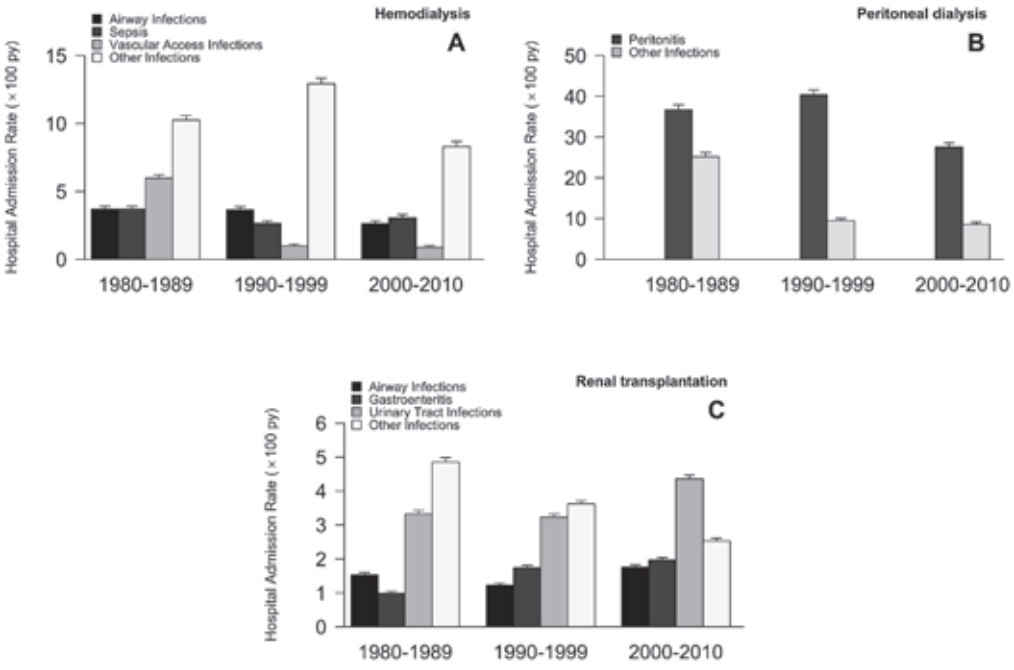

Figure 4 | Hospital Admission Rate for most frequent type of infections by RRT modality. Error bars represent 95% CI.

Of the 155 PD-related admissions due to infection, peritonitis was by far the most common cause of admission (111, 71.6%). The peritonitis-specific admission rate remained constant throughout the follow-up period (Figure 4B), however, we found a significant increase in peritonitis/other infections ratio from the '80s (1.4, 95%CI 1.3–1.5) to the later decades (3.2, 95% CI 3.0–3.5 in 2000s).

Of the 422 Tx-related admissions due to infection, the most common were urinary tract infection (149, 35.3%), airway infections (61, 14.5%) and gastroenteritis (66, 15.6%). Especially the admission rate due to urinary tract infections (UTI) showed an increase over the decades (Figure 4C). The majority of UTIs occurred in transplant patients affected by Congenital Abnormalities of the Kidney

and Urinary Tract (HARs of 4.8/100 py, 95% CI 4.6–5.0; 3.9/100 py, 95% CI 3.7–4.1 and 5.6/100 py, 95% CI 5.3–5.8 during the 3 study decades respectively), which was higher compared to patients with other renal diseases (HARs of 2.6/100 py, 95% CI 2.5–2.7; 2.9/100 py, 95% CI 2.8–3.0 and 3.8/100 py, 95% CI 3.6–3.9 in the 3 study decades respectively, p=0.014). In this patients UTIs in the first year after transplantation were significantly more frequent than later in 2000s (HAR 18.1/100 py, 95% CI 16.9–19.3 vs 3.6/100 py, 95% CI 3.5–3.8, p<0.001), and in '80s (HAR 7.8/100 py, 95% CI 7.4–8.3 vs 2.7/100 py, 95%CI 2.6–2.9 p=0.005), but not in the '90s. Furthermore, as expected we found a large difference between the rate of UTIs in male (HARs of 8.5/100 py, 95% CI 8.2–8.8; 6.0/100 py, 95% CI 5.8–6.2 and 9.8/100 py, 95% CI 9.5–10.1 in the 3 study decades respectively) and female patients (HARs of 0.7/100 py, 95% CI 0.6–0.8; 1.8/100 py, 95% CI 1.7–1.9 and 1.7/100 py, 95% CI 1.6–1.8 in the 3 study decades respectively, p<0.01), and this difference was significant both for CAKUT (p=0.005) than for non-CAKUT patients (p=0.02).

Of the 757 infection-related admissions recorded during the study period, 482 (63.7%) were classified as bacterial, 163 (21.5%) as viral, and 15 (1.9%) as fungal or due to mycoplasma, while 95 (12.5%) were of unknown origin. We found no significant trends in bacterial infections (changing from a HAR of 5.9/100 py, 95% CI 5.8–6.1 in '80s to 6.8/100 py, 95% CI 6.6–6.9 in 2000s, p=0.213), whereas the number of viral infections significantly decreased over time, from 3.7/100 py, 95% CI 3.6–3.8 in '80s to 2.9/100 py, 95% CI 2.8–3.1 in 2000s (p=0.021).

DISCUSSION

We analyzed the burden of severe infections over 30 years of RRT in patients with pediatric start of RRT using hospitalizations as a marker. We found a consistent increase in the Infection/Non-infection hospitalization rate ratio, suggesting an increase in the relative contribution of infections on hospital admissions over the past decades. This increase was exclusively found in patients living with a functioning renal graft, where urinary tract infections accounted for the majority of admissions.

Very few data exist on the long-term effects of RRT as most studies report on data covering much shorter periods of observation. Our data shows a high burden of transplant-related infections, not only during the first year after transplantation, as previously described by others, [24-27] but also long thereafter. We found no significant changes in the 1st-year/later infection ratio throughout the observation period. This is especially remarkable as these patients were on average between 30 and 40 years old in 2000–2010, an age that is associated with the lowest risk of death by infection according to most RRT registry studies. [28;29] Our findings therefore most probably reflect a more general trend towards a relative increase in infections in renal transplant patients over the last 10 years. This trend is in line with the shift from cardiovascular to infectious disease as primary cause of death on which we previously reported, [15] as well as with reports on admission rates for infections during the first post-transplant year. [13;24;28;30;31]

Infections, even if not lethal, are especially worrying in transplantation patients as they may lead to graft loss. UNOS data have shown an increase in death-censored graft failures due to infections between 1997 and 2006 from 6.4 to 10.1%. [32] Infection may lead to graft failure in several ways.

It may activate the immune system and trigger cytokines that may induce interstitial inflammation, leading to chronic allograft nephropathy. BK and CMV virus may cause tubulo-interstitial nephritis and bacterial pyelonephritis and may also directly damage the renal graft. [19] According to the UNOS data, urinary tract infections related to urological complications were associated with an 8.8-times increased risk of death-censored graft failure. [32]

The most plausible cause for the increase in burden of transplant-related infections is the concurrent tendency towards the use of more potent immunosuppressive strategies in renal transplantation over the last 20 years. [33] There is abundant evidence for a direct relationship between the extent of immunosuppression after transplantation and the risk of infections. [34-36] Not the specific type of drug, but the use of higher dosages, especially of calcineurin inhibitors and the use of triple instead of double therapy have found to be associated with both a decrease in acute rejections and, as a tradeoff, more infections, such as polyomavirus and urinary tract infections. [37-41] In the Netherlands, and similarly in many other countries, all centers for adult renal transplantation have introduced IL-2 blockers during the early 2000s as part of the induction therapy, and all centers have switched from cyclosporine to high dose tacrolimus in combination with mycophenolate mofetil as part of the induction therapy. This indeed implies a substantial increase in average immunosuppressive dose over the last 10 years. [33] A Spanish observational study showed that basiliximab as part of the induction therapy was indeed associated with urinary tract infections after renal transplantation. [27] The observed rise in hospital admissions related to urinary tract infections in transplantation patients may also be due to an increasing use of antibiotic prophylaxis after renal transplantation causing a rise in multi-resistant infections that frequently require intravenous antibiotics treatment and hospitalization. [41;42] In addition, a general increase for the incidence of infections in Western countries has been reported, possibly due to several factors, such as an increase in multi-resistant infection incidence and improved detection and reporting practices. [43-46]

For PD, we observed a gradual decrease over time in infection-related admissions, except for peritonitis. The persisting burden of PD-related peritonitis contrasts with data from two European centers, an Australian center, and a Canadian Registry, all showing a decreasing trend over time. [47-50] An explanation might be that these studies have analyzed different patients in different eras in contrast to ours, whereas we followed one closed cohort of patients over time. In these studies, profiles of patients within the different eras did not vary significantly in duration of RRT and, consequently, co-morbidity, whereas in our study, patients who were on PD in the decade 2000–2010 had, per definition, more years of RRT and more dialysis burden than in the years before. Conversely, those surviving up to 2000–2010 might be considered less susceptible to various peritonitis risk factors as they can be considered as "survivors". Therefore, this finding rises concern, especially as it is also in contrast to the major reduction in vascular access related infections in HD over time.

This study has several limitations. First, we used hospitalization as a marker for the burden of severe infections. Hospitalization has been used as an indicator of disease severity for various other diseases, as severity assessment scores may have even more limitations. [51-53] Changes in hospitalization rates over time are fraught with difficulties because they may be subject to underlying trends in patterns of care. A change in rate of hospitalizations does not only reflect disease severity or incidence, but also organizational issues such as improved methods for outpatient care, a change in

diagnostic criteria for infections, and changes in nephrologist hospitalization and treatment policies from the eighties up to present. In Europe there is a general trend towards lower numbers and shorter duration of hospitalization. This was clearly reflected in the decreasing number of non-infectious related hospitalizations. Therefore, the relatively constant rate of infectious hospitalizations might even be flawed, as in reality there may have been a sharp increase in the number of infections, be it that patients were not admitted for them. Another limitation is the retrospective collection of the data which in some cases hampered an accurate distinction between bacterial and other causes of infection. Finally, following a closed cohort of patients over such a long period, patients surviving up to 2000 after a long history of RRT may represent a very specific population that may be difficult to compare to all prevalent RRT patients. For instance, patient returning to dialysis after transplant failure could be at higher risk of infection compared to naïve dialysis patients.

In short, we found evidence for a significant increase in the burden of clinically important infections in transplanted patients over the past decades, not only in the first year after transplantation but also among patients who have been living with a functioning graft for a prolonged period of time. This high risk of infection should be taken into account in the management of patients with a long history of RRT, such as a more tailored down immunosuppressive regimen in patients with no history of rejection and specific analysis of urological function in patients with recurrent urinary tract infections.

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Contribution: research idea and study design: JG; data acquisition: JV and JG; data analysis/ interpretation: DL, JV, KvS, KJ and JG; statistical analysis: DL; supervision or mentorship: KJ and JG. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. JG takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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06

Substantial long-term risk of cancer in survivors of pediatric end-stage renal disease

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ABSTRACT

Background and objectives: End-stage renal disease (ESRD) is associated with an increased risk of malignancies. As long-term data on survivors of pediatric ESRD are lacking, we analyzed the prevalence of cancer in patients with pediatric ESRD after long-term follow-up.

Design, setting, participants, and measurements: All Dutch patients, born before 1979 who started Renal Replacement Therapy (RRT) at age <15 years in 1972-1992 were followed until 2010. We explored type and incidence of malignancies in patients in comparison with the general population (GP) using the national cancer registry.

Results*:* After a median of 25.3 years (1.3–37.8) of RRT at a median age of 33.5 (11.0–49.0), 105 primary malignancies had occurred in 54 out of 249 patients. Among them cutaneous squamous cell carcinoma (cSCC) was by far most frequent. Patients aged 25–30 years had developed 16.5 times as many de novo tumors and 991.4 as many de novo cSCC as their GP counterparts; in survivors aged 45–50 years these numbers were 81.5 and 2610.0, respectively. Cumulative Incidence Competing Risk analysis showed that after 30 years of pediatric transplantation 41% of the survivors had developed cancer; 31% had developed a second de novo cancer <1 year after initial cancer diagnosis.

Conclusions*:* Cancer, especially disabling and life threatening forms of cSCC, is highly prevalent among pediatric ESRD patients after 25.3 years of RRT with a high rate of recurrence. Stricter sun protection and lowering immunosuppression might reduce the cancer burden in these and future RRT patients.

INTRODUCTION

Currently, cancer is the major cause of death in upper-middle and high-income countries. [1] This makes it important to detect populations that are at increased risk of developing a malignancy. Previous studies have shown that patients suffering from end-stage renal disease (ESRD) belong to such populations. The increased risk of cancer applies both to patients on dialysis and renal graft recipients. [2-5] Cancer screening is effective only when it leads to survival benefit (usually expressed as days of life saved In organ transplant recipients the occurrence of malignancies has been strongly linked to the use of immunosuppressive agents as such agents impair the body's ability to locate and destroy cancer cells and to control viral infections related to cancer. [6]

Malignancies and frequent recurrences of malignancies contribute significantly to mortality and morbidity rates. However, since nearly all studies have been performed in patients receiving kidney transplants in adulthood, few data exist on the occurrence of malignancies in adult patients who have received a renal graft in childhood [3;7;8] carried out in 454 paediatric recipients at the three paediatric transplant centres of the North Italy Transplant programme (NITp, Italy. In a previous report in 2000 we showed that in the latter group the probability of developing a malignancy was 17% (95% CI: 9 to 24%) once these children reached an age between 20 and 40 years. [9] This was consistent with a 10 times increase in the incidence of de novo malignancy compared to the general population, [9] also found in studies in patient with adult onset of ESRD. [3-5;10-12]

As in our previous analyses most malignancies occurred towards the end of follow-up, we hypothesized that their occurrence might increase dramatically with further ageing of our cohort. We therefore extended follow-up until 2010. The aim of this paper is to describe the occurrence and the type of cancer after transplantation, at very long term follow-up in patients who started RRT before the age of fifteen.

MATERIAL AND METHODS

Study design

This study is part of a 10-year extension of a comprehensive long-term follow-up study into the Late Effects of Renal Insufficiency (LERIC) in patients on RRT since childhood in the Netherlands. The LERIC cohort comprised all Dutch patients born before 1979 who had started chronic RRT (dialysis or a pre-emptive transplant) at <15 years of age between 1972 and 1992. Patients who needed more than three consecutive months of RRT were considered to receive chronic renal replacement therapy. In 2000, we conducted the first study in these 249 patients. [9] In 2010, the 10-year extension study was performed covering the period from the last chart review in 2000 until the last chart review in 2010 or the patient's death. Incidence rates of cancer were compared to those in the general population.

We obtained permission from the medical ethical committee and informed consent from all patients who were alive in 2000.

Data collection

Data were collected in 2000 and 2010. To this end, LERIC co-workers visited all 37 hospitals that had been involved in the medical care of study patients. Data collection of the first period up to 2000 has been described in detail. [9] For the second follow-up period, we reviewed the medical charts of all patients between June 1st 2010 and February 1st 2011. In patients who were alive, the day of chart review was considered the end of the observation period for that particular patient.

Among others, we collected data on the total period the patient lived on a functioning graft, the use of immunosuppressive agents, the diagnosis of non-cutaneous cancer and the diagnosis of non-melanoma skin cancer (NMSC). Only patients with histologically proven basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) were considered to have NMSC. A second de novo cancer was defined as a cancer that was located at a different site and occurred at least 3 months after treatment of the previous malignancy.

Statistical analysis

We used Cumulative Incidence Competing Risk (CICR) for calculation of the probability of a first and a second de novo malignancy after the first transplant. This analysis corrects for death from other causes.

In patients who were still alive we calculated incidence rates (IR), defined as the number of malignancies per 100 patient years (pys) after the first transplant. We also calculated incidence rate ratio's (IRRs), defined as the IR of a certain malignancy in a given age category in RRT patients divided by the IR in the Dutch general population (GP) for the same malignancy in that age category as obtained from the National Cancer Registry. [13] This national database maintains records of cancer incidence in the GP with a completeness of more than 95%. All malignancies are registered, except for BCC and in situ cSCC. As both of these types of malignancies are often removed without confirmation of the diagnosis by pathologist laboratories, registration of their incidence would not be reliable. IR and IRR of these types of cancer could therefore not be calculated.

All comparisons of the LERIC cohort used an age-matched group of the general population. Unfortunately, no statistics exist on the incidence of malignancies in the Dutch GP before 1989. To compare the incidence of malignancies among the LERIC patients and the Dutch GP we therefore calculated the IRR of malignancies from 1990 to 2010.

IR of de novo malignancies all types, cSCC and non-cutaneous malignancies, were calculated. The latter comprises all malignancies except for BCC, cSCC and malignant melanoma.

SPSS 21.0 was used for statistical analysis.

RESULTS

Cohort description

Information on the total LERIC cohort of 249 patients is displayed in Table 1. From first RRT until end of follow-up in 2010 a total of 5709 patient years were recorded. For 72 patients (29%) follow up was more than 30 years. Three patients were lost to follow-up. Ninety-one patients had been transplanted once, 85 twice, 43 three times, 12 patients more than 3 times, whereas 18 patients

never underwent transplantation. Those 18 patients died relatively soon after start RRT after a median time on dialysis of 1.2 years.

Table 1 | Cohort Characteristics

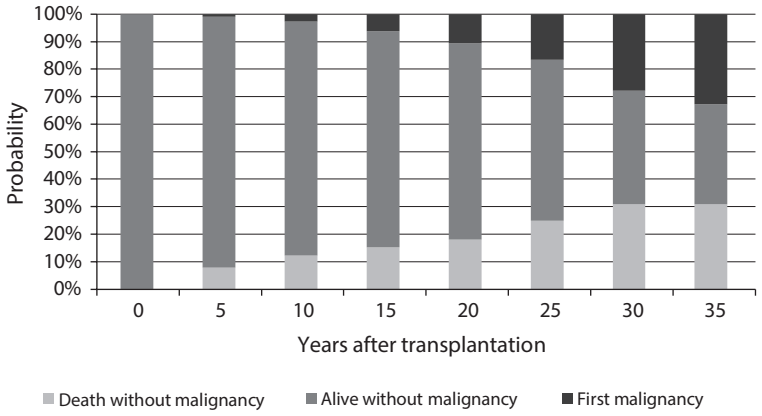
	LERIC-cohort	Range	Percentage
All patients			
Number of pts starting RRT	249		
Median age survivors in 2010 in years	39.9	20.9–52.4	
Median age at start RRT, y	11.2	1.9–25.4	
Median time on RRT, y	25.3	0.3–39.3	
Median time on Tx, y	19.7	0.0–39.3	
Median time on dialysis, y	5.6	0.0–36.5	
Deaths			
Number of deaths	95		38.2%
Median age at death, y	22.7	4.2–46.3	
Median time on RRT at death, y	11.0	0.3–32.3	
Median time after first Tx at death, y	14.4	0.0–29.7	
Cause of death			
– Cardiovascular	29		30.5%
– Infection	29		30.5%
– Malignancy	12		12.6%
– Other	23		24.5%
– Unknown	2		2.1%
Transplant recipients			
Number of transplant recipients	231		
Median age at first Tx, y	12.7	3.9–23.1	
Median time on RRT	26.1	1.5–39.9	
Median time on Tx, y	19.7	0.0–39.3	
Median time on dialysis, y	3.1	0.0–36.5	
Transplant recipients developing malignancy			
Number of transplant recipients developing malignancy	53		
Median age at first malignancy, y	33.5	11.0–49.0	
Median time on RRT at development of first malignancy, y	25.0	1.3–37.8	
Median time on Tx at development of first malignancy, y	18.4	0.0–37.2	
Median time on dialysis at development of first malignancy, y	3.3	0.0–36.5	
Malignancies			
Number of de novo malignancies	105		

Probability of developing a malignancy after transplantation

Of all 249 patients, 54 patients developed cancer. Of all 54 patients who developed cancer, only 1 patient did not receive a renal transplant. Figure 1a shows the probabilities of a first malignancy, death without malignancy and being alive without malignancy at several time points after transplantation.

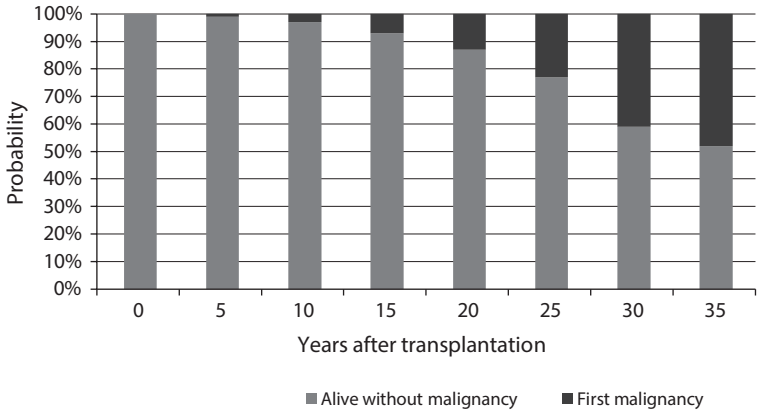
As outlined in Figure 1b, 20, 25 and 30 years after renal transplantation 13, 23 and 41% of survivors had suffered from a malignancy respectively.

Finally, Figure 1c shows the probabilities of being alive with a second de novo malignancy, alive without a second de novo malignancy and death after first malignancy 1, 2, 3 and 4 years after the first malignancy. In figure 1d patients who died after their first malignancy were excluded. In clinical practice these numbers can be used to explain the risk of developing a second de novo malignancy and emphasize the need for regular follow-up.



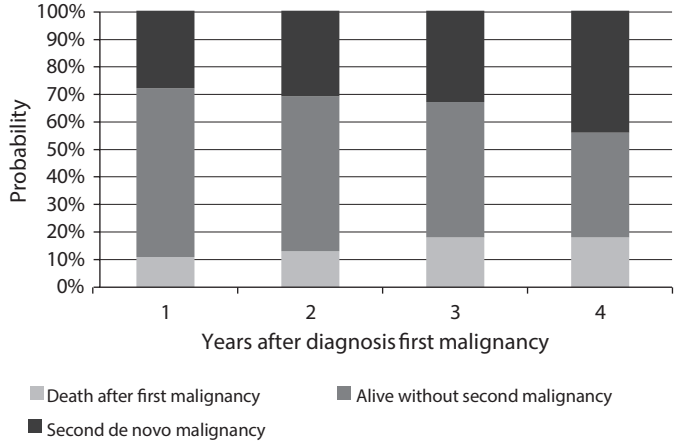
	0	5	10	15	20	25	30	35
First malignancy %, *(N)*	0 *(0)*	1 *(2)*	3 *(6)*	6 *(11)*	11 *(17)*	17 *(16)*	28 *(11)*	33 *(3)*
Alive without malignancy %, *(N)*	100 *(231)*	91 *(192)*	85 *(168)*	79 *(141)*	71 *(109)*	58 *(55)*	41 *(17)*	36 *(3)*
Death without malignancy %, *(N)*	0 *(0)*	8 *(17)*	12 *(24)*	15 *(27)*	18 *(28)*	25 *(23)*	31 *(13)*	31 *(2)*
N	231	211	198	179	154	94	41	8

Figure 1a | Cumulative incidence competing risk of de novo malignancy in pediatric transplantation patients



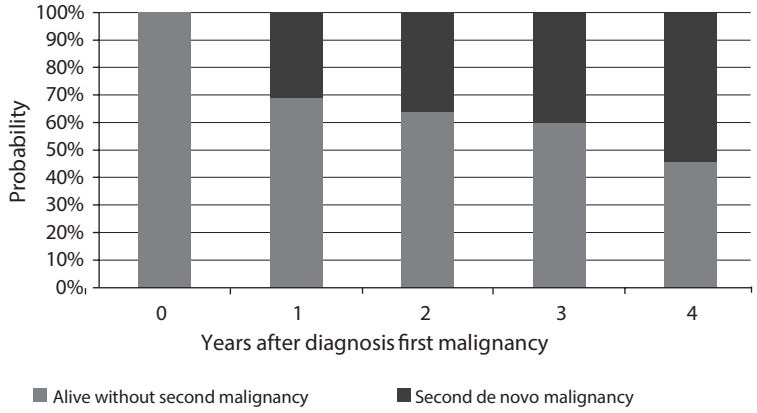
	0	5	10	15	20	25	30	35
First malignancy %, *(N)*	0 *(0)*	1 *(2)*	3 *(6)*	7 *(11)*	13 *(17)*	23 *(16)*	41 *(11)*	48 *(3)*
Alive without malignancy %, *(N)*	100 *(231)*	99 *(192)*	97 *(168)*	93 *(141)*	87 *(109)*	77 *(55)*	59 *(17)*	52 *(3)*
N	231	194	174	152	126	71	28	6

Figure 1b | Cumulative incidence competing risk of de novo malignancy in survivors of pediatric transplantation



	0	1	2	3	4
Second de novo malignancy %, *(N)*	0 *(0)*	28 *(8)*	31 *(7)*	33 *(6)*	44 *(6)*
Alive without second malignancy %, *(N)*	100 *(53)*	61 *(17)*	56 *(12)*	49 *(10)*	38 *(5)*
Death after first malignancy %, *(N)*	0 *(0)*	11 *(3)*	13 *(3)*	18 *(4)*	18 *(2)*
N	53	28	22	20	13

Figure 1c | Cumulative incidence competing risk of developing a second de novo malignancy in pediatric transplantation patients



	0	1	2	3	4
Second de novo malignancy %, *(N)*	0 *(0)*	31 *(8)*	36 *(7)*	40 *(6)*	54 *(6)*
Alive without second malignancy %, *(N)*	100 (*53)*	69 *(17)*	64 *(12)*	60 *(10)*	46 *(5)*
N	53	25	19	16	11

Figure 1d | Cumulative incidence competing risk of developing a second de novo malignancy in survivors of pediatric transplantation

Incidence Rates of de novo malignancies

IR and IRR for all tumors (except BCC), all non-cutaneous tumors, cSCC en BCC are displayed in Table 2. This table shows that, overall, the risk to develop a malignancy in this cohort was 21.7 times higher than in to the general Dutch population. Patients in the age category 25–30 years are 16.5 times as likely to suffer from malignancies than their peers in the GP. In the age category 45–50 years the IRR has increased to 81.5 for all tumors. Patients in that age category are 2610 times as likely to develop a cSCC than the age matched general population.

Tumor characteristics

In total 105, de novo malignancies were registered in 54 patients. Table 3 shows the characteristics of the malignancies. We found 82 NMSC (78% of all de novo tumors) in 39 patients. NMSC mortality rates were low. No one died of BCC; 2 patients died due to metastases of a cSCC. Of all malignancies, NMSC was most common to recur. There were almost twice as many cSCCs as BCCs.

Besides NMSC there were eleven other types of tumors. Malignant Melanoma (MM) accounted for five de novo tumors in five patients. The median age at diagnosis was 29.0 years (range 14.3–37.6, median 31.1). All but one patient with MM had been transplanted at least once. One patient died due to metastases of a MM.

Lymphoproliferative disorders accounted for seven de novo tumors in six patients. Three out of those six patients died, whereas one out of two leukemia patients died. The mortality rate (MR) in those diseases was therefore considerably higher than in NMSC and MM.

Table 2 | IR and IRR of different types of malignancies after first transplantation

		Years at risk of malignancy after first transplantation	IR	IRR
All malignancies*	20–25	643.7	1.1	35.6
	25–30	883.5	0.8	16.5
	30–35	874.0	1.5	19.4
	35–40	562.8	3.4	28.5
	40–45	271.5	4.1	21.2
	45–50	65.5	26.0	81.5
	All	**3768.0**	**2.0**	**21.7**
All non-cutaneous cancer	20–25	643.7	0.8	25.5
	25–30	883.5	0.5	9.5
	30–35	874.0	0.6	7.5
	35–40	562.8	0.5	4.6
	40–45	271.5	0.4	2.0
	45–50	65.5	1.5	4.9
	All	**3768.0**	**0.5**	**5.7**
SCC	20–25	643.7	0.3	1915.1
	25–30	883.5	0.3	991.4
	30–35	874.0	0.9	927.5
	35–40	562.8	2.8	1235.1
	40–45	271.5	3.7	756.0
	45–50	65.5	24.4	2610.0
	All	**3768.0**	**1.5**	**743.8**
BCC**	20–25	643.7	0	
	25–30	883.5	0.1	
	30–35	874.0	0.6	
	35–40	562.8	1.4	
	40–45	271.5	2.9	
	All	**3768.0**	**0.7**	

*Excluding BCC; **We were not able to calculate the IRR of BCC because the national cancer statistics do not register BCC.

Table 3 | Tumor characteristics

	Patients	N of de novo tumors*	Median Age at Diagnosis, y (range)	Median Interval between Tx and diagnosis, y (range)	Deaths
Total	54	105	37.6 (11.1–50.4)	25.0 (1.3–37.8)	12
Skin cancer					
Non Melanoma Skin Cancer	40	82	39.1 (21.8–50.4)	26.2 (5.5–36.2)	2
Basal Cell Carcinoma	21	29	38.8 (21.8–49.3)	26.7 (5.5–36.1)	0
Squamous Cell Carcinoma	29	53	39.9 (22.5–50.4)	26.2 (10.2–36.2)	2
Malignant Melanoma	5	5	31.1 (14.3–37.6)	22.5 ** (15.7–25.8)	1
Non-cutaneous cancer					
Leiomyosarcoma	1	1	32.9	21.1	1
Lymphoproliferative disorders	6	7	25.5 (11.1–32.0)	15.1 (0.6–20.8)	3
Leukaemia	2	2	29.2 (27.3–32.2)	16.7 (11.1–22.2)	1
Fibrosarcoma	1	1	12.8	0.1	1
Adenocarcinoma	1	1	45.8	27.5	1
Brown's tumor	1	1	35.6	25.0	0
Grawitz tumor	1	1	23.3	8.4	0
Parotis carcinoma	1	1	42.1	26.0	0
Thyroid carcinoma	1	1	28.3	18.6	1
Lymphoreticular malignancy	1	1	35.1	23.4	1
Mammacarcinoma	1	1	44.5	26.7	0

**some patients had more than one type of malignancy and were therefore included in both categories.*

DISCUSSION

This study provides the longest complete follow-up of a cohort of patients with pediatric ESRD to date. We found a probability of cancer of 41% after 30 years after first transplantation, the majority being NMSC and lymphoproliferative disorders. Malignancies recurred frequently, 31% of the patients with cancer developed a second de novo malignancy within 1 year. Compared to the

general Dutch population the risk of developing a malignancy in this cohort was more than twenty-fold higher. Malignancies contributed to a significant proportion of overall mortality (12.6%).

The IRR of all malignancies in our cohort was almost 22 times higher than in the general population. This number is higher than seen in earlier adult studies, which consistently report a three to seven-fold increased incidence in patients with ESRD. [4;5;11;12;14] no study on humans has been done in which the reference population was the same as that in which the cancer cases arose and in which there was a sufficiently long period of follow-up. Information on 5,692 Nordic recipients of renal transplants in 1964–1982 was linked with the national cancer registries (1964–1986 This could be explained by the fact that our study is based upon a nationwide cohort with an exceptionally long period of follow-up. Our cohort is exposed to RRT and immunosuppression from childhood onwards and this may have led to an exponential growth in malignancies. Our results show that after 20 years of transplantation the incidence abruptly increases, confirming our hypothesis. However, it is not known how generalizable these results are to other populations, as these are mostly older and have a shorter time of follow-up.

CICR analysis showed a cumulative incidence of 41% after 30 years after first transplantation. The use of immunosuppressive agents is associated with an increased incidence of malignancies. The presumed pathophysiology is that such agents impair the ability to locate and destroy cancer cells as well as to control viral infections that are potentially oncogenic. [6] Consequently, types of cancer with the highest standardized IRR after organ transplantation with immunosuppression are those who are related to infection. Immunosuppression may enable different viruses to become carcinogenic (i.e. posttransplant lymphoproliferative disorder (PTLD), Kaposi sarcoma, anogenital dysplasias) or prevent repair of affected cells in areas exposed to solar radiation (i.e. skin, head and neck cancer).

In a previous study we showed an early effect on the occurrence of malignancy of cyclophosphamide. This effect had disappeared in 2010. An explanation might be that cyclophosphamide was only given in the early years of start of RRT and most often before start of RRT. After 1990, cyclophosphamide had never ever been used in our patients.

Another problem that we faced while trying to analyze the effect of specific immunosuppressive therapy was the change over time in immunosuppressive regiments. In the seventies and early eighties patients only received azathioprine and prednisolone as standard surveillance immunosuppressive medication. In the late 1980's this was switched to cyclosporine and prednisolone and by the mid-nineties to triple therapy, cyclosporine, azathioprine and prednisolone. In the early 00, this regime was gradually replaced the combination of tacrolimus, prednisolone, and mycophenolate mofetil. From 2004 on, this was combined with anti-Interleukin-2 induction therapy. These switches of immunosuppressive medication over the last 10–15 years appeared to be a major hurdle in the analysis of the specific impact of the various immunosuppressive regimes.

Nevertheless, the fact that we found such a high impact of long lasting, relatively mild immunosuppressive therapy to current standards implies that the risk of cancer will certainly might be even greater in currently transplanted children.

There is discussion in the literature to what extent being on dialysis may contribute to the increased risk of cancer as compared to transplantation. [15] There are several insuperable hurdles that make

investigation of the impact of dialysis on cancer occurrence virtually impossible. Firstly, an increase in risk of cancer will only occur after a certain exposure time of the risk factor. All physicians will try to shorten dialysis time in children and young adults as much as possible. As a consequence, the average overall time on dialysis in young RRT patients is relatively short. Those children who are forced to stay for a relatively long period on dialysis are at extremely high risk for early death due to cardiovascular disease long before they may have developed cancer. This practice is illustrated by the course of the patients in our cohort. Of the total RRT time, our patients spend 6 times as much time with a functioning graft as on dialysis.

The most important cancer registered in this study is cSCC. Many of the other more deadly cancers, especially lymfoproliferative disorders, occurred earlier and have killed some of the transplant recipients, so cutaneous cancer, with low mortality, was what was left behind. The incidence of cSCC was 744 times as high as in the age-matched population. This outnumbers previous reports, which confirm NMSC and virus related cancers to be the predominant types of cancers found in transplanted patients. [3-5;10-12] Studies that have included NMSC have found a 3 to 5-fold increased risk for all cancers and 13 to 222-fold increased risk for NMSC after transplantation. [4;9-12;16] As these reports concern adult recipients, the total exposure time is far less than exposure time in the LERIC-cohort. Studies done in the Dutch population of adult kidney transplant recipients found a lower incidence rate of SCC than is presented in this paper. [17] As mentioned above the discrepancy between the results is due to the fact that the LERIC-cohort is an unique cohort with an exceptionally long exposure to immunosuppressive agents and RRT.

In contrast to the general population, [13] the incidence of cSCC in this patient population exceeded that of BCC. The cSCC incidence was nearly twice that of BCC. Earlier studies also described a reversed ratio of BCC to cSCC with the general population in which BCC is the most common one. The predominance of SCC over BCC is more pronounced in pediatric than in adult transplant recipients (SCC: BCC 2.8:1 vs. 1.7:1). [18] UV exposure and human papilloma virus (HPV) in combination with immunosuppression are thought to be the most important causative factors for the development of post-transplant cSCC. UV radiation is probably one of the most important factors. [19] This would explain the extremely high incidence of cSCC in Australia, a country with a majority of genetically ill-protected Caucasian people and a very high sun exposure, with a 93% proportion of skin cancer among all post-transplant malignancies. [20] Sun protection is therefore of utmost importance. cSCC may appear in the absence of any pre-existing skin lesion, but is often preceded by actinic keratosis, which could mean some involvement of HPV in its pathogenesis. There is, however, no conclusive evidence regarding the causal role of HPV in actinic keratosis yet. Additional evidence for the role of HPV comes from a study on post-transplant SCC that occurred in a cohort of 500 allograft recipients; HPV DNA could be detected in nearly 50% of all SCC. [21-23]

Malignancies recurred often; 31% of the patients had a second de novo malignancy within a year. Most of them were NMSC, one was a leiomyosarcoma and two were malignant melanoma. Although in most cases not lethal at time of investigation, NMSC (cSCC especially) tended to recur very often within short interlude. Some patients seemed more susceptible for multiple reoccurrences or distant metastasis of NMSC than others. One patient was diagnosed 12 times with NMSC. Eventually, two patients died due to metastases of a cSCC. Unfortunately, we had no information on

potential risk factors, such as HPV status and the extent of UV exposure. [24] Previous studies in adult transplantation confirm that post-transplant cSCC tend to be far more aggressive than in the GP.

As we continue to improve the life expectancy of our patients by better cardiovascular risk management and prevention of infection, we elongate the exposure on RRT. With longer exposure, the risk at malignancy will increase. The follow-up in our patient cohort may be too short to fully appreciate its final impact on mortality and therefore further research must be conducted.

CONCLUSION

This long-term follow-up study of late effects of renal insufficiency in children shows a cumulative cancer incidence of 41% after 30 years post-transplantation. cSCC is by far most frequent, occurs relatively late after transplantation and tends to recur frequently. Although in most cases not lethal at short follow-up, the high recurrence rate may affect the outcome on a longer term. Moreover, the chronicity of the disease may have an important negative impact on the quality of life due to frequent hospital visits, excisions and cosmetic consequences. Besides that, the threat of becoming a lethal disease is always present.

We therefore advise that all risk factors concerning skin cancer must be reduced. The most important risk factor is sunburn at an early age. This reduction could take place through education, parental role modeling and sunscreen vigilance.

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Part III

Quality of life

07

Long-term quality of life and social outcome of childhood end-stage renal disease

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ABSTRACT

Objective: To assess quality of life (QoL) and social status after 30 years of renal replacement therapy (RRT) and to explore determinants of this QoL.

Study design: The cohort comprised all Dutch patients, born <1979, who started RRT at age <15 years in 1972–1992. All patients still alive in 2010 were asked to complete questionnaires on QoL (RAND-36) and socio-demographic outcomes. Scores were compared with those in the age-matched general population and with previous patient scores obtained in 2000. We performed logistic regression analysis for prediction of QoL outcomes.

Results: 89 out of 152 patients still alive in 2010 participated. Compared with the general population, QoL was more often impaired in dialysis patients for most physical domains, in transplanted patients only on general health perception. Both transplanted and dialysis patients had normal or high scores on mental health. Scores in most physical domains were lower than in 2000. Patients were less often employed (61.8% vs. 81.0%), had less often offspring (31.5 vs. 64.8%) and less often had an income equal to- or above average (34.8% vs. 61.1%) compared to the general population. Disabilities, co-morbidity and unemployment were associated with impaired QoL.

Conclusions: After 30 years of RRT, adult survivors of pediatric ESRD have an impaired physical, but a good mental QoL. The decrease of general health perception and physical functioning over time is worrying and may further hamper employment status and social functioning of these relatively young patients.

INTRODUCTION

As renal replacement therapy (RRT) in children with end stage renal disease (ESRD) has become routine treatment, concern has arisen about its implications for adult life. Outcomes measured in clinical trials typically include biochemical values, infections, cancer and patient survival. However, quality of life (QoL) is an important marker of disease burden and also can be used to assess treatment effectiveness and predict risk for adverse outcomes. [1]

In adult ESRD patients, studies report ESRD to impose substantial effects on the patient's Qol by negatively affecting their social, financial and psychological well-being. [2-4] Low QoL scores are associated with hospitalization, graft failure and long term mortality. [5-7] QoL has also been associated with mortality in other populations such as individuals with chronic obstructive pulmonary disease [8] and diabetes. [9] and individuals with cardiovascular disease. [10;11]

Determinants found to be associated with an impaired QoL in the ESRD population include both medical (i.e. disabilities, comorbidities, RRT modality and prolonged time on dialysis) and socio demographic factors (i.e. older age, female gender, low level of educational attainment, unemployment status and low income). [12-17] However, despite the major interest to young patients and their families, few data exists on the effect of intensive, chronic therapy since childhood on physical and social development in adulthood.

In 2000, we performed a comprehensive study to the Late Effects of Renal Insufficiency in Children (LERIC) in a cohort of all Dutch patients who had started chronic renal replacement therapy (RRT) in childhood. In contrast to reports on adult onset of ESRD, we found close to normal Qol in transplanted patients and significantly impaired physical, but normal mental QoL in dialysis patient. [18] We hypothesized that an even longer period on RRT would affect their physical condition and that ageing would negatively influence their QoL and social functioning. We therefore conducted a 10-year follow up of this study with the aim to assess QoL and social status after 30 years of RRT and to explore determinants (both medical and socio-demographic) associated with an impaired QoL.

METHODS

Study design and procedures

This study is part of a further 10-year follow-up of a comprehensive long-term follow up study into the Late Effects of Renal Insufficiency (LERIC) in patients on renal replacement therapy (RRT) since childhood in the Netherlands. The LERIC cohort comprised all Dutch patients who had started chronic RRT at <15 years of age between 1972 and 1992, and who were born before 1979. In 2000, the first follow-up study, 152 out of 187 surviving patients of childhood RRT participated in this part of the study on QoL. [18] In the current study, patients still alive in 2010 were invited to participate again. Patients who declined participation in the QoL study in 2000 were excluded. The end of the study was marked by the day of the examination of the last participant. After informed consent was obtained, a survey was sent to the home addresses of the participants. To assure anonymity, the returned questionnaires contained only a study number. Non-respondents were sent a reminder

letter and a questionnaire after 3 and 6 months. The medical ethical committees of all participating centers approved the study.

Data collection

Data on clinical characteristics and potential determinants in relation to QoI were collected from medical charts from June 2010 to February 2011. The predefined variables were: age at time of investigation, age at start of RRT, gender, renal replacement therapy at time of investigation, total duration of renal replacement therapy and of dialysis, the occurrence of disabilities and co-morbidity. Co-morbidity was defined as the presence of one or more of the clinical diseases as defined by Davies *et al.* [19] (i.e. malignancy, clinically apparent ischemic heart disease, peripheral vascular disease, clinically apparent left ventricular dysfunction, diabetes mellitus, systemic collagen vascular disease, cerebrovascular disease, chronic obstructive airway disease or other significant pathology). Disabilities were defined as being present in case of severe deafness, blindness or being disabled by motor function disorders.

Data on socio-demographic outcomes including employment status, current income (below vs. national average or above), educational attainment (high level vs intermediate- or low level), marital status (married or living together with partner vs. no partner or divorced), and having offspring were collected by a questionnaire. We categorized the educational attainment according to the highest successfully completed level of schooling: low level (low vocational training, "Lager Beroeps Onderwijs"), intermediate level (intermediate vocational training, "Middelbare Beroeps Onderwijs" or "HAVO/VWO") and high level (high level vocational training, "Hoger Beroeps Onderwijs" or university). According to the definition of the National Dutch Bureau of Statistics, [20] unemployment was defined as less than 30% of full-time equivalent (FTE) spent on paid work.

Age-matched data from the general Dutch population were available on employment, current income, educational attainment, and having offspring. [20]

As in 2000, we used the RAND-36 questionnaire to assess QoL. The RAND-36 is a reliable and valid instrument. [21] It has been used previously to assess QoL in former pediatric ESRD patients [18] and is also widely used in the evaluation of patients with other medical conditions, including rheumatoid arthritis [22] and cancer. [23] The questionnaire is almost identical to the MOS SF-36 75. The difference lies in the slightly different formulation of some questions as well as a slightly different scoring system in the domains of bodily pain and general health. [24;25]

The RAND-36 is made up of 36 questions and standardized response choices, which measure 8 distinct aspects of QoL: physical functioning (PF, e.g. "Does your health now limit you in climbing several flights of stairs?"), social functioning (SF, e.g "To what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?"), role limitation due to physical problems (RP, e.g. "Have you had any problems with your work or other regular activities as a result of your physical health?"), role limitation due to emotional problems (RE, e.g. "Have you had any problems with your work or other regular activities, as a result of any emotional problems (such as feeling depressed or anxious)?"), mental health (MH, e.g. "How much of the time have you felt calm and peaceful?"), vitality (VT, e.g. "How much of the time did you have a lot of energy?") , bodily pain (BP, e.g. "How much did pain interfere with your normal work,

including both work outside the home and housework?"), and general health perception (GH, e.g. "In general, would you say your health is …") All crude scores are converted to a 0-100 scale, in which a higher score indicates a higher level of functioning or wellbeing. Overall physical health and mental health are assessed by aggregation of all domain scores according to an algorithm described by Ware *et al.* [26] leading to the so-called Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. In contrast to the 0–100 scale of the eight RAND 36 scales, both the PCS and MCS have a mean of 50 and a standard deviation of 10 in the general population.

Because the age-range of the available SF-36 normative sample matched the patients better than the available RAND-36 normative sample, we used the SF-36 data from the general Dutch population [27] for comparison with the patients.

Statistical analysis

Data are presented as means, medians and percentages. Differences between participants and non-participants were examined by Chi square test or independent t-test.

QoL of the patients was examined in several ways. First, independent t-tests were performed to compare the mean QoL scores of the patients (total sample, dialysis, transplanted) with the mean scores in the general population. Second, using the 95% confidence interval (CI), the percentage of patients with impaired QoL (total sample, dialysis, transplanted) was compared with the percentage impaired QoL in the general population. Following Rose *et al.*, [28] impaired QoL was considered as a score below the 25th percentile value in the general population. In other words; patients who scored below the value of the 25th percentile in the Dutch population [27] were considered to have impaired QoL. We considered the average Qol for a certain domain as 'impaired for the group' if scores were impaired in a percentage of patients that was significantly higher than 25%, i.e. that the lower value of the CI 95% was at least 25%. Third, to assess the QoL over time, we compared the RAND-36 scores of the patients in 2010 with their scores in 2000 using paired t-tests.

Regarding the dichotomous socio-demographic outcomes, differences between patients and the general population were based on the 95% CI belonging to the patient outcomes. If the value of the general population did not fall within the 95% CI, the patients were considered to differ from the general population.

Finally, to examine potential determinants of impaired QoL, multiple logistic regression analyses (backward) were performed in the total RRT group. First, a pre-selection of potential determinants was made. Age and gender were included in all logistic regression models. In addition, significant determinants from univariate analysis (entry level set at $P<0.3$) were used in the final logistic regression analysis. The independent impact of the determinants was expressed as adjusted ORs, with 95% CIs. The Nagelkerke's R^2 was used as measure of model fit, which ranges from 0 to 1 with higher scores indicating better fit.

A significance level of 0.05 was used for all analyses. We used SPSS 19.0 for Mac (SPSS INC., Chicago, IL, USA) for all statistical analyses.

RESULTS

Study population

The original LERIC cohort consisted of 249 patients of whom 187 were alive in 2000. Of these 187 patients, 35 died between 2000 and 2010. Causes of death included cardiovascular disease (12%), infections (44%), malignancies (20.5%) and other causes (20.5%). Details on mortality have been reported previously [29] Of all 152 patients alive in 2010, 26 were excluded because they declined participation in 2000. Of the 126 patients approached for this part of this study, 89 (70.6%) agreed to participate, of whom 7 had not completed the QoL questionnaire in 2000, leaving 82 patients completing the questionnaires in both 2000 and 2010. The algorithm of the cohort formation is provided in supplementary Figure S1 (published online). Demographic and treatment characteristics of participants and non-participants are shown in Table 1. Non-participants had on average received dialysis for a longer period of time than participants; however, as examined by an independent t-test, this difference was not statistically significant. Data on other clinical characteristics were similar between both groups of patients.

Table 1 | Characteristics of the LERIC 2010 cohort

	Participants (N = 89)	Non-participants (N = 37)
Gender (female)	44 (49.4%)	14 (37.8%)
Mean age at start of RRT in years (range)	11.0 (1.9–21.3)	11.3 (2.7–15.9)
Mean age at time of investigation in years (range)	40.6 (32.0–52.4)	40.3 (32.4–49.6)
Mean duration of RRT in years (range)	29.1 (18.1–39.6)	28.9 (19.1–37.1)
Median duration of dialysis in years (range)	2.7 (0,03–36.5)	4.0 (0.4 –36.5)
Median duration of functioning renal graft in years (range)	23.6 (0.2–39.3)	21.1 (0.2–32.8)
On dialysis at time of investigations	16 (17.9%)	10 (27.0%)
Lifetime dialysis > transplantation	8 (9.0%)	7 (18.9%)
Disabilities	22 (24.7%)	13 (35.1%)
Co-morbidity	48 (53.9%)	18 (48.6%)

RRT = renal replacement therapy; Differences were not statistically significant.

QoL: mean scores

Compared with the general population, the mean scores of all participants were significantly lower in the domains PF, VT and GH. In contrast, patients reported significantly higher scores on BP, indicating that suffering from bodily pain was even less prevalent than in the general population. In addition, the mean scores of the overall study group as well as in the transplanted subgroup were higher on the emotional domains including RE and MH. However, this was not significant (Table 2). Dialysis patients scored significantly lower than the general population on PF, RP and GH.

Transplanted patients only showed significantly worse QoL than the general population on GH, while they reported a significantly better score on BP.

Table 2 | Mean RAND-36 scale scores (SD) of LERIC 2010 (LERIC 2) compared to the general population.

	Gen population age 41–60[1] (N = 571)	LERIC 2 total (N = 89)	LERIC2: TX (N = 73)	LERIC2: DX (N =16)
PF	84.0 (19.6)	78.5 (24.5)*	80.8 (23.1)	68.1 (28.3)*
SF	83.5 (22.1)	82.2 (22.4)	83.6 (22.4)	75.8 (22.1)
RP	74.5 (36.8)	69.9 (40.4)	76.0 (37.6)	42.2 (42.4)**
RE	81.6 (33.2)	83.5 (33.8)	84.0 (33.4)	81.2 (36.5)
MH	75.6 (18.5)	78.3 (16.5)	79.2 (16.1)	74.2 (18.3)
VT	68.6 (20.2)	63.6 (20.6)*	64.2 (20.3)	60.6 (22.3)
BP	71.8 (24.1)	77.7 (24.2)*	77.9 (24.4)*	77.2 (24.7)
GH	69.7 (20.6)	58.3 (23.2)**	59.8 (23.1)**	51.3 (22.7)**
PCS	NS	46.5 (11.3)	47.5 (11.3)	42.3 (11.1)
MCS	NS	50.5 (9.9)	50.7 (9.8)	49.4 (10.9)

TX = transplantation; DX = dialysis; PF = physical functioning; SF = social functioning; RE = role limitations physical problems; RE = role limitations emotional problems; MH = mental health; VT = vitality, BP = bodily pain; GH = general health; PCS = physical component scale, MCS = mental component scale; NS = Not stated

* $p<0.05$: patient group versus general population; ** $p<0.01$ patient group versus general population

[1]Neil K. Aaronson,Martin Muller, 1 Peter D. A. Cohen,Marie-Louise Essink-Bot,Minne Fekkes,Robbert Sanderman,Mirjam A. G. Sprangers, Adrienne te Velde,and Erik Verrips. Translation, Validation, and Norming of the Dutch Language Version of the SF-36 Health Survey in Community and Chronic Disease Populations. *J Clin Epidemiol* Vol. 51, No. 11, pp. 1055–1068, 1998

QoL: proportions of patients with impaired QoL

In the total study sample as well as in the transplanted subgroup, only GH was significantly more often impaired than in the general population (Figure 1). In contrast, in those patient groups MH was significantly better than in the general population, as shown by a lower percentage of impaired QoL with a 95% CI not including 25%. In dialysis patients, the QoL was more often impaired than in the general population for the domains RP, VT and GH.

Change in QoL over the last 10 years

The scores in physical domains were significantly lower than in 2000, including PF, BP, GH and PCS. In contrast, all domains relating to psychosocial functioning (SF, RE, MH and MCS) remained stable over the last 10 years (supplementary Table S1, published online).

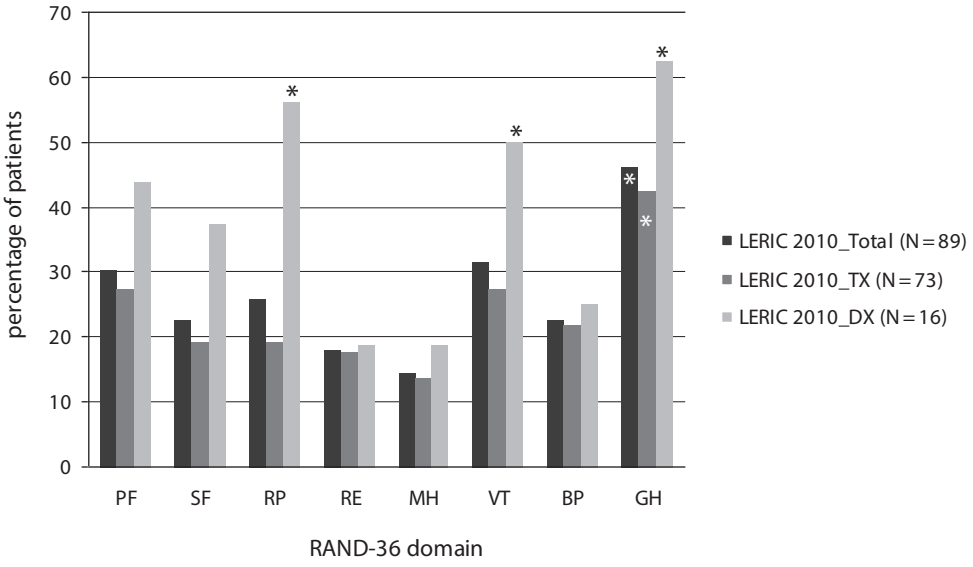

Figure 1 | Percentage of LERIC 2010 with RAND-36 scores below the 25th percentile value of the general population

PF = physical functioning; SF = social functioning; RE = role limitations physical problems; RE = role limitations emotional problems; MH = mental health; VT = vitality; BP = bodily pain; GH = general health; Tx = functioning transplant; Dx = dialysis

Dotted line represents the 25% of the Dutch norm population with impaired QoL according to their RAND 36 score.

* QoL is considered impaired in LERIC if significantly ($p<0.05$) more than 25% of the patients scored below the 25th percentile value of the general population.

Socio-demographic outcomes

Compared to the general population, patients were significantly less often employed (61.8% vs. 81.0%, $P<0.05$). Of the employed patients, 81.8% spent at least 50% of their FTE on paid work. Among patients on dialysis at time of investigation, only 31.3% were employed. 34.8% of the patients in the study sample had an income equal to or above the national average of €2500 (about $ 3200) gross per month, a significantly smaller proportion compared to the general population (61.1% $P<0.05$). Among the patients, 22.1% had completed a high vocational training or scientific degree, compared to 31.2% in the general Dutch population ($P>0.05$). Of all 89 patients, 60 (67.4%) were married or lived with a partner and 28 (31.5%) had offspring compared to respectively 74.4% ($P>0.05$) and 64.8% ($P<0.05$) in the general population.

Determinants of QoL

Both clinical as well as socio-demographic variables were associated with impaired QoL of the total LERIC 2010 study sample (Table 3). Co-morbidity was associated with an increased risk of impaired QoL in the domains of PF, RP and BP. Having disabilities was associated with an increased risk of impaired QoL regarding PF, VT and BP. Mode of RRT at time of investigation was not correlated

Table 3 | Determinants of impaired QoL in LERIC 2010: backward logistic regression model of RAND-36 scores below the 25th percentile (ORs with 95% CI)

	PF	SF	RP	RE	MREH	VT	BP	GH
Age	–	–	–	–	–	–	–	–
Gender[1]	–	–	–	–	–	–	–	–
RRT modality at time of investigation[2]	–	–	–			–		–
Total RRT yrs	–	–		–				–
Dialysis> transplantation[3]	–		17.4 (2.6–116.9)**	–			–	–
Disabilities3	6.4 (1.9–21.0)**	–	–		–	3.3 (1.1–9.8)*	4.2 (1.3–14.0)*	
Co-morbidity3	4.1 (1.3–13.6) *	–	8.5(2.0–35.9)**	–		–		
	5.0 (1.4–17.7)*	–						
Work3	0.2 (0.1–0.6)**	–	–	–	–	0.3 (0.1–0.8)*		0.3 (0.1–0.7)**
Income ≥ € 2500/ month (average) [3]	–	–	0.2 (0.0–0.7)*	–		–	–	
Partner3				–				
Children3		0.2 (0.0–0.9)*	–	–				
Educational attainment[4]			–			–		
R^2	0.337	0.099	0.392			0.157	0.195	0.112

PF = physical functioning; SF = social functioning; RE = role limitations due to emotional problems; RE = role limitations due to physical problems; MH = mental health; VT = vitality; BP = bodily pain; GH = general health; RRT = Renal Replacement Therapy; *$P<0.05$, **$P<0.01$; '-': entered into multiple logistic regression analysis but not significant.

[1]coding 0=female, 1=male; [2]coding 0=functioning transplant, 1=dialysis [3]coding 0=no, 1=yes; [4]coding: 0=low- or intermediate level educational attainment (low vocational training, "Lager Beroeps Onderwijs", intermediate vocational training, "Middelbare Beroeps Onderwijs, HAVO/VWO), 1=high level educational attainment (high level vocational training, "Hoger Beroeps Onderwijs" or University)

with impaired QoL in any domain. However in case lifetime on dialysis exceeded lifetime on renal transplant, we found an increased risk of impaired RP. Regarding the socio-demographic variables, being employed appeared to be associated with a lower risk of impaired QoL in the domains of PF, VT and GH. Having offspring was associated with a lower risk of impaired QoL regarding SF and an income equal to or above the national average of €2500 (about $ 3200) gross per month, was associated with a lower risk of RP.

DISCUSSION

This study is part of a 10-years extension of a nationwide Dutch study to the Late Effects of Renal Insufficiency in Children (LERIC). It is unique for its long period of follow-up of patients who started RRT in childhood.

According to our data, middle aged survivors of pediatric ESRD have a remarkably good mental QoL even after 20 to 40 years of renal replacement therapy. At the same time, physical health had become more impaired over the last 10 years. In 2000, we reported on the surprisingly good mental Qol of patients within our cohort on dialysis, which contrasted sharply with age-matched dialysis patients with adult onset of ESRD[11]. Current data show that ageing has not negatively influenced the perception of me (pgntal health of both dialysis and transplanted patients. The mental Qol scores of transplanted patients were similar or even superior to those in the general population. This high level of QoL after renal transplantation has been found in previous studies [30-32] but these have all been conducted in patients with adult onset of ESRD and consequently with much shorter history of renal disease.

The relatively high scores on mental health are consistent with findings in other studies of adolescents and adults with chronic illness since childhood including sickle cell patients, cystic fibrosis and asthma. [33-35] This fact could be directly related to their nearly life-long chronic disease status. [36] Patients with chronic disease since childhood might not have experienced or might not be able to recall life without kidney disease and lack reference of life without disease. As a consequence, their lives will probably meet their expectations, despite their physical disabilities. This could explain the differences with the far more adverse outcomes in patients with adult onset of ESRD. [4] The fact that scores on mental health have remained high over time after 30 years of RRT with a concurrent decline in physical health and subsequently physical Qol is nevertheless striking. Nearly 75% of patients stated that their disease had brought them something positive in life. The perceived benefits of having ESRD included more satisfaction with (small things in) life, having developed a sense of perseverance and positive responses from friends and relatives (data not presented).

We found a significant decrease of physical Qol over time in our cohort, also in transplanted patients. This is largely explained by a normal effect of ageing in line with the trend in the general population. Previous studies also identified older age as most important negative predictor of perceived physical health status. [13;14;17;37;38] However, in patients with considerable co-morbidities and disabilities, one could expect an even sharper decline in physical QoL. One explanation might be that the shift

in point of reference for standards in life, as we described above, also accounts for physical QoL. As most patients who survived after 2000 had a good function renal graft, a positive selection might also have been of influence. Nevertheless, the ongoing deterioration superposed on lower scores on some domains might become problematic for social functioning of these patients in the coming years.

Although significantly lower than in the general Dutch population and despite the deteriorating physical condition, a substantial proportion of nearly two-third of patients had remained employed. This is similar to the situation in 2000 [39] and in line with recent findings in transplanted patients with adult onset of ESRD. [40] In contrast with the situation in 2000 when transplanted and dialysis patients were equally employed, we now found an important difference between dialysis patients of whom only 31.3% was employed and transplanted patients in whom 68.5% was employed. The prevalence of low income was significantly higher than in the general population, which is partly explained by a larger proportion of patients on unemployment benefit. Chronic fatigue and physical motor disabilities are most commonly mentioned reasons in relation to unemployment by our patients. Furthermore, the relatively lower educational attainment could be of disadvantage on the labor market. Finally, some patients reported that termination of their employment contract appeared to be a direct result of the disclosure of their dialysis status. We found co-morbidity and the presence of disabilities, but not renal replacement therapy modality at time of investigation to be most predictive for an impaired physical QoL. This implies that after such a long period of time with RRT, the overall health status including co-morbidities and disabilities is more important than the actual modality of RRT. In line with previous studies involving adult patients with ESRD, [15;39;41;42] unemployment was another important factor associated with impaired physical QoL. We do not know the direction of this association. Yet, it is obvious that severe physical impairment puts people at risk of unemployment and, as a consequence, low income. Surprisingly and contrary to some other reports, [12;16;43] being highly educated (versus low or intermediate level of education) did not affect Qol in any way. We found no relationship between QoL and marital status, while having children was related to a lower risk for impaired SF. In other psychosocial health domains we were not able to identify any determinant. It is possible that we didn't include determinants specifically important to those domains, such as strategies of coping with the disease, social support and psychological problems. [44]

This study has several limitations. The main limitation is the small sample size, especially concerning patients currently on dialysis. However, the sample still represents 59% of all living Dutch patients who started renal replacement therapy (RRT) at age 15 years or below between 1972 and 1992 and who were born before 1979. In addition, we had complete clinical information on the 41% non-participants in this part of the study, so that we could estimate the extent of a potential bias of the outcomes. Second, our outcomes might have been affected by a selection bias towards patients with a better physical condition, as the total time on dialysis of the non-participants was slightly (though not statistically significantly) longer than of the participants. Third, the assessment of psychiatric comorbidities by means of a standardized screening test was not performed in this study. However, based on data from clinical charts and answers to the questionnaires there was no reason to suspect the presence of severe psychiatric comorbidities within this cohort.

In conclusion, our findings indicate that after 30 years of renal replacement therapy, adult survivors of ESRD since childhood have an impaired physical, but remarkably good mental QoL. Physical QoL was largely determined by the existence of co-morbidities or disabilities. Taken into account that the management and outcome of children with ESRD have improved over the last 20 years, the favorable scores on the psychosocial domains of QoL may be supportive to the coping process of children with renal failure and their caretakers to maintain good hope for the future. Although the level of employment is still acceptable among transplanted patients, unemployment is a significant problem among dialysis patients. Employers should be encouraged to adjust work-load and tasks to the capabilities of the patients. Finally, future research should be directed at psychosocial factors such as social support and coping, in order to be able to detect and support the children and adolescents who are at risk for impaired QoL.

PUBLISHED ONLINE

Table S1 | Mean RAND-36 scale scores (SD) of patients (N = 82) who completed the RAND-36 in both 2000 (LERIC1) and 2010 (LERIC2)

	LERIC1	LERIC2
PF	87.2 (16.3)	79.4 (24.8)*
SF	86.6 (18.3)	82.9 (22.3)
RP	77.1 (35.6)	71.0 (40.3)
RE	87.4 (29.9)	83.3 (33.6)
MH	78.8 (13.5)	78.9 (15.5)
VT	68.1 (17.6)	63.9 (20.0)
BP	87.8 (18.7)	79.4 (24.0) *
GH	70.6 (19.2)	58.4 (23.2) *
PCS	52.0 (8.7)	47.0 (11.4) *
MCS	50.0 (8.3)	50.6 (9.5)

PF = physical functioning; SF = social functioning; RE = role limitations physical problems; RE = role limitations emotional problems; MH = mental health; VT = vitality; BP = bodily pain; GH = general health, PCS = physical component scale; MCS = mental component scale

* $p<0.01$: LERIC1 versus LERIC 2

Table S2

Domain	Example item
PF	"Does your health now limit you in climbing several flights of stairs?
SF	"To what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?"
RP	"Have you had any problems with your work or other regular activities as a result of your physical health?"
RE	81.6 "Have you had any problems with your work or other regular activities, as a result of any emotional problems (such as feeling depressed or anxious)?
MH	75.6 "How much of the time have you felt calm and peaceful?"
VT	68.6 "How much of the time did you have a lot of energy?"
BP	71.8 "How much did pain interfere with your normal work (including both work outside the home and housework)?"
GH	69.7 "In general, would you say your health is..(excellent/very good/ good/fair/poor)"

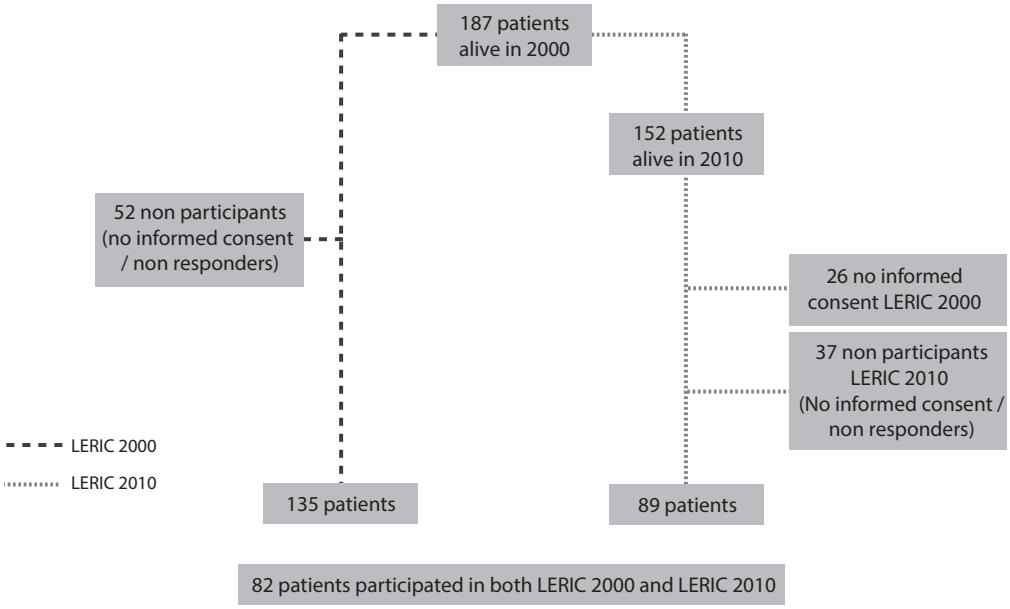

Figure S1 | LERIC cohort formation for psychosocial data collection

LERIC = Late Effects of Renal Insufficiency in Children

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08

General discussion

GENERAL DISCUSSION

In the context of this thesis, we studied the very long-term outcomes of renal replacement therapy (RRT) in children collected by the Late Effects of Renal Insufficiency in Children (LERIC) study. To our knowledge, this cohort study has the longest follow-up so far reported in pediatric RRT. In this chapter we will discuss the main results and put these into perspective. Recommendations for current clinical practice and further research in this field will be discussed.

We had several research questions and aims. The first part of this thesis focuses on mortality, change of pattern over time in causes of death and on potential determinants for this pattern. The second part focuses on the prevalence of infections and malignancies as important outcomes in pediatric and adult ESRD in relation to RRT exposure as well as era of onset of RRT. The third part presents the results of the quality of life after 30 years of RRT and the determinants (both medical and socio-demographic) associated with impaired QoL.

In this chapter, after presentation of the most important results, we will discuss the impact of these results on clinical practice, and present our recommendations for the research agenda.

1. Mortality and causes of death. Did cardiovascular death become an even more pronounced problem after 2000? And was there a change in the prevalence of cardiovascular risk factors potentially relating to changes in cardio protective treatment over the past decade?

We found a substantial shift in causes of death in our cohort after more than 25 years of renal replacement therapy since childhood over the last 10 years. Cardiovascular mortality decreased significantly in the last 10 years compared with the period 1972–1999, whereas infectious mortality increased. We also found a decrease in cardiovascular events and risk factors for cardiovascular death in our cohort over the last 10 years when compared with the period up to 2000. This decrease ran parallel to a significant increase in cardio protective therapy and life-style.

Cardiovascular disease is generally regarded as by far the most important cause of death in young patients with end-stage renal disease. [1-4] In addition to classical risk factors, such as hypertension, dyslipidemia and physical inactivity, other chronic kidney disease-specific factors could have influenced the impressive prevalence of cardiovascular disease, such as uremic toxins, a high FGF-23, low klotho, low fetuin A, inflammation, hyperhomocysteinemia, and hyperparathyroidism. [5-8] As a result of this, 300 to more than 500 fold increased risk for early cardiovascular mortality has been reported in young ESRD patients. [9;10] These data are in line with earlier data from the LERIC cohort, but in contrast to what we found over the last decade as cause of death.

There are 2 explanations for our findings:

Improvement of cardiovascular management and reduction of risk factors. A possible reason for the decrease in cardiovascular death over the last 10 years could be a reduction in cardiovascular burden over time as a result of improved cardio protective management. Indeed, we found a significant decrease in the prevalence of left ventricular hypertrophy (LVH), hypertension and hypercholesterolemia over the last decade. We found a simultaneous significant increase in both cholesterol-lowering medication and antihypertensive medication, especially of ACE inhibitors/

ARBs, between 2000 and 2010. In parallel, we found a trend towards a decrease in nonfatal cardiovascular events.

The USRDS data also showed a declining burden of cardiovascular mortality among the dialysis patients of all ages over the last years. [11] Also ANZDATA showed decreasing cardiovascular mortality rates for all dialysis patients. [12] In our study among patients who started RRT at very young age, the decline in cardiovascular deaths over time was far more pronounced than in both the USRDS and ANZDATA studies. USRDS data also confirm a trend towards a decrease in cardiovascular casualties over the last decade and a concurrent intensified management of cardiovascular disease in patients on RRT. [13]

Our data suggest that cardio protective measures, such as a strict blood pressure control, especially by ACE inhibitors or angiotensin receptor blockers and reduction in dyslipidemia are effective in reducing cardiac threat in patients with ESRD even after a long lasting burden of cardiovascular disease. This policy should therefore be encouraged, especially given the fact that a recent study indicates that the majority of patients with ESRD still have suboptimal treated hypertension. [14]

An increased impact of transplantation versus dialysis over the last 10 years. Over 75% of patients who survived up until 2000 were living with a renal graft at that time. Also, most patients who died between 2000 and 2010 were transplanted patients. Therefore, contrary to the situation before 2000, the mortality risk factors were by far more determined by the time spend with a renal graft than by the time on dialysis. From the adult ESRD literature it is well known that being on chronic dialysis has much more impact on the cardiovascular system than having a functioning renal graft. [15;16]

2. The impact of infections in ESRD and in ESRD in children after 25 years of renal replacement therapy. Infections and malignancies are the most common non-cardiovascular causes of death in patients on RRT and in patients of the LERIC cohort in 2000. [17;18] Our aim was to evaluate the most common non-cardiovascular cause of death compared to the general population in patients on dialysis or living with a renal transplant. For this reason we also analyzed death by infections and malignancies in a large cohort of adult onset RRT patients, using data from the ERA-EDTA registry. In the LERIC cohort we found that the infection had become the most important cause of death of the last decade of follow-up, followed by malignancies. The main results from the ERA-EDTA Registry data showed that young patients on dialysis, especially females with multisystem disease, are at a relatively high risk of infection-related mortality. In the general population the risk of death due to infections is extremely low and women have even lower death rates than men. Mortality rate ratios were calculated to compare mortality in RRT patients with that in the general population. While the high infection-related mortality rate ratio in young women may be partially explained by the low risk in women in the general population, this finding suggests a loss of the "survival advantage" of women regarding infection-related causes of death. The fact that the largest differences between men and women in our study occurred at relatively young age, aged 0–39 years, may suggest a role of sex hormones on the immune system. [19] Among young women, in the fertile age category, on dialysis, estradiol levels (which enhance phagocyte function of neutrophils) are generally lower than

in transplant recipients and the general population, which may at least in part explain the loss of female survival advantage. [20;21]

In the LERIC cohort, we investigated the total burden of severe infections in patients with a long history of RRT. We showed evidence for a significant increase in the burden of clinically important infections in transplanted patients over the past decades, not only in the first year after transplantation but also among patients who have been living with a functioning graft for a prolonged period of time. Infections have for a long time been found to be the second cause of death in patients with ESRD. [13] We found a trend in infectious mortality in three different time periods that suggests an increased risk of death by infections in 2000–2010 when compared with 1972–1989 and 1990–1999. Our data could not be explained by the trend in the general population, in which infection plays a minor, and over time even a decreasing role in the cause of death, at least in the western world. [22;23] However, the USRDS showed a significant increase in hospitalization due to infection in dialysis patients from 1993 to 2005, as well as in transplanted patients between 1991 and 1998. [24;25] Therefore, we explored the burden of severe infections over 30 years of RRT in patients with pediatric onset of ESRD using hospitalizations as a marker. As hospitalization patterns in the Netherlands have adopted a higher threshold for admission over the last 30 years, [22] we also analyzed the infection/non-infection admission rate ratio over time in order to correct for this change in admission policy. We found a consistent increase in the Infection/Non-infection hospitalization rate ratio, suggesting a relative increase in the burden of infections over the past decades. This increase was exclusively found in patients living with a functioning renal graft, where urinary tract infections accounted for the majority of admissions. Over the last decade, patients of the LERIC cohort spent relatively more time with a functioning renal graft than during the earlier time periods. Our data showed a high burden of transplant-related infections, not only during the first year after transplantation, but also long thereafter. We did not find significant changes in the 1st-year vs. after first year infection ratio throughout the observation period. This is especially remarkable as these patients were on average between 30 and 40 years old in 2000–2010, an age that is associated with the lowest risk of death by infection according to most RRT registry studies. [23;26] Our findings therefore most probably reflect a more general trend towards an increase in infections in renal transplant patients over the last 10 years, which is a worrying development. Infections, even if not lethal, are especially worrying in transplantation patients as they may lead to graft loss. UNOS data have shown an increase in death-censored graft failures due to infections. [27] Recent studies showed that the increase in burden of transplant-related infections is the concurrent trend towards the use of more potent immunosuppressive strategies in renal transplantation over the last 20 years. [28] Other studies showed evidence for a direct relationship between the extent of immunosuppression after transplantation and the risk of infections. [29-31]

We found evidence for an increasing burden of lethal infections, mostly transplantation-related. The most plausible cause is the concurrent trend towards the use of more potent immunosuppressive strategies in renal transplantation over the last 20 years. [28] Not the specific type of drug, but the use of higher dosages, especially of calcineurin inhibitors and the use of triple instead of double therapy have been found to be associated with both a decrease in acute rejections and more infections. [32-35] In the Netherlands, all centers for adult renal transplantation have introduced IL-2

blockers during the early 2000s as part of the induction therapy, and all centers have switched from cyclosporine to high dose tacrolimus in combination with mycophenolate mofetil as part of the induction therapy. This indeed implies a substantial increase in average immunosuppressive dose over the last 10 years. [28] Physicians should consider to dose the amount of immunosuppressive medication to the risk of rejection of a renal transplant of a patient. They can also consider to reduce the amount of immunosuppressive medication to a minimum in patients who did not show a rejection after one year after renal transplantation.

3. The impact of malignancies in patients with ESRD and with 25 years of renal replacement therapy. We wondered what the most common non-cardiovascular causes of death (infections and malignancies) in patients treated with dialysis or living with a kidney transplant compared to the general population were. In the LERIC cohort, most malignancies occurred towards the end of follow-up in 2000. [36] Would this rise in malignancy prevalence continue with further ageing of our cohort? Which malignancies would be prevalent?

End-stage renal disease (ESRD) is associated with an increased risk of malignancies. In the ERA-EDTA Registry data including patients having started RRT across all age categories we found a small, but significantly increased risk of malignancy-related mortality compared to the general population. In LERIC we found that cancer, especially disabling and potentially life threatening forms of cutaneous squamous cell carcinoma (cSCC), is highly prevalent among pediatric end-stage renal disease patients after more than 25 years of RRT. cSCC occurs relatively late after transplantation and tends to recur frequently. Data from the LERIC cohort showed that also the risk of death due to malignancies was only moderately increased, but 30 years after first renal transplantation 41% of survivors had suffered from a malignancy. This concerned predominantly cutaneous squamous cell carcinomas (cSCC), known for their relatively mild course in the general population. In transplanted patients, however, these skin tumors appear to behave far more aggressively than in the general population with an extreme high rate of recurrence, 31% within 1 year, This might therefore increase the number of cancer deaths in this group within the next decade. The incidence of primary cSCC within our cohort was 744 times higher than in the age-matched population. This outnumbers previous reports on adults, but confirms non-melanoma skin cancer (NMSC) and virus related cancers to be the predominant types of cancers found in transplanted patients. [37-40] As these reports concern patients starting RRT at adult age, these patients have had far less total exposure time of RRT than the LERIC patients. Our findings confirmed our hypothesis that the effect of exposure to RRT from childhood onwards might lead to an exponential increase in number of malignancies. Moreover, the chronicity of the disease may have an important negative impact on the quality of life due to frequent hospital visits, excisions and cosmetic damage.

Measures should be taken to reduce the burden of cSCC. UV exposure and human papilloma virus (HPV) in combination with immunosuppression are thought to be the most important causative factors for the development of post-transplant cSCC. UV radiation is probably one of the most important factors. [41] We therefore advise that all risk factors must be reduced. The most important risk factor is sunburn at an early age. [42] This reduction could take place through education, parental

role modeling and sunscreen vigilance. In addition, it can also be considered to vaccinate all ESRD patients against HPV.

4. Quality of Life. In 2000, in the LERIC cohort, we found close-to-normal Quality of Life (QoL) in patients who underwent transplantation, and significantly impaired physical but normal mental QoL in patients receiving dialysis. [43] Would the meanwhile longer period on RRT affect their physical condition and would aging negatively influence their QoL and social status?

In 2010, patients had kept this remarkably good mental QoL, Physical health, on the other hand, had become more impaired. Previous studies confirmed this. [44;45] However, in patients with considerable comorbidities and disabilities, one could expect an even sharper decrease in physical QoL because of an impaired physical health. One explanation might be that the shift in point of reference for standards in life also applies to physical QoL.Current data also show that ageing has not negatively influenced the perception of mental health in both dialysis and transplanted patients. The mental QoI scores of transplanted patients were similar or even superior to those in the general population. Our study showed, as in patients with adult onset of ESRD who receive a renal transplant, a high level of QoL after renal transplantation. Despite the deteriorating physical condition a substantial proportion of nearly two-thirds of patients had remained employed. This is in line with recent findings in transplanted patients with adult-onset ESRD. [46] Reasons for unemployment of our patients were chronic fatigue and physical motor disabilities. The prevalence of low income was significantly higher than in the general population. This could be explained by relatively lower educational attainment and by a larger proportion of unemployed patients. Having children was related to a lower risk for impaired social functioning but we found no relationship between QoL and marital status.

Taken into account that the management and outcome of children with ESRD have improved over the last 20 years, the favorable scores on the psychosocial domains of QoL may be supportive to the coping process of children with renal failure and their caretakers to maintain good hope for the future. Although the level of employment is still acceptable among transplanted patients, unemployment is a significant problem among dialysis patients. It is obvious that severe physical impairment puts people at risk of unemployment and, as a consequence, low income. Employers should be encouraged to adjust work-load and tasks to the capabilities of the patients.

RECOMMENDATIONS FOR FUTURE RESEARCH

1. In order to get answers to the questions that the LERIC follow-up study has generated, one can think of the following lines for further research.
2. Further follow-up of the LERIC cohort in order to establish the development of the high infection rate and increased incidence of malignancies that were found. It is also important to have an intensified follow-up of these patients after childhood.

3. Research pertaining to the factors leading to the increased risk of infection-related mortality and the high burden of transplant-related infections. Better prevention of infections in RRT patients is needed.
4. The incidence of malignancies post-transplantation is highly increased. The chronicity of the disease may have an important negative impact on the quality of life. Research to improve prevention of skin cancer in post-transplantation patients is needed. For example, investigation of the role of HPV vaccinations in children with ESRD and the role on the development of SCC in adult age.

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09

Summary

Nederlandse samenvatting

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Curriculum Vitae

Summary

This thesis describes the most important results of LERIC, a very a long-term follow-up study to the late somatic and psychosocial consequences of renal insufficiency in children. LERIC is a comprehensive study to evaluate the late effects of renal insufficiency in all Dutch children who had started chronic renal replacement therapy (RRT) between 1972 and 1992 at an age less than 15 years and who were born before 1979. We established the actual health status of patients, especially focusing on cardiovascular abnormalities, infections, malignancies and quality of life. Since the literature over the last decades has indicated that infections and malignancies form potentially lethal comorbidity in end-stage renal disease (ESRD), we broadened our study by using data from the European Renal Association – European Dialysis and Transplantation Association (ERA-EDTA) Registry.

This thesis consists of an introductory chapter followed by three parts and a general discussion. **Chapter 1**, which is the general introduction, gives an overview of the most important findings of LERIC up to 2000. At that time, cardiovascular disease was by far the most important cause of death within the cohort, accounting for 41% of all deaths. Moreover, cardiovascular disease was highly prevalent. The second and the third cause of death were, respectively, infections and malignancies. Finally, transplanted patients reported an overall good quality of life and, surprisingly, patients on dialysis only reported an impaired physical quality of life. They scored relatively good on vitality, physical pain and had a remarkably good mental quality of life. As data on the very long outcome were lacking, we aimed to follow this unique group of patients for another 10 years in order to have a comprehensive picture of the burden of a median of 25 years of RRT in patients with pediatric ESRD. Based on the outcomes in 2000, we speculated that cardiovascular casualties would be even more common in 2010 than in 2000 and, otherwise, that also infections may play an important role in non-cardiovascular mortality and morbidity. As the majority of malignancies appeared in the oldest patients in 2010, we presumed that this problem would worsen. Finally, we assumed that a longer burden of RRT would have impact on Quality of Life (QoL) on the long run.

Part I concerns the long-term cardiovascular complications of patients with renal replacement therapy since childhood. In **chapter 2**, we investigated the actual trend in long-term mortality and causes of death after 2000. In 2010, a second follow-up study of the LERIC study was conducted covering the period from the last chart review in 1999 until the last chart review in 2010–11 or the patient's death. We analyzed data on mortality and causes of death in the total cohort from 1972 until 2010 and compared two time periods, 1990 until 1999 and 2000 until 2010, with the time period 1972 until 1989. In contrast to our expectations, we found a substantial shift from cardiovascular disease to non-cardiovascular disease as the cause of death over the last 10 years. This occurred while the overall mortality had stabilized over time. A possible reason for the significant decreased risk of cardiovascular mortality is the awareness of the cardiovascular burden in these patients that urged a strict cardiovascular management. In **chapter 3**, we aimed to investigate whether there was a decrease in the prevalence of cardiovascular risk factors that may pertain to changes in cardio protective treatment over the past decade. We found indeed a significant decrease in the prevalence of left ventricular hypertrophy (LVH), hypertension and hypercholesterolemia over the last decade. We also found a trend towards a decrease in nonfatal cardiovascular events. This was consistent

with the significant decrease in cardiovascular death over the same period on which we reported in chapter 2. We found a simultaneous significant increase in both cholesterol-lowering medication and antihypertensive medication, especially of ACE inhibitors/ARBs, between 2000 and 2010. These outcomes indicate that a strict blood pressure control, especially by ACE inhibitors or angiotensin receptor blockers and reduction in dyslipidemia may be effective in reducing cardiovascular risk in patients with ESRD even after a long lasting burden of cardiovascular disease.

Part II describes the impact of infections and malignancies in ESRD in patients of the ERA-EDTA registry and in patients with ESRD since childhood (after a median of 25 years of renal replacement therapy). In **chapter 4**, we aimed to quantify the occurrence of the most common non-cardiovascular causes of death, infections and malignancies, in patients treated with dialysis or living with a kidney transplant; to compare rates of these fatal events with those in the general population; and to assess the role of age, sex and primary renal disease as determinants of mortality due to infections and malignancies in these patients. We used data from the European Renal Association – European Dialysis and Transplantation Association (ERA-EDTA) Registry, which collects data on RRT patients via national and regional renal registries in Europe. We found infection-related mortality to be highly increased among both dialysis patients and kidney transplant recipients. Young patients on dialysis, especially females with multisystem disease, were at a relatively high risk of infection-related mortality. In **chapter 5**, we evaluated the burden of severe infections in patients with pediatric onset of ESRD over a 25 years follow-up. We found evidence for a significant increase in the burden of clinically important infections in transplanted patients over the past decades, not only in the first year after transplantation but also among patients who have been living with a functioning graft for a prolonged period of time. The most plausible cause for the increase in burden of transplant-related infections was the concurrent trend towards the use of more potent immunosuppressive strategies in renal transplantation over the last 20 years. Physicians can consider dosing immunosuppressive medication to be commensurate with the risk of rejection of a renal transplant of a patient. In **chapter 6**, we described the prevalence and risk factors of cancer after very long term follow-up in patients who started RRT before the age of fifteen. We showed a cumulative cancer incidence of 41% after 30 years since first transplantation. Cutaneous squamous cell carcinoma was by far the most prevalent, and occurred relatively late after transplantation. Malignancies (especially cutaneous squamous cell carcinoma) recurred frequently, 31% of the patients with cancer developed a second de novo malignancy within 1 year. Compared to the general Dutch population, the risk of developing a malignancy in this cohort was more than twenty-fold higher. Malignancies contributed to a significant proportion of overall mortality (12.6%). Although in most cases these malignancies were not lethal at short follow-up, the high recurrence rate may affect the outcome on an even longer term. Moreover, the chronicity of the disease may have an important negative impact on the quality of life due to frequent hospital visits, excisions and cosmetic consequences. Besides that, the threat of becoming a lethal disease is always present, with a subsequent high psychological burden.

Part III describes the quality of life (QoL) and socio-demographic outcomes in patients with pediatric onset of end-stage renal disease after at least a median of 25 years of renal replacement therapy. In **Chapter 7**, we assessed QoL and social status after at least a median of 25 years of RRT and explored determinants (both medical and socio-demographic) associated with an impaired

QoL. Data on clinical characteristics and potential determinants in relation to QoL were collected from medical charts. Data on socio-demographic outcomes including employment status, current income (below vs. national average or above), educational attainment (high level vs intermediate- or low level), marital status (married or living together with partner vs. no partner or divorced), and having offspring were collected by a questionnaire. As in 2000, we used the RAND-36 questionnaire to assess QoL. Age-matched data from the general Dutch population were available on employment, current income, educational attainment, and having offspring. According to our data, middle-aged survivors of pediatric ESRD still had a remarkably good mental QoL even after 20 to 40 years of renal replacement therapy. At the same time, physical health had become more impaired over the last 10 years. Physical QoL was largely determined by the existence of co-morbidities or disabilities. In 2000, we reported on the good mental QoL of patients within our cohort on dialysis, which contrasted sharply with age-matched dialysis patients with adult onset of ESRD. Current data show that ageing has not negatively influenced the perception of mental health of both dialysis and transplanted patients. The mental QoL scores of transplanted patients were still similar or even superior to those in the general population. The prevalence of low income was significantly higher than in the general population. This could be explained by relatively lower educational attainment and by a larger proportion of unemployed patients. Having children was related to a lower risk for impaired social functioning but we found no relationship between QoL and marital status.

Finally, in **chapter 8**, the general discussion of all findings, the implications for clinical practice and directions for future research are outlined.

Nederlandse samenvatting

LERIC (Late Effects of Renal Insufficiency in Children) is een lange termijn follow-up studie naar de late somatische en psychosociale effecten van patiënten die vanaf de kinderleeftijd afhankelijk zijn van nierfunctie-vervangende therapie. Het LERIC cohort omvat alle Nederlandse patiënten, geboren voor 1979 die tussen 1972 en 1992, op een leeftijd jonger dan 15 jaar gestart zijn met chronische dialyse en niertransplantatie. We hebben de gezondheidsstatus van die patiënten onderzocht en daarbij met name gefocust op hart- en vaat ziekten, infecties, kanker en kwaliteit van leven. In 2000 is het cohort voor het eerst onderzocht. In 2010 hebben we het onderzoek herhaald. In dit proefschrift worden de belangrijkste resultaten van de bevindingen uit 2010 beschreven.
Uit de literatuur van de afgelopen decennia weten we dat infecties en kanker een mogelijke lethale co- morbiditeit kunnen zijn in eind stadium nierfalen. Om deze reden hebben we onze studie in 2010 uitgebreid met data van volwassen patiënten met terminale nierinsufficiëntie uit heel Europa, die ongeveer dezelfde leeftijd hebben bereikt als de LERIC patiënten ten tijde van het onderzoek. Hiervoor hebben we gebruik gemaakt van de data van de European Renal Association – European Dialysis and Transplantation Association (ERA-EDTA) Registry).

In **hoofdstuk 1**, wordt een algemene introductie gegeven over de belangrijkste bevindingen tot het jaar 2000 van de LERIC studie. Op dat moment vormden hart- en vaatziekten bij uitstek de belangrijkste doodsoorzaak binnen het cohort. Infecties en kanker waren doodsoorzaak nummer twee en drie. Opvallend was dat getransplanteerde patiënten over het algemeen een goede kwaliteit van leven hadden. Dialysepatiënten rapporteerden een verminderde fysieke kwaliteit van leven maar daarentegen een goede mentale kwaliteit van leven.

Aangezien data op de langere termijn ontbraken hebben we deze unieke groep patiënten nog 10 jaar langer vervolgd. Zo hadden we een goed beeld van de late complicaties van 25 jaar nierfunctie-vervangende therapie in patiënten die sinds kinderleeftijd kampen met eindstadium nierfalen. Naar aanleiding van de uitkomsten in 2000, hadden we verwacht dat in 2010 hart- en vaatziekten een nog groter probleem zouden worden en dat zowel infecties als kanker een belangrijke rol zouden zijn gaan spelen m.b.t. mortaliteit en morbiditeit. Tenslotte namen we aan dat de langere blootstelling aan nierfunctie-vervangende therapie een impact zou hebben op de kwaliteit van leven.

Deel I van het proefschrift gaat over de lange termijn complicaties van hart- en vaatziekten van patiënten die sinds de kinderleeftijd nierfunctie-vervangende therapie krijgen.

In **hoofdstuk 2** hebben we gekeken naar de trend in lange termijn mortaliteit en doodsoorzaken na 2000. In het vervolgonderzoek van de LERIC studie hebben we data uit medische statussen verzameld van 2000 tot 2010. We vonden in de afgelopen 10 jaar een substantiële shift van hart- en vaatziekten als doodsoorzaak naar niet-hart- en vaatziekten als doodsoorzaak. Een mogelijke reden voor de afname in hart- en vaatziekten als doodsoorzaak kan zijn dat behandelaars zich bewuster zijn geworden van de noodzaak van het behandelen van hart- en vaatziekten in patiënten met nierfunctie-vervangende therapie.

In **hoofdstuk 3** hebben we onderzocht of er een afname was in de prevalentie van risicofactoren van hart- en vaatziekten. We vonden inderdaad een significante afname in het vóórkomen van linker ventrikel hypertrofie, hypertensie en hypercholesterolemie in de afgelopen 10 jaar. Tevens

vonden we tussen 2000 en 2010 een significante toename in cholesterol verlagende medicijnen en antihypertensieve medicatie. Onze data veronderstelt dat een strikte behandeling van hoge bloeddruk en hoog cholesterol effectief kunnen zijn in de daling van het voorkomen hart- en vaatziekten in patiënten met eind stadium nierfalen.

In **deel II** van het proefschrift wordt de impact van infecties en kanker in patiënten met eind stadium nierfalen van de ERA-EDTA Registry en van patiënten met eind stadium nierfalen sinds kinderleeftijd (dus na 25 jaar van nierfunctie vervangende therapie) beschreven.

In **hoofdstuk 4**, hebben we de gekeken naar de incidentie van de meest vóórkomende niet-cardiovasculaire doodsoorzaken (infecties en kanker) in dialyse- en transplantatie patiënten. We hebben deze uitkomsten vergeleken met dezelfde uitkomsten in de algemene bevolking. Tevens hebben we in deze patiënten de invloed van leeftijd, geslacht en primaire nierziekte op mortaliteit door infecties en kanker onderzocht. Hiervoor hebben we data van de ERA-EDTA Registry gebruikt. Deze registratie verzamelt data van patiënten met nierfunctie vervangende therapie via nationale en regionale registraties in Europa. We vonden een sterk verhoogde mortaliteit door infecties in dialyse- en transplantatiepatiënten. Jonge patiënten op dialyse, met name in de leeftijd 0-39 jaar en vrouwen met multisysteem ziekten, hadden een verhoogd risico om te overlijden door een infectie. Deze groep verdient daardoor extra aandacht van specialisten.

In **hoofdstuk 5**, hebben we gekeken naar het vóórkomen van infecties in patiënten met nierfunctie vervangende therapie sinds kinderleeftijd en dus met een follow-up van 25 jaar. In de laatste decennia vonden we een significante toename in belangrijke infecties in transplantatiepatiënten. We zagen deze toename niet alleen in het eerste jaar na transplantatie maar ook in patiënten die al een geruime periode een transplantatie-nier hadden. Deze toename kan verklaard worden door de krachtige immuunsuppressieve strategie die de afgelopen 20 jaar wordt gevoerd in transplantatie-patiënten. Specialisten kunnen daarom worden geadviseerd om de dosis van de immuunsuppressieve medicatie af te stemmen op het risico op rejectie van de transplantatie-nier een individuele patiënt.

In **hoofdstuk 6**, hebben we gekeken naar de prevalentie en risicofactoren van kanker na een lange follow-up van patiënten die voor hun vijftiende levensjaar zijn begonnen met nierfunctie vervangende therapie. Dertig jaar na de eerste transplantatie had 41% van de patiënten kanker. Plaveiselceltumoren van de huid kwamen het meeste voor en ontstonden pas relatief laat na transplantatie. Van de patiënten met kanker kreeg 31% een tweede maligniteit binnen 1 jaar. Het risico op het ontwikkelen van kanker was in ons cohort meer dan 20 keer hoger vergeleken met de algemene Nederlandse populatie. Alhoewel in de meeste gevallen de kanker niet dodelijk was op de korte termijn kan de hoge herhaalkans de uitkomsten op de langere termijn beïnvloeden. Door het chronische aspect van de ziekte, de frequente ziekenhuisbezoeken en de chirurgische en cosmetische consequenties kan de kwaliteit van leven negatief beïnvloed worden. Tevens kan het besef dat de ziekte tot de dood kan leiden een grote psychologische belasting voor de patiënt vormen.

In **deel III**, worden de kwaliteit van leven en sociaal-demografische uitkomsten van patiënten met nierfunctie-vervangende therapie sinds kinderleeftijd besproken.

In **hoofdstuk 7**, hebben we de kwaliteit van leven en sociale status geëvalueerd na 25 jaar nierfunctie-vervangende therapie. Tevens hebben we gekeken naar determinanten (medische en sociaal-demografische) die geassocieerd kunnen zijn met een verminderde kwaliteit van leven. We hebben de klinische data verzameld uit de medische dossiers van de patiënten. Data over sociaal-demografische uitkomsten, zoals het hebben van werk en inkomen, opleidingsniveau, huwelijkse staat en kinderen hebben we verzameld middels vragenlijsten. Om de kwaliteit van leven te beoordelen gebruikten we, net zoals in 2000, de RAND-36 vragenlijst. Voor het hebben van werk, inkomen, opleidingsniveau en het hebben van kinderen waren data van de Nederlandse algemene populatie beschikbaar.

We vonden dat de overlevers van nierfunctie-vervangende therapie, zelfs na 20 tot 40 jaar nierfunctie-vervangende therapie, op middelbare leeftijd een opvallend goede kwaliteit van leven hadden. Fysieke gezondheid is in het afgelopen decennium wel verslechterd. In 2000 rapporteerden we over de goede mentale kwaliteit van leven in dialyse-patiënten van ons cohort. Dit stond in scherp contrast met leeftijdsgenoten die op volwassen leeftijd waren begonnen met nierfunctie-vervangende therapie. Recente data laten zien dat de stijgende leeftijd geen negatieve invloed heeft gehad op de mentale gezondheid in dialyse- en transplantatiepatiënten. De mentale kwaliteit van leven in transplantatie-patiënten was gelijk of zelfs hoger dan deze in de algemene populatie. Patiënten in onze populatie hadden een significanter lager inkomen dan de algemene bevolking. Dit kan verklaard worden door het relatieve lagere opleidingsniveau en de grotere groep werkloze patiënten. Het hebben van kinderen was geassocieerd met een lager risico op verminderd sociaal functioneren maar we vonden geen relatie tussen kwaliteit van leven en de huwelijkse staat.

Tot slot wordt in **hoofdstuk 8** de algemene discussie van alle resultaten van dit proefschrift beschreven en worden er aanbevelingen gedaan voor het verbeteren van de kwaliteit van zorg voor patiënten met nierfunctie-vervangende therapie sinds de kinderleeftijd.

Portfolio

Name PhD student: Judith Leonoor Vogelzang
PhD period: October 2009 – September 2015
Name PhD supervisors: prof. dr. J.B. van Goudoever, prof. dr. A. Abu – Hanna

PHD TRAINING

General courses

2011	Scientific Writing in English
2010	Clinical Epidemiology
	Clinical Data Management
	Practical Biostatistics
2009	World of Science

Seminars, workshops and master classes

2011	ERA-EDTA Epidemiology course (European Renal Association – European Dialysis and Transplantation Association)
2010	PD University Basic Course, Division of Nephrology

Oral presentations

2012	Young women on dialysis are at relatively high risk of death from infections – ERA EDTA Registries, Department of Medical informatics
2011	In RRT patients non-cardiovascular mortality is as important as cardiovascular Mortality – Invited Speaker ERA-EDTA congress
	Late mortality in patients with cRRT since childhood is predominantly caused by non-cardiovascular disease – ESPN congress (European Society for Pediatric Nephrology)
	Late mortality in patients with renal replacement therapy since childhood is predominantly caused by non-cardiovascular disease – Amsterdam Children Symposium
	LERIC-2: late cardiovascular mortality and morbidity – Pediatric Nephrology course

Poster presentations

2012	Young women on dialysis are at relatively high risk of death from infections – ESPN Congress
	Mortality and infections in patients with renal replacement therapy – Amsterdam Children Symposium
2011	Late mortality in patients with renal replacement therapy is predominantly caused by non-cardiovascular disease – Amsterdam Children Symposium
2010	LERIC-2: Late Effects of Renal Insufficiency in Children, a follow-up study – Amsterdam Children Symposium

(Inter)national conferences

2010 – 2013	Amsterdam Children Symposium
2010 – 2013	Dutch Society for Pediatrics Annual Meeting
2011	European Society for Pediatric Nephrology Meeting (ESPN)
	European Renal Association – European Dialysis and Transplant Association Meeting (ERA-EDTA Meeting)

Publications

Judith L. Vogelzang, Karlijn J. van Stralen, Kitty J. Jager, Jaap W. Groothoff.**Trend from cardiovascular to non-cardiovascular late mortality in patients with renal replacement therapy since childhood**. Nephrol Dial Transplant. 2013 Aug;28(8):2082-9.

Judith L. Vogelzang, Lara W.A.A. Heestermans, Karlijn J. van Stralen, Kitty J. Jager, Jaap W. Groothoff. **Simultaneous reversal of risk factors for cardiac death and intensified therapy in long-term survivors of pediatric end-stage renal disease over the last 10 years**. Nephrol Dial Transplant. 2013 Oct;28(10):2545-52.

Judith L. Vogelzang, Karlijn J van Stralen, Marlies Noordzij, Jose Abad Diez, Juan J Carrero, Cecile Couchoud, Friedo W. Dekker, Patrik Finne, Denis Fouque, James G. Heaf, Andries Hoitsma, Torbjorn Leivestad, Johan de Meester, Wendy Metcalfe, Runolfur Palsson, Maurizio Postorino, Pietro Ravani, Raymond Vanholder, Manfred Wallner, Christoph Wanner, Jaap W. Groothoff, Kitty J Jager. Nephrol **Mortality from infections and malignancies in patients treated with renal replacement therapy: data from the ERA-EDTA Registry**. Neprhol Dial Transplant. 2015 Jan 29.

Lidwien L. Tjaden, Judith L. Vogelzang, Kitty J. Jager, Karlijn J. van Stralen, H. Maurice-Stam, Martha A. Grootenhuis, Jaap W. Groothoff. Long-term quality of life and social outcome of childhood end-stage renal disease. J Paediatr. 2014 Aug;165(2):336-342.

Danilo Lofaro, Judith L. Vogelzang, Karlijn J. van Stralen, Kitty J. Jager, Jaap W. Groothoff. **Increase in burden of severe infections over time in patients with pediatric ESRD and 30 years of renal replacement therapy.** Submitted Pediatric Nephrology

Sophie Ploos van Amstel, Judith L. Vogelzang, Karlijn J. van Stralen, Kitty J. Jager, Marcus V. Starink, Jaap W. Groothoff. **Substantial long-term risk of cancer in survivors of pediatric end-stage renal disease**. Resubmitted CJASN

M. van Huis, J.H. van der Lee, A.M. Boot, J.L. Vogelzang, J.W. Groothoff. **Low bone mineral density measured with DEXA does not predict bone disease in adulthood after childhood renal failure.** Submitted CJASN

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-x- Judith

CURRICULUM VITAE

Judith Leonoor Vogelzang, dochter van John en Mieke Vogelzang, werd op 31 oktober 1979 geboren te Haaksbergen. Hier groeide ze samen met haar broer en zus op. In 1999 ontving ze haar VWO-diploma aan het Assink Lyceum te Haaksbergen. Omdat ze werd uitgeloot voor de studie Geneeskunde besloot ze twee jaar Medische Biologie te gaan studeren aan de Universiteit van Amsterdam. Mede dankzij de behaalde propedeuse werd ze in 2001 dan toch eindelijk ingeloot voor de studie Geneeskunde aan dezelfde universiteit. Haar wetenschappelijke stage en keuze- en oudste co-schappen heeft zij bij de Kindergeneeskunde van het Emma Kinderziekenhuis en het Onze Lieve Vrouwe Gasthuis doorlopen. In 2007 behaalde ze haar artsexamen en begon ze als arts-assistent Kindergeneeskunde in het Onze Lieve Vrouwe Gasthuis te Amsterdam. Hierna vervolgde ze haar carrière op de afdeling Kinderoncologie van het Emma Kinderziekenhuis AMC te Amsterdam. In 2009 startte Judith als arts-onderzoeker bij de Kindernefrologie. Ze werkte aan het LERIC follow-up project (Late Effects of Renal Insufficiency in Children), resulterend in dit proefschrift. In januari 2013 is Judith gestart met de opleiding tot kinderarts in het opleidingscluster Emma Kinderziekenhuis AMC, met als opleider dr. D.K. Bosman.