Progression of CKD form pre-dialysis : natural course, risk factors, and outcomes

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Chapter 6 |

Association between time of referral and survival in the first year of dialysis in diabetics and elderly

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Abstract

Objective

The objective of the study was to estimate the association between time of referral and survival during dialysis in diabetics and patients aged ≥70 years.

Design, setting, and subjects

This study was a prospective follow-up study in 1438 incident dialysis patients (1996-2004, 62% male, 60±15 years) in the Netherlands.

Main outcome measures

Referral (time between first pre-dialysis visit to a nephrologist and dialysis initiation) was classified as: late (<3 months), early (3–12 months) or very early (≥12 months). All-cause mortality risk within the first year of dialysis was calculated [HR (95% confidence interval, CI), adjusted for age, sex and primary kidney disease (PKD)]. Additive interaction between time of referral and diabetes mellitus (adjusted for age and sex) or age (adjusted for sex and PKD) was assessed by synergy index [S (95% CI)].

Results

Thirty-two percent were late referred, 12% early and 56% very early; 21% had diabetes; and 30% were ≥70 years. Early and late referrals were associated with increased mortality compared with very early referral [$HR_{adj,early}$: 1.5 (1.0, 2.4), late: 1.8 (1.3, 2.5)]. A similar trend was observed in diabetics and non-diabetics. However, no interaction between time of referral and diabetes was present [S_{late} 0.8 (0.4, 1.9), S_{early} 1.2 (0.4, 3.6)]. Likewise, in patients aged <70 and ≥70 years, time of referral was associated with increased mortality, without interaction [S_{late} 0.9 (0.4, 1.8), S_{early} 0.8 (0.3, 2.0)].

Conclusion

Late referral is associated with increased mortality in the first year of dialysis. Diabetes or high age does not have an additional worsening effect, implying that timely referral is important in future dialysis patients irrespective of diabetes or high age.

Introduction

The incidence and prevalence of chronic kidney disease and the number of patients needing renal replacement therapy increases worldwide.[1;2] This is a consequence of technical developments, improved access to renal replacement therapy, an ageing population and an increase in the incidence of diabetic nephropathy.[2-4] In addition, due to the high prevalence of risk factors like hypertension and diabetes, morbidity and mortality in patients on dialysis is considerably higher compared to the general population.[5]

Late referral to a nephrologist, resulting in short pre-dialysis care, is considered as another risk factor for increased morbidity and mortality after initiation of dialysis treatment.[6;7] More precisely, late referral is associated with a high mortality, a high hospitalization rate, impairment of the patient's quality of life, more comorbidities and less favorable levels of biochemical parameters such as hemoglobin and serum albumin at initiation of dialysis.[8] In addition, late referral impairs the choice of the initial dialysis modality.[9] In the case of late referral, there is no time for elaborate multidisciplinary pre-dialysis care. In contrast, early referral provides the opportunity for preparation of a good access and the initiation of high-quality cooperative treatment, which is, amongst other treatments, aimed at maintaining a desired nutritional status.[10]

A few studies showed that late referral in specific high-risk subgroups of dialysis patients, such as diabetics and the elderly, was associated with a high mortality.[11-13] It remains unclear, however, whether late referral in these specific high-risk patients is more dangerous than in dialysis patients without these additional risk factors. Therefore, the aims of the present prospective cohort study were to determine (i) the association between time of referral and mortality in the first year of dialysis in specific subgroups of (a) patients with diabetes mellitus and (b) patients 70 years and older and (ii) whether late referral in these high-risk patients has an additional negative effect on top of the presence of diabetes mellitus or advanced age. To that end, it was examined whether additive interaction between time of referral and diabetes mellitus or age is present.

Materials and methods

Design

End-stage renal disease patients were selected from The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) study. This is a multi-centre prospective cohort study in 38 dialysis centers in The Netherlands. At 3 months after the start of dialysis, blood and 24-hour urine samples were taken for further determinations (see below). Patients were followed up till the time of death or censoring. Censoring was defined as leaving the study because of kidney transplantation, withdrawal from the study or a transfer to a dialysis centre that did not participate in the study. For the present analysis, follow-up was maximized at 1 year.

Patients

Adult patients (≥18 years) starting dialysis for the first time were eligible for inclusion in the study. For the present analysis, patients were included when they started dialysis between August 1996 and March 2004. Medical ethics committees of all participating hospitals gave their approval for the study. All participants gave their written informed consent prior to inclusion in the study.

Data collection

Data regarding time of referral were collected from patient records. The following data were collected at baseline (i.e. the period between 4 weeks prior to and 2 weeks after start of dialysis): age, gender, body mass index (BMI), dialysis modality (hemodialysis or peritoneal dialysis), ethnicity and blood pressure (both systolic and diastolic). Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplantation Association.[14]. The severity of comorbidities was reflected by the Khan comorbidity score, which is a combination of the effects of comorbidity and age giving rise to three risk groups: low, medium and high.[15] Comorbidities were recorded as doctors' diagnosis of diabetes mellitus, cardiovascular disease or malignancies. The standardized and validated seven-point subjective global assessment (SGA) scale was used by trained research nurses to assess nutritional status.[16;17] An SGA score equal to or above 6 was regarded as 'good nutritional status', whereas scores below 6 were regarded as 'poor nutritional status'. Creatinine and urea levels were determined in plasma and 24-h urine samples. Residual renal function (residual glomerular filtration rate, rGFR) was calculated as the mean of creatinine and urea clearance and corrected for body surface area (mL/min/1.73m^2) and as weekly kt/V_{urea}, in which V was estimated according to the formula of Watson et al.[18] The protein equivalent of nitrogen appearance (PNA) was calculated according to Bergström et al.[19] and normalized to standard body weight (V_{Watson}/0.58).

Time of referral

Time of referral was determined by calculating the time in months between the first pre-dialysis visit to a nephrologist and the initiation of dialysis. This difference was categorized into three categories: 'late referral' (defined as first contact with nephrologist 0–3 months before start of dialysis), 'early referral' (first contact with nephrologist between 3 and 12 months before start of dialysis) or 'very early referral' (first contact with nephrologist at least 12 months before start of dialysis).

Statistical analyses

Baseline characteristics were expressed as mean and standard deviation (SD) or percentage and compared using analysis of variance for continuous variables and chi-square tests for categorical variables. To determine the association between time of referral and mortality during the first year of dialysis, absolute mortality rates were calculated [expressed as mortality rates per 100

person years (py)] in the total study population and within the three categories of time of referral. One-year cumulative survival was estimated by Kaplan–Meier analysis. Log-rank tests were used to compare survival probabilities. Cox regression analysis was used to calculate hazard ratios (HR) for mortality together with 95% confidence intervals, adjusted for age, sex and primary kidney disease. Within specific subgroups, that is diabetics *versus* non-diabetics, and patients aged <70 *versus* ≥70 years of age, the presence of interaction between the risk factor of interest (i.e. either diabetic status or age) and time of referral in relation to mortality was examined. The presence of diabetes mellitus was defined as having diabetes mellitus either as primary kidney disease or as comorbidity. Interaction is the phenomenon whereby the joint effect of two risk factors is larger than the sum of their independent effects. In the present study, interaction was defined as departure from additivity and was estimated by calculating the synergy index (S) together with 95% confidence interval.[20;21] For the evaluation of presence of additive interaction in multiplicative regression models, such as Cox regression models, no interaction terms have to be included in the regression model. However, a Cox regression model should be constructed including a new composite variable containing four exposure categories. The four categories indicate (i) the reference category (background risk, no exposure, or − −), (ii) a category for exposure to one of the risk factors under study (− +), (iii) a category for exposure to the other risk factor to be examined (+ −) and (iv) a category for joint exposure to both risk factors under study (+ +). Subsequently, based on the hazard ratios derived from the Cox regression model, the synergy index can be calculated as follows: Synergy index (S) = (HR_{++} − 1)/[(HR_{+-} − 1) + (HR_{-+} − 1)]. The synergy index is a measure for additive interaction in multiplicative regression models and can be interpreted as the extra risk due to exposure to the combination of both risk factors of interest relative to the risk due to exposure of both risk factors separately when the two risk factors were independent of each other (i.e. without interaction). When there is no interaction, the synergy index equals 1.[22] These analyses were adjusted for age, sex and chronic comorbidities (malignancies, liver cirrhosis, cardiovascular diseases, left ventricular hypertrophy and psychiatric diseases) in the subgroup of diabetics *versus* non-diabetics and for sex, primary renal disease and chronic comorbidities (diabetes mellitus, malignancies, liver cirrhosis, cardiovascular diseases, left ventricular hypertrophy and psychiatric diseases) in the subgroup of patients aged <70 *versus* ≥70 years of age. All statistical analyses were performed with SPSS statistical software (v.16.0.2; SPSS, Chicago, IL, USA).

Results

Patients

In the period between August 1996 and March 2004, 1835 patients were included in the NECOSAD study. Of these, 1438 patients with a mean (SD) age of 60.0 (15.1) had data on time of referral available and were therefore included in the present analysis. Patients not included were not different from the patients included with respect to age and sex but had slightly lower Khan comorbidity scores. Of the patients included, 56% were referred very early, whereas 12%

Table 1. Baseline characteristics and clinical parameters (at start of dialysis) in dialysis patients (N=1438) grouped by time of referral (late: <3 months; early: 3-12 months or very early: ≥12 months before start of dialysis).

	Time of referral			*p*
	Late (N=456)	Early (N=172)	Very early (N=810)	
Age *years*	60.3 (16.3)	60.1 (14.5)	59.8 (14.5)	0.89
≥70 year *%*	32.7	27.9	29.1	0.34
Sex *% male*	58.3	62.2	64.2	0.12
BMI *kg/m^2*	24.3 (4.2)	25.1 (4.6)	25.2 (4.4)	<0.01
Systolic BP *mmHg*	149.4 (24.3)	146.1 (22.4)	149.1 (23.5)	0.28
Diastolic BP *mmHg*	82.7 (14.5)	82.4 (13.5)	82.5 (13.0)	0.95
Chronic therapy *% HD*	70.0	65.1	61.9	0.02
Primary renal disease *%*				0.02
Diabetes Mellitus	14.5	19.8	16.3	
Glomerulonephritis	9.6	15.1	15.8	
Renal vascular disease	22.1	19.8	17.9	
Khan comorbidity score *%*				0.01
Low	33.6	35.5	38.3	
Medium	32.7	28.5	35.8	
High	33.8	36.0	25.9	
Comorbidities				
Diabetes Mellitus *%**	20.9	29.3	23.3	0.09
Cardiovascular disease *%*	39.6	39.2	39.1	0.98
Malignancies *%*	13.8	12.7	6.7	<0.01
Nutritional status				
Serum albumin *g/L*	34.3 (6.4)	35.5 (5.5)	36.0 (5.8)	<0.01
nPNA *g/kg/day*	1.0 (0.2)	1.1 (0.2)	1.2 (0.3)	0.20
rGFR *mL/min/1.73m^2*	4.4 (4.3)	5.1 (3.0)	5.5 (2.8)	<0.01
Kt/V_{urea} *week*	2.0 (0.5)	2.2 (0.3)	2.3 (0.6)	0.14

Unless otherwise stated: mean (SD) or percentage; N: number of patients; BMI: body mass index; BP: blood pressure; HD: hemodialysis; nPNA: normalized protein equivalent of nitrogen appearance; rGFR: residual glomerular filtration rate; Kt/V: dialysis adequacy; *Diabetes Mellitus as primary renal disease + comorbidity.

and 32% were referred early and late, respectively. The majority of the patients were male (62%), 23% had diabetes mellitus, and 30% were aged ≥70 years. Most patients started with hemodialysis (65%). The majority of the patients (72%) had a good nutritional status. Patients who were referred late started more frequently with hemodialysis and had relatively higher comorbidity scores at the start of dialysis. This was possibly due to a higher prevalence of

malignancies. They also had a lower residual renal function at the start of dialysis compared to those who were referred very early (Table 1).

Important clinical parameters such as hemoglobin and serum albumin, which were only available 3 months after initiation of dialysis treatment, were not correlated to time of referral. SGA score and rGFR at 3 months after the start of dialysis, however, were slightly lower in patients who were referred early or late compared with patients referred very early (Table 2). After 3 months of dialysis treatment, 89% of the patients used phosphorus binders, 86% were using erythropoietin (EPO), and 35% were treated with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). Medication use was not different between categories of referral. During the 1-year follow-up, 13% of all patients died, 5% of the patients were censored because of receiving a kidney transplant, 4% were censored because of refusal of further treatment, and 2% were censored because of recovery of renal function.

Table 2. Clinical parameters (at 3 months after start of dialysis) in dialysis patients (N=1374) grouped by time of referral (late: <3 months; early: 3-12 months or very early: ≥12 months before start of dialysis).

	Time of referral			*p*
	Late (N=433)	Early (N=164)	Very early (N=777)	
Nutritional status				
Serum albumin *g/L*	35.5 (5.5)	35.7 (5.5)	36.0 (5.0)	0.29
nPNA *g/kg/day*	1.1 (0.3)	1.1 (0.2)	1.2 (0.4)	0.71
SGA *% good*	63.2	71.0	76.9	<0.01
Hb *g/dL*	10.9 (1.7)	11.2 (1.6)	11.2 (1.6)	0.04
Ca^{2+} *mmol/L*	2.3 (0.2)	2.3 (0.3)	2.4 (0.3)	<0.01
PO_4^- *mmol/L*	1.8 (0.6)	1.9 (0.6)	1.8 (0.5)	0.07
PTH *pmol/L*	20.4 (24.8)	21.6 (21.8)	23.2 (32.5)	0.32
HCO_3^- *mmol/L*	23.5 (3.9)	23.0 (3.9)	23.2 (3.6)	0.23
rGFR *mL/min/1.73m²*	3.4 (3.2)	3.4 (2.4)	4.0 (3.1)	<0.01
Total Kt/V_{urea} *week*	3.0 (1.0)	2.9 (0.9)	3.0 (1.0)	0.35

Unless otherwise stated: mean (SD) or percentage; N: number of patients; nPNA: normalized protein equivalent of nitrogen appearance; SGA: subjective global assessment; Hb: hemoglobin; Ca^{2+}: plasma calcium; PO_4^-: plasma phosphorus; PTH: parathyroid hormone; HCO_3^-: plasma bicarbonate; rGFR: residual glomerular filtration rate; Kt/V_{urea}: combination of renal and dialysis adequacy.

All-cause mortality in the first year of dialysis: all patients

The cumulative incidence of mortality during the first year of dialysis in patients referred late, early and very early was 18%, 15% and 9%, respectively (p<0.001). Absolute all-cause mortality rates within the first year of dialysis were higher for late referred patients (18.7/100 py) compared to early referred patients (15.5/100 py) or very early referred patients (10.0/100 py).

Both unadjusted and adjusted hazard ratios for death during the first year of dialysis were higher in late and early referred patients compared to very early referred patients (Table 3).

Table 3. Time of referral in 1438 dialysis patients associated with the all-cause mortality risk (hazard ratio, HR and 95% confidence interval) in the first year after start of dialysis treatment.

Time of referral	N	HR (95% CI)	HR_{adj} (95% CI)
Very early (≥12 months)	810	1.0 (ref)	1.0 (ref)
Early (3-12 months)	172	1.6 (1.0, 2.6)	1.5 (1.0, 2.4)
Late (<3 months)	456	2.1 (1.6, 2.9)	1.8 (1.3, 2.5)

N: number of patients; HR_{adj}: adjusted for age, sex, and primary kidney disease

All-cause mortality in the first year of dialysis: diabetics *versus* non-diabetics

The all-cause mortality rate was higher in patients with diabetes compared to patients without diabetes [HR (95% CI) 1.9 (1.4, 2.6)]. In addition, the all-cause mortality risk was higher when patients were referred late or early (compared to very early referred patients) in both diabetics and non-diabetics (Figure 1A) even after adjustment for possible confounders (Table 4).

Table 4. Time of referral in subgroups of dialysis patients with and without diabetes mellitus and patients aged <70 *versus* ≥70y was associated with all-cause mortality risk (hazard ratio, HR and 95% confidence interval) in the first year after start of dialysis treatment.

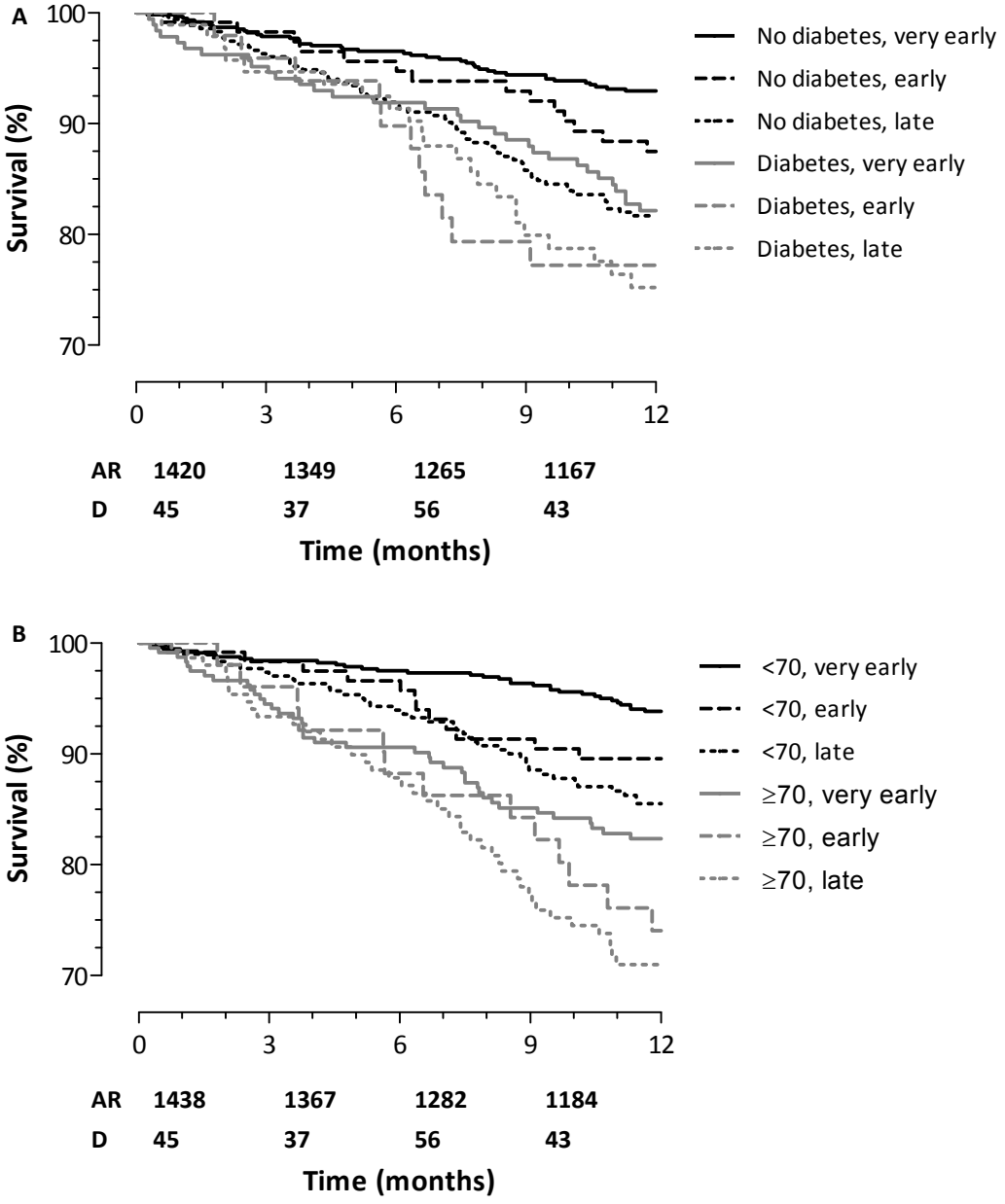
Diabetes	Time of referral*	N	MR/100py	HR (95% CI)	HR_{adj} (95% CI)[1]	HR_{adj} (95% CI)[2]
No	Very early	616	7.3	1.0 (ref.)	1.0 (ref)	1.0 (ref)
No	Early	118	11.6	1.8 (1.0, 3.3)	1.7 (0.9, 3.0)	1.5 (0.8, 2.8)
No	Late	356	18.7	2.7 (1.8, 4.1)	2.6 (1.7, 3.9)	2.3 (1.6, 3.4)
Yes	Very early	187	19.5	2.6 (1.7, 4.2)	2.4 (1.5, 3.8)	2.0 (1.2, 3.2)
Yes	Early	49	30.2	3.6 (1.9, 7.0)	3.5 (1.8, 6.9)	2.9 (1.4, 5.7)
Yes	Late	94	19.6	3.8 (2.3, 6.3)	3.3 (2.0, 5.5)	2.9 (1.7, 4.9)
≥70 yrs	Time of referral*	N	MR/100py	HR (95% CI)	HR_{adj} (95% CI)[3]	HR_{adj} (95% CI)[4]
No	Very early	571	6.4	1.0 (ref.)	1.0 (ref)	1.0 (ref)
No	Early	121	9.8	1.8 (0.9, 3.4)	1.6 (0.8, 3.2)	1.8 (0.9, 3.5)
No	Late	305	11.0	2.5 (1.6, 3.9)	2.1 (1.3, 3.4)	2.2 (1.4, 3.6)
Yes	Very early	239	19.6	3.2 (2.0, 5.0)	2.6 (1.6, 4.1)	2.1 (1.3, 3.3)
Yes	Early	51	29.8	4.6 (2.4, 8.8)	3.7 (1.9, 7.1)	2.4 (1.2, 4.7)
Yes	Late	151	35.4	5.4 (3.4, 8.5)	4.0 (2.5, 6.4)	3.0 (1.9, 4.9)

N: number of patients; MR: mortality rate per 100 person years (py); HR_{adj} (95% CI): [1]adjusted for sex and age; [2]adjusted for age, sex, and chronic comorbidities (malignancies, liver cirrhosis, cardiovascular diseases, left ventricular hypertrophy, psychiatric diseases); [3]adjusted for sex and primary kidney disease; [4]adjusted for sex, primary kidney disease and chronic comorbidities (diabetes mellitus, malignancies, liver cirrhosis, cardiovascular diseases, left ventricular hypertrophy, psychiatric diseases); *Time of referral, defined as very early: ≥12 months, early: 3-12 months, or late: <3 months before start of dialysis.

All-cause mortality in the first year of dialysis: <70 years *versus* ≥70 years

Patients aged ≥70 years had higher mortality rates compared to patients aged <70 years [HR (95% CI) 2.6 (2.0, 3.5)]. In both age groups, delayed referral was associated with an increased mortality risk in the first year of dialysis (Figure 1B, Table 4).

Figure 1. Effect of time of referral on one-year survival in high-risk subgroups of diabetics and non-diabetics (p<0.001, panel A), and patients aged <70 and ≥70 years of age (p<0.001, panel B). Time of referral is categorized as very early (≥12 months), early (3-12 months), or late (<3 months). The tables below the graphs indicate the number of patients at risk (AR) and number of events (D) per 3 months interval.



Additive interaction

Within subgroups of diabetics *versus* non-diabetics and patients aged <70 years *versus* ≥70 years, the presence of additive interaction between the risk factor of interest (diabetes and age) and time of referral could be assessed by calculating the synergy index (S) derived from the fully adjusted models (Table 4). In late referred diabetics, no interaction between diabetic status and time of referral was found [S_{late} (95% CI) 0.8 (0.4, 1.9)]. The synergy index (95% CI) in early referred diabetics was 1.2 (0.4, 3.6), indicating the absence of additive interaction. In late referred patients aged ≥70 years and in early referred patients aged ≥70 years, S (95% CI) was 0.9 (0.4, 1.8) and 0.8 (0.3, 2.0), respectively.

Discussion

In our cohort consisting of 1438 incident dialysis patients, 32% were referred late, 12% early and 56% very early. The time of referral was positively associated with survival in the first year of dialysis treatment. Late referral resulted in a nearly doubled all-cause mortality risk in the first year of dialysis; early referral resulted in a 1.5-fold risk compared to very early referral. After adjustment for possible confounders, no additive interaction effect was observed between time of referral and diabetic status or between time of referral and age. The present results indicate that delayed referral (i.e. late or early, compared to very early referral) is associated with an increased mortality risk in the first year after initiation of dialysis, regardless of diabetic status or age.

To our knowledge, this study is the first assessing the association between time of referral and mortality during dialysis in specific subgroups of high-risk patients within the setting of a prospective cohort study. Our results are in line with previous studies, which showed that late referral increases the risk of morbidity and mortality once on dialysis.[23;24] Risk factors identified for late referral were, among others, the number and severity of comorbidities, ethnicity and not having a health insurance.[25;26] It has been shown that late referral is associated with poorer prognosis related to undesired levels of clinically important parameters such as serum albumin and hemoglobin at the start of dialysis.[27;28] Two studies investigated whether the risk was different in type II diabetics either on hemodialysis[11] or peritoneal dialysis.[13] To our knowledge, only one study investigated the association between late referral and poor outcome in very elderly (≥75 years) dialysis patients.[12] However, these three studies included a relatively small number of patients. The first two studies, on the relationship between pre-dialysis care and mortality within diabetics, showed that early referral, defined as first contact with a nephrologist >6 months before start of dialysis, was associated with improved long-term survival in patients with diabetes. The latter study showed that the relative risk of death for late referral in patients aged 75 years and over was similar to the risk in patients aged <75 years of age. The present study is in line with these previous findings and adds that after adjustment for possible confounders, there is no extra detrimental effect of age or diabetic status on the effect of time of referral, as shown by absence of additive interaction (synergy index ~ 1).

Several methodological issues in this study require careful consideration. First, since this is an observational study looking at the effect of a treatment, the risk of confounding by indication is considerable. Patients may, for example, be referred late because of their worse clinical condition, resulting in a poor prognosis, which might lead to biased results. Since in our study patients who were referred late or early had a slightly increased comorbidity burden (i.e. higher comorbidity score and higher prevalence of malignancies) at initiation of dialysis compared to very early referred patients, it seems that the presence of confounding by indication cannot be excluded. However, the prevalence of mortality due to different causes (e.g. malignancies) was not different between the groups. Therefore, we can assume that the present results are valid. With respect to precision of the results, the precision of our results is reflected by the width of the confidence intervals. Concerning adjustment, it should be noted that adjustment of our analysis for possible confounders was performed with caution. Since many confounding risk factors for mortality in our dialysis patients could have been influenced by treatment during pre-dialysis follow-up, the risk of correction within the causal pathway is present. Therefore, the present analyses were adjusted only for age, sex, primary kidney diseases and chronic comorbidities which are associated with prognosis but not influenced by the pre-dialysis treatment regimen.

In a sensitivity analysis, we checked whether our definition of time of referral influenced the results. When using a more strict definition for late referral (i.e. only those who never received pre-dialysis care were categorized as being late referred instead of all patients having had up to 3 months pre-dialysis care) the results were similar to those of the present analysis. Finally, since the present analysis included mainly Dutch Caucasians, with a relatively low prevalence of diabetes mellitus, it should be investigated whether these findings are applicable to other populations.

How can the present results be explained? It might be that patients had to start dialysis treatment unplanned because of a sudden worsening of their clinical situation. Unplanned dialysis start decreases the likelihood that patients have a mature arteriovenous fistula or peritoneal dialysis catheter, which is associated with poor outcome on dialysis.[29] Another explanation might be that, in our study, 3 months after the initiation of dialysis treatment, nutritional status, reflected by the SGA score, was lower in late referred patients compared to early or very early referred patients. It has been shown that a low SGA score is strongly associated with both an increased short-term and long-term mortality risk.[30] Furthermore, late referred patients started more frequently on hemodialysis. Hemodialysis is associated with a faster decline of residual renal function compared to peritoneal dialysis.[31] Not surprisingly, after 3 months of dialysis treatment, rGFR in early or late referred patients was slightly lower compared to very early referred patients. Although at start of dialysis rGFR was slightly lower in these patients as well, it can be argued that the decline in the lowest range of renal function might have more impact than the decline at relatively better renal functions. Therefore, we suggest that in our cohort the rate of decline of residual renal function might explain the higher

mortality risk in dialysis patients who were referred early or late compared to patients who were referred very early.

Our data have clinical implications. The present analysis showed that very early referral (>12 months before the start of dialysis treatment) has beneficial effects in all patients preparing for dialysis. Moreover, in patients having diabetes mellitus and patients aged 70 years and over, the protective effect of early referral is still present. Since early referral is beneficial irrespective of diabetic status or age, all dialysis patients should be prepared for dialysis as early as possible. There is no reason to refrain high-risk patients like diabetics and the elderly from timely referral.

To summarize, time of referral is associated with increased mortality in the first year after the initiation of dialysis. This association is not influenced by older age or the presence of diabetes mellitus. These data implicate that timely referral is important in all future dialysis patients.

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