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Summary

Ethnic differences in survival on dialysis in Europe. The role of demographic, clinical and psychosocial factors.

The general objective of this thesis was to investigate to what extent ethnic differences in survival on dialysis exist in European countries. In particular, the role of demographic, clinical and psychosocial factors in ethnic differences in survival on dialysis was studied.

In **chapter 1**, an introduction was provided to the studies presented in this thesis. In the North-American subcontinent, non-white dialysis patients have a better survival compared with white dialysis patients. Although extensively studied, this finding is not yet completely understood. We postulated that exploring ethnic differences in survival on dialysis in Europe may help to identify factors responsible for ethnic survival disparities. The identification of factors responsible for ethnic differences in survival on dialysis may result in the identification of specific risk factors for mortality in the whole dialysis population and could raise new ideas or have implications for improved renal replacement therapy for specific ethnic groups.

Chapter 2 concerns a literature review of the existing data on non-white dialysis patients within Europe. A limited number of studies on non-white dialysis patients in Europe were available. Firm conclusions about the survival of these patients could not be drawn. Consequently, there is a need for carefully and systematically collected data on the survival of non-white dialysis patients in Europe.

In **chapter 3**, survival data were analysed from native and immigrant dialysis patients who entered a renal service of an urban hospital in the Netherlands between 1996 and 2005. It was demonstrated that, compared with native patients (n=177), immigrant patients (n=126) were 13 years younger, had a lower prevalence of vascular and coronary artery diseases, a lower prevalence of malignancies and a higher prevalence of hypertension. Furthermore, immigrant patients had lower levels of haematocrit and calcium compared with natives. Native patients were found to have a 2.7-fold higher risk of death compared with immigrants. We explored whether this difference in survival could be explained by differences in demographic and clinical characteristics. After adjustment for differences in age, native patients still had a 1.9-fold higher mortality risk compared with immigrants. After gradually adjusting for more demographic and clinical characteristics, an approximately 2-

fold higher mortality risk in native patients compared with immigrants remained. Thus, besides age, the studied demographic and clinical factors did not explain the difference in survival between native and immigrant dialysis patients. It was proposed that, to generalize these results to a larger population, the study should be replicated in a multicentre setting. In addition, it was hypothesized that psychosocial factors may explain ethnic differences in survival on dialysis, as evidence suggests that psychosocial factors are independent risk factors for mortality in dialysis patients. Before studying ethnic differences in survival on dialysis in a multicenter setting and exploring the role of psychosocial factors in these differences (chapter 6), a tool to measure depressive symptoms was examined (chapter 4) and how depressive symptoms are associated with mortality over time was studied (chapter 5).

In **chapter 4**, the usefulness of the 5-item Mental Health Inventory (MHI-5) as a screening instrument for depressive symptoms in dialysis patients was assessed. The MHI-5 is a subscale of the 36-item Short Form Health Survey Questionnaire (SF-36) and has been previously established as a simple and valid tool for detecting depressive symptoms in the general population and in various populations of chronically ill patients. In the dialysis population, however, the MHI-5 had not been validated as a screening tool for depressive symptoms. Therefore, the MHI-5 was compared with the standard, but relatively extensive, Beck Depression Inventory (BDI) self-report questionnaire. Firstly, it was demonstrated that the MHI-5 has high discrimination in screening for depressive symptoms in dialysis patients and may, therefore, be considered as a useful screening instrument for depressive symptoms in dialysis patients. Secondly, it was demonstrated that in general the optimal MHI-5 cut-off score to screen for depressive symptoms is 70. This cut-off score was determined by the optimum value of the sum of the sensitivity and specificity (MHI-5 score ≤ 70 had 77% sensitivity and 72% specificity with the presence of depressive symptoms determined with the BDI). In the discussion section, however, it was proposed that the selection of a cut-off score depends largely on the purpose of use. In clinical-screening practice where potential cases of depressive disorders need to be identified, high sensitivity is of great importance. However, in epidemiological research with, for example, a focus on understanding the association between depressive symptoms and mortality, sensitivity is not necessarily more important than specificity and a lower cut-off value may be useful.

In **chapter 5**, the association between the presence of depressive symptoms at the start of dialysis treatment and short-, medium- and long-term mortality in incident dialysis patients in the Netherlands was examined. Short-term was defined as 0-6 months, medium-term as 6-24 months, and long-term as 24-60 months after the completion of the questionnaire. In line with other studies using a cut-off score of ≤ 52 , patients were considered to have depressive symptoms at a MHI-5 score of ≤ 52 . It was shown that the presence of depressive symptoms three months after the start of dialysis was associated with mortality at short-, medium- and long-term follow-up. This result remained present in analyses in which adjustments were made for differences in socio-demographic and clinical factors. The results differed for non-cardiovascular and cardiovascular mortality. Depressive symptoms posed a strong risk factor for non-cardiovascular mortality on the short-, medium- and long-term, whereas the association between depressive symptoms and cardiovascular mortality was only observed on the medium- and long-term. It was concluded that the presence of depressive symptoms in the initial period of dialysis treatment is an independent risk factor for mortality over time in dialysis patients.

In **chapter 6**, ethnic differences in survival on dialysis were studied in a multicenter setting in the Netherlands. Special emphasis was put on whether psychosocial factors could explain ethnic differences in survival on dialysis. One thousand seven hundred and ninety-one whites, 45 blacks and 108 Asians who initiated dialysis treatment in the Netherlands between 1997 and 2007 were followed until 2008. At the initiation of dialysis, the three ethnic groups differed significantly in age, residual glomerular filtration rate (GFR), the presence of diabetes mellitus, erythropoietin use, calcium levels, parathormone (PTH) levels and creatinine levels, marital status and general health perception. No ethnic differences were found in health related quality of life as measured by the SF-36 or in depressive symptoms as measured by the MHI-5. It was demonstrated that white patients had a 3.1-fold higher risk of death compared with black patients, but an equal risk of death compared with Asian patients. After adjusting for a range of potential explanatory variables, including psychosocial factors, white patients still had a 2.5-fold higher risk of death compared with black patients and an equal risk of death compared with Asian patients. No evidence was found for psychosocial factors being an explanation for ethnic differences in survival on dialysis. However, due to sample size limitations, no interaction terms were entered into the regression models. Consequently, it was assumed that the effect of a covariate on mortality was equal among different ethnic groups. However, theoretically the effect of a covariate on mortality could differ among ethnic groups (effect modification). Therefore, it was

recommended that future research should focus on whether the association between a particular risk factor and mortality differs between ethnic groups. This was further studied in chapter 7. In addition, it was recommended that in future studies detailed information is needed on the various aspects of ethnicity, such as country of origin and migration history. This topic was addressed in chapter 8.

In **chapter 7**, we examined whether the association of calcium, phosphate and PTH with mortality was different in white, black and South Asian incident dialysis patients. In the literature, it is reported that, among individuals without overt kidney disease, levels of calcium, phosphate and PTH differ between ethnic groups (most likely as a consequence of differences in skin pigmentation). In chapters 3 and 6, ethnic differences in calcium and PTH were found. Therefore, we hypothesized that optimal levels of calcium, phosphate and PTH in dialysis patients vary between ethnic groups. To study this, data of the United Kingdom Renal Registry were used. Data were studied of 30,021 white, 1,740 black and 2,878 South Asian incident dialysis patients who initiated dialysis treatment in the United Kingdom between 1997 and 2008. In line with the findings in chapters 3 and 6, in this cohort it was demonstrated that white patients were more likely to die on dialysis than black and South Asian patients. Calcium, phosphate and PTH levels were found to differ between ethnic groups shortly after the start of dialysis. Calcium and phosphate levels were highest in whites, followed by South Asians and blacks. On the contrary, PTH levels were highest in blacks, followed by South Asians and whites. We divided calcium, phosphate and PTH levels into categories because of the U-shaped associations of these levels with mortality. It was demonstrated that calcium below target was associated with increased mortality among whites, but not with mortality among South Asians and blacks. Phosphate levels above and below target were associated with increased mortality among whites, but not among South Asians and blacks. PTH above target tended to be associated with increased mortality among whites, but among blacks extremely elevated PTH concentrations seemed to exhibit the opposite trend. Thus, we showed ethnic differences in the association of calcium, phosphate and PTH levels with mortality in dialysis patients. These findings led to the statement that additional studies are urgently required to elucidate whether ethnic specific targets in the control of mineral metabolism in dialysis patients are needed.

In **chapter 8**, the group of patients starting chronic dialysis treatment in Denmark between 1995 and 2010 was studied. The survival of native Danish patients (n=8,459) was compared with that of patients originating from other Western countries (n=344); North Africa or West

Asia (n=79); South or South-East Asia (n=173); and Sub-Saharan Africa (n=54). Moreover, it was explored whether duration of residence in Denmark before the start of dialysis was associated with mortality on dialysis. It was shown that native Danes were older, less likely to be in the lowest tertile of household income and had different primary kidney diseases compared with most other ethnic groups. Native Danes had the highest mortality, followed by patients originating from other Western countries; North Africa or West Asia; South or South-East Asia; and Sub-Saharan Africa, respectively. Native Danes were found to have a greater estimated hazard for mortality compared with all other ethnic groups, both crude and after adjustment for differences in socio-demographic and clinical characteristics. An intriguing observation was that the survival advantage for immigrants became smaller with increased duration of residence in Denmark. It was concluded that these findings provide preliminary evidence that environmental and migration factors play a role in ethnic differences in survival on dialysis.

In **chapter 9**, whether black and white patients starting pre-dialysis care in the Netherlands have differences in the time until the start of renal replacement therapy and in rate of decline in renal function was studied. At initiation of pre-dialysis care, blacks (n=49) were younger, had more diabetes mellitus, higher levels of proteinuria and a higher estimated GFR than whites (n=946). No difference was found in the percentage of deaths prior to the start of renal replacement therapy (RRT). It was demonstrated that black and white patients had approximately the same estimated hazard for starting RRT. However, after adjustment for differences in patient characteristics, blacks had a 1.5-fold higher risk of starting dialysis treatment compared with whites. Blacks had a 0.18 mL/min/1.73m² per month faster decline in renal function than whites, which did not change after adjustment. These findings implicate that black patients with CKD should be referred to pre-dialysis care earlier than white patients to assure timely preparation for renal replacement therapy. Fortunately, in the Netherlands this seems to already be the case.

In **chapter 10**, the main findings presented in this thesis were discussed. Firstly, methodological issues were considered by discussing the internal and external validity of the studies presented in this thesis. Secondly, the concept of ethnicity was considered and a theoretical framework was presented illustrating potential mechanistic pathways underlying the association between ethnic origin and survival on dialysis. Using this framework, explanations for ethnic differences in survival on dialysis were discussed. We were able to conclude that the better survival for ethnic minority patients on dialysis is partly explained

by the younger age of ethnic minority patients compared with majority patients. No indications were found that clinical or psychosocial factors explain ethnic differences in survival on dialysis. Furthermore, we concluded that migration and environmental factors may play a role in ethnic differences in survival on dialysis. Finally, implications and recommendations for future research were provided. It was postulated that future research should focus on the role of migration and environmental factors and on the exact role of clinical and psychosocial factors in ethnic differences in survival on dialysis.

In conclusion, in this thesis we demonstrated better survival for most ethnic minority groups on dialysis in Europe compared with the ethnic majority. The better survival for most ethnic minority groups was partly explained by the younger age of ethnic minority patients. No indications were found that clinical or psychosocial factors explain these differences in survival. Preliminary evidence that migration and environmental factors play a role in ethnic differences in survival on dialysis was provided. The role of these factors, as well as the exact role of clinical and psychosocial factors, need to be investigated in future studies.