Why minorities live longer on dialysis: an in-depth examination of the Danish nephrology registry

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Epidemiological data have consistently shown that various racial and ethnic minorities, including black, Hispanic, Indo-Asian and Arab-Israeli populations, have a disproportionately higher prevalence of end-stage renal disease (ESRD) compared with those of white European ancestry [1–3]. Among minorities with ESRD, numerous disparities have been observed, including less access to pre-ESRD nephrology care, poorer achievement of dialysis performance measures (e.g. hemoglobin and parathyroid hormone levels) and lower kidney transplantation rates [4–6]. Despite these inequities, population-based studies show that racial/ethnic minorities receiving dialysis have a paradoxical survival advantage compared with their white counterparts [1, 2, 5, 7–9]. While these racial/ethnic differences in ESRD survival have been well documented in US and Canadian-based populations, there have been few studies of European dialysis patients, and these have largely been restricted to populations in the UK and The Netherlands (Table 1) [3, 10–14]. Further examination of dialysis populations from other countries of the European Union are warranted, given their (i) disparate racial/ethnic compositions, (ii) lower comorbidity burden and mortality rates, (iii) differential age distributions and (iv) distinct health care delivery systems across different European Union nations.

In this issue of Nephrology Dialysis Transplantation, van den Beukel et al. [14] conducted one of the largest European-based studies of race, ethnicity and survival among incident dialysis patients to date using the Danish National Registry, which has comprehensive capture of all Danish ESRD patients from 1990 onward. The investigators granularly examined the survival of various immigrant racial/ethnic populations and found that all immigrant subgroups had lower mortality risk compared with native Danes in crude and adjusted analyses. Linkage of patient-level data to Statistics Denmark, a Danish governmental organization under the Ministry for Economic and Interior Affairs, also permitted examination of the association between the duration of residence and death risk among immigrants, which demonstrated that in Western immigrants, the survival benefit attenuated over time but remained robust among those of non-Western origin [14, 15].

Access to the Danish Nephrology Registry allows for in-depth examination of the entire Danish incident dialysis population, from whom inferences can be drawn without substantial selection or survivor bias. For example, the study’s low proportion of immigrant dialysis patients (~9%) was similar to that of the broader Danish population (~7%), and was largely comprised of patients of Western, Arab, South and Southeast Asian and sub-Saharan African origin [14, 15]. The predominantly white population, in conjunction with the relatively low burden of diabetes as the primary cause of ESRD (23%), may account for Denmark’s decline in ESRD over the past decade (incidence rates of treated ESRD patients as of 2000 and 2013 were 132 and 117 per million, respectively, according to longitudinal international data from the United States Renal Data System (USRDS)) [1]. Another notable observation was the similar age-adjusted rates of kidney transplantation among immigrant subgroups and native Danes, which stands in contrast to other Western nations, where black and Hispanic dialysis patients are less likely to undergo transplantation [1, 5]. Given their equivalent transplant rates, it is unlikely that the diminution of healthier native Danish dialysis patients due to kidney transplantation is an explanatory factor for lower mortality risk among immigrants; in addition, competing risk methods used to address differential transplantation rates across race/ethnicity demonstrated a robust immigrant survival advantage.

Direct study of the Danish dialysis population also provides a unique opportunity to dissect potential mechanisms underlying the paradoxical minority survival advantage pervasive in other Western and international ESRD populations (Figure 1). For example, Denmark provides a well-established universal health care system in which most health care is...
Table 1. Selected studies of race, ethnicity, and mortality among dialysis cohorts from the European Union

<table>
<thead>
<tr>
<th>Author et al. (Year)</th>
<th>Country</th>
<th>Cohort (n)</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasad et al. (2004) [3]</td>
<td>United Kingdom</td>
<td>Incident dialysis patients from a single center (1340)</td>
<td>Black patients had ↓ mortality risk versus whites</td>
<td>N/A</td>
</tr>
<tr>
<td>van den Beukel et al. (2008) [10]</td>
<td>Netherlands</td>
<td>Incident dialysis patients from a single center (303)</td>
<td>Immigrant patients had ↓ mortality risk versus native Dutch patients</td>
<td>Effect modification by age: &gt;survival benefit in middle and older age groups (56–70, &gt;70 years) but not in younger age group (≤55 years)</td>
</tr>
<tr>
<td>Roderick et al. (2009) [11]</td>
<td>England and Wales</td>
<td>Incident dialysis patients from the UK Renal Registry (2495)</td>
<td>South Asians and black patients had ↓ mortality risk versus white patients</td>
<td>N/A</td>
</tr>
<tr>
<td>Kalantar-Zadeh et al. (2010) [2]</td>
<td>Israel</td>
<td>Dialysis patients from the Renal Registry of the Israeli Society of Nephrology and Hypertension</td>
<td>Arab-Israeli patients had ↓ mortality risk versus Jewish-Israeli patients</td>
<td>The hypothetical impact of nutritional status was speculated</td>
</tr>
<tr>
<td>van den Beukel et al. (2012) [12]</td>
<td>Netherlands</td>
<td>NECOSAD cohort (1791)</td>
<td>Black patients had ↓ mortality risk versus white patients. Asian patients had equivalent mortality risk versus white patients</td>
<td>N/A</td>
</tr>
<tr>
<td>Cole et al. (2014) [13]</td>
<td>UK</td>
<td>Incident hemodialysis patients from a single center (465)</td>
<td>Indo-Asian and Afro-Caribbean patients had equivalent mortality risk versus whites</td>
<td>N/A</td>
</tr>
<tr>
<td>van den Beukel et al. (2015) [14]</td>
<td>Denmark</td>
<td>Danish nephrology registry (8459)</td>
<td>All immigrant groups had ↓ mortality risk versus native Danish patients</td>
<td>Immigrant groups consisted of Western countries, Arabic countries, South and Southeast Asia and sub-Saharan Africa.</td>
</tr>
</tbody>
</table>

NECOSAD, Netherlands Cooperative Study on the Adequacy of Dialysis.

**IN FOCUS**

**IMMIGRANT & MINORITY DIALYSIS PATIENTS IN DENMARK AND OTHER COUNTRIES**

- **Selection bias**
  - Survivor bias
  - Migration of healthier pts

- **Socioeconomic factors**
  - Income
  - Education
  - Community-level assets & deficits

- **Health care access**
  - Insurance
  - Geographic proximity

- **Sociocultural & lifestyle**
  - Diet
  - Physical activity
  - Coping
  - End-of-life preferences
  - Social networks
  - Health beliefs & behaviors

- **Biologic**
  - Inflammation
  - Nutrition
  - Body composition
  - Dialysis treatment
  - Genetics
  - Geo-evolutionary variations in gene polymorphisms

**Figure 1:** Potential explanatory factors for paradoxical survival advantage in minority dialysis patients.
across all age groups in a population with universal health care access or nonuniform medical care. Furthermore, the availability of data through linkage to the Danish National Patient and Danish National Prescription Registries enabled exploration of potential causal pathway intermediates using incrementally adjusted survival models. Compared to immigrant dialysis patients, native Danes were of older age and had higher comorbidity burden (e.g. higher prevalence of cardiovascular disease and greater antihypertension medication use) as potential explanatory factors for their higher death risk in crude analyses. However, hierarchical adjustment for sociodemographic, socioeconomic and clinical covariates led to only minimal attenuation of the strong survival advantage among immigrant versus native Danish patients.

It is important to highlight that point estimates of the association between race/ethnicity and mortality did not substantially differ according to underlying age (≤50 years versus >50 years) in this study. This stands in contrast to multiple population-based studies conducted in the USA and Europe, in which age was found to be a critical modifier of racial/ethnic survival disparities [5, 7–10]. In a study of >1.3 million incident dialysis patients from the USRDS registry, Kucirka et al. [8] demonstrated that in older age groups (>50 years), black patients had lower mortality versus whites, whereas in younger age groups (≤50 years) they had higher mortality risk. In a subsequent study that separately considered Hispanic ethnicity, Yan et al. [9] observed that Hispanic, black and non-Hispanic white dialysis patients from the USRDS registry had the lowest, intermediate and highest mortality risks across all age strata, respectively, except within the 18–30 years age category, in which blacks had a higher mortality risk than non-Hispanic whites. Since data limitations precluded the ability to comprehensively account for differential comorbidity and metabolic profiles in these prior studies, Rhee et al. [5] reexamined the association between age, race, ethnicity and survival among >130,000 prevalent dialysis patients from a large US dialysis organization and similarly observed that, compared with white patients, black patients had a lower mortality risk in older age groups (>60 years) but a similar or higher mortality risk in younger age groups (≤60 years) [5]. It has been suggested that the observed attenuation or reversal of the minority survival advantage in younger black dialysis patients may be due to limited insurance and access to health care prior to dialysis initiation, or lack thereof, resulting in a higher comorbidity burden at the time of dialysis initiation [5, 8]. The present study’s demonstration of a persistent immigrant survival advantage across all age groups in a population with universal health care access adds support to this hypothesis [14].

The proposed mechanisms underlying the paradoxical survival advantage among immigrant minority dialysis patients in Denmark and minority dialysis patients in other countries may be due to multiple, complementary factors (Figure 1). First, although the present study did not examine data prior to the initiation of dialysis, it is possible that death of more sickly predialysis chronic kidney disease (CKD) patients prior to developing ESRD or the emigration of fitter patients from their native countries of origin may have resulted in selection bias and a healthier immigrant incident dialysis population [17, 18]. Second, while the immigrant survival advantage persisted even with adjustment for household income, it is possible that the associations may still be explained by other unmeasured socioeconomic factors (e.g. education, occupation) [19]. In addition, despite Denmark’s universal health care delivery system, other factors related to health care access (i.e. related to geographic residence and distance to health care centers) may still persist [20]. Third, the observed attenuation in survival advantage among Western immigrants with a longer duration of residence in Denmark also raises the possibility of sociocultural and lifestyle factors (dietary habits, social networks, physical activity, tobacco and alcohol use) being contributory [2]. Fourth, differential perceptions of quality of life, coping mechanisms and subsequent preferences for aggressive treatment in chronic illness and at the end of life may also play a role in racial/ethnic disparities in survival [21–23]. In addition, although some markers of comorbidity burden were accounted for using hospitalization and prescription data, the robust paradoxical racial/ethnic survival benefit suggests that other biologic factors are likely to be a factor in the Danish immigrant survival advantage. For example, past studies suggest that racial/ethnic differences in survival may be due in part to more favorable inflammatory, body anthropometry and nutritional profiles (e.g. higher serum prealbumin and creatinine as well as higher body mass index) in black versus white dialysis patients in the USA [24–26]. Lastly, it is plausible that differences in dialysis treatment characteristics may play a role in the mortality differential. While a greater proportion of native Danes received initial treatment with hemodialysis versus peritoneal dialysis, initial dialysis modality and type of vascular access among those receiving hemodialysis were not accounted for in survival analyses due to data limitations. In other Western studies, it has also been suggested that a higher likelihood of receiving activated vitamin D due to higher parathyroid hormone level distributions may partially account for the longevity of black dialysis patients [2, 4].

In conclusion, the van den Beukel et al. [14] study adds new knowledge to a growing body of evidence demonstrating lower mortality risk among immigrant dialysis patients versus native residents in European-based countries, and provides greater insight into potential explanatory factors specific to the Danish population. Future studies that test the impact of interventions upon modifiable factors (e.g. socioeconomic, dietary, physical activity, social support, pharmacologic) of the survival disparity in dialysis patients are needed. Moreover, further investigations of the racial/ethnic dialysis mortality paradox within other understudied populations and of underlying causes are urgently needed. For example, black dialysis patients have been observed to have lower hemoglobin levels than their white counterparts, and how this impacts mortality differences is largely unknown [27]. In addition, there are substantial knowledge gaps as to whether the differential expression of genetic polymorphisms (e.g. apolipoprotein 1 (APOL1), glucose 6-phosphate dehydrogenase (G6PD) and glutathione S-transferase class mu enzyme (GSTM1) gene mutations) among black versus non-black patients may contribute to survival disparities.
[28–30]. Insights gleaned from future studies may lead to the identification of factors that can be leveraged to improve the health and survival of the broader dialysis population.

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CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by van den Beukel et al. Differences in survival on chronic dialysis treatment between ethnic groups in Denmark: a population-wide, national cohort study. Nephrol Dial Transplant 2016; 31: 1160–1167)

REFERENCES

10. van den Beukel TO, Dekker FW, Siegert CE. Increased survival of immigrant compared to native dialysis patients in an urban setting in the Netherlands. Nephrol Dial Transplant 2008; 23: 3571–3577
12. van den Beukel TO, Verduijn M, le Cessie S et al. The role of psychosocial factors in ethnic differences in survival on dialysis in the Netherlands. Nephrol Dial Transplant 2012; 27: 2472–2479

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