

Exploring the Association between Macroeconomic Indicators and Dialysis Mortality

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Summary

Background and objectives Mortality on dialysis varies greatly worldwide, with patient-level factors explaining only a small part of this variation. The aim of this study was to examine the association of national-level macroeconomic indicators with the mortality of incident dialysis populations and explore potential explanations through renal service indicators, incidence of dialysis, and characteristics of the dialysis population.

Design, setting, participants, & measurements Aggregated unadjusted survival probabilities were obtained from 22 renal registries worldwide for patients starting dialysis in 2003–2005. General population age and health, macroeconomic indices, and renal service organization data were collected from secondary sources and questionnaires. Linear modeling with log–log transformation of the outcome variable was applied to establish factors associated with survival on dialysis.

Results Two-year survival on dialysis ranged from 62.3% in Iceland to 89.8% in Romania. A higher gross domestic product per capita (hazard ratio=1.02 per 1000 US dollar increase), a higher percentage of gross domestic product spent on healthcare (1.10 per percent increase), and a higher intrinsic mortality of the dialysis population (*i.e.*, general population-derived mortality risk of the dialysis population in that country standardized for age and sex; hazard ratio=1.04 per death per 10,000 person years) were associated with a higher mortality of the dialysis population. The incidence of dialysis and renal service indicators were not associated with mortality on dialysis.

Conclusions Macroeconomic factors and the intrinsic mortality of the dialysis population are associated with international differences in the mortality on dialysis. Renal service organizational factors and incidence of dialysis seem less important.

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Introduction

There is considerable international variation in mortality on dialysis, with patient-level factors such as age, primary renal disease, and comorbidities explaining only a small part of the variation (1–4). Even when general population mortality rates (5–7) and differences in treatment characteristics, such as the use of arteriovenous fistulae (8), are taken into account, a major part of the variation in dialysis mortality remains unexplained.

Because renal replacement therapy (RRT) is an expensive treatment, accounting for 2%–3% of the national healthcare budgets (9), macroeconomic factors may also contribute to the explanation of the variation in mortality on RRT (10–13). The International Study of Health Care Organization and Financing (ISHCOF) examined the relationship between the annual expenditure per ESRD patient and mortality in 12 high-income countries but did not find an association (14). Furthermore, single country studies examining the association of mortality with individual renal service indicators provided contradictory results (15–17). Finally, to our knowledge, the association between national dialysis incidence rates, known to be affected by

macroeconomic factors (18), and mortality on dialysis has not been investigated to date.

In 2008, the Explaining the Variation in Epidemiology of RRT through Expert Opinion, Secondary Data Sources, and Trends over Time (EVEREST) study set out to investigate the detailed interplay between economic characteristics of countries and their (1) incidence of RRT, (2) dialysis modality mix, and (3) mortality on dialysis (18,19). The primary aim of this paper is to examine the association of *a priori*-selected macroeconomic indicators with mortality of incident dialysis patient populations. Analyses then explore potential explanations for any association of macroeconomic determinants with mortality on dialysis and particularly, the relationship between renal service indicators, the incidence of dialysis and dialysis population characteristics, and the mortality in incident dialysis patients.

Materials and Methods

Data Collection

This EVEREST study used aggregated data from 22 countries across the globe for which the renal

Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

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registries were able to provide data on mortality on dialysis.

Outcome Measure—Mortality. Renal registries in Europe annually submitting patient data to the European Renal Association—European Dialysis and Transplantation Association registry gave permission for the calculation and use of their country-specific aggregated mortality data. The other renal registries provided aggregated mortality data specifically for this study (19). Kaplan–Meier tables for mortality on dialysis (censored for renal transplantation and end of follow-up, which was December 31, 2006) had to be calculated for all patients who started dialysis in 2003, 2004, and 2005 and were still alive on day 91. For Iceland, to limit random variability because of the low number of patients, this period was extended to 2001–2007. Because the national expert survey (19) focused on dialysis-related organizational factors, 2-year mortality on dialysis was adopted as the primary outcome.

Theoretical Framework. A theoretical framework (Figure 1) was developed to summarize how macroeconomic determinants may be associated with mortality of a country's dialysis population. We hypothesized that macroeconomic indicators are related to mortality on dialysis through both an incidence of dialysis pathway (Figure 1, dotted lines) and a quality of dialysis care pathway (Figure 1, solid lines).

Primary Determinants of Mortality. National-level data on determinants of mortality were collected for the period 2003–2005 (Table 1). We explored the impact of two macroeconomic indicators, gross domestic product (GDP) per capita (adjusted for purchasing power parity, which eliminates the differences in price levels between countries) and healthcare expenditure as a percentage of GDP, as primary potential determinants of mortality.

Secondary Determinants of Mortality. To explore potential explanations for an association between macroeconomic factors and mortality on dialysis, we investigated six national-level secondary determinants (Table 1)

representing renal service organization (three indicators), incidence of dialysis, and characteristics of the incident dialysis population (two indicators). For the calculation of the intrinsic mortality risk (Table 1) of the dialysis population, we used the general population mortality rates per sex and 5-year age bands. These rates were multiplied with the proportion of the corresponding sex and age groups within the incident dialysis population of that country and added, resulting in the intrinsic mortality risk of the dialysis population of that country. This intrinsic mortality risk represents, at least in part, the selection of dialysis patients in a specific country, with lower values representing a patient population with better survival prospects. For example, Romania has the highest general population mortality risk. However, after standardization to the very young dialysis population, Romania has the third lowest intrinsic age- and sex-related mortality risk on dialysis (Supplemental Table 1).

Potential Confounders. In the analysis of the association between each of the eight primary and secondary determinants and the mortality on dialysis, the other seven determinants were considered as potential confounders. In addition, we considered a number of additional national-level indicators for the same 2003–2005 period as possible confounders (Table 1).

Additional information on indicators and methods used for data collection for the EVEREST study has been published previously (19).

Data Analysis

The association between each determinant and the 2-year mortality on dialysis was analyzed using univariable and multivariable linear modeling. To be able to analyze mortality probabilities using linear modeling, we performed log–log transformation, where log is the natural logarithm. The estimated coefficients were then transformed back to the original scale, and they can be interpreted as hazard ratios (HRs) (20).

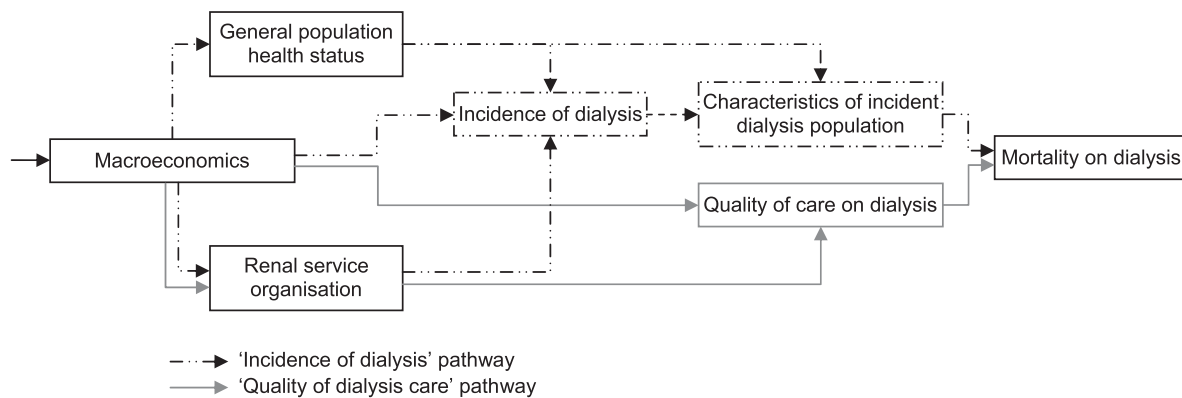


Figure 1. | Theoretical framework of the different indicator groups and their hypothesized relation with the survival on dialysis through two different pathways. Considering the incidence of dialysis pathway, macroeconomic indicators may be associated with the health status of the general population in a country as well as its renal service organization. Both macroeconomic factors and the health status of the general population have been shown to be associated with the incidence of renal replacement therapy (RRT) (18). Moreover, they are likely to be associated with the characteristics of the incident dialysis population, because a higher incidence frequently goes hand in hand with the inclusion of more high-risk patients (26,28). The latter has shown to be related to mortality on dialysis (1,2,44). Considering the quality of dialysis care pathway, we hypothesized that macroeconomic indicators and the organization of renal services may directly be linked with the quality of dialysis care, something that has previously been known to be related to mortality on dialysis (10,44,45).

To investigate the possibility of an independent relationship between each determinant and the 2-year mortality on dialysis, an etiological approach was adopted (21). Therefore, for each determinant, we constructed a separate linear model, in which all other indicators were considered as possible confounders. A maximum of two confounders per model was allowed because of the small number of participating countries ($n=22$) (22). Potential confounders were selected using recognized criteria for confounding (23). In addition, collinear confounders and confounders that caused less than 10% change in the β -value of the determinant were excluded from the models. Finally, for each determinant, a multivariate linear model was constructed using the strongest two confounders based on the percentage change in the β -value of the determinant after adding the potential confounder to the univariable linear model. All assumptions for linear modeling were tested and found to be satisfied.

For sensitivity analyses, we repeated all analyses using the following outcome measures: the 3-year mortality on dialysis, the 2-year mortality on RRT, and the 2-year mortality on dialysis for those younger and older than 65 years. Potential confounders were adapted to match the different outcome measures (e.g., in the analyses of mortality on RRT, we used the mean age at the start of RRT).

The number of observations and the number of variables available did not allow the study of separate associations of macroeconomic indicators with mortality through the different pathways.

Statistical analyses were performed using SPSS version 16.0 and SAS version 9.2.

Results

Supplemental Table 1 presents the countries and their variable values and ranking positions together with the overall median for the 2-year mortality on dialysis and the determinants. The countries were ranked by their 2-year mortality on dialysis. Figure 2 shows that the 2-year survival on dialysis ranged from 62.3% in Iceland to 89.8% in Romania. For patients younger than 65 years at the start of dialysis, it ranged from 75.8% (United States) to 92.5% (Japan), and for those patients older than 65 years at the start of dialysis, it ranged from 47.9% (Iceland) to 81.0% (Romania).

Primary Analyses

Table 2 presents the HRs derived from univariable and multivariable linear models (after backtransformation from log–log-transformed outcome variables) for the association between the potential determinants and 2-year mortality of a country's dialysis population.

Primary Determinants (Macroeconomic Determinants). In the multivariable analyses, a 1000 US dollar higher GDP per capita was associated with a 2.3% (95% confidence interval [CI]=0.2%–4.5%) higher mortality risk, whereas a 1% increase in the healthcare expenditure as a percentage of GDP was related to a 10.3% (95% CI=3.5%–17.5%) higher mortality risk.

Secondary Determinants.

Renal Service Organization Determinants. The private for-profit share of hemodialysis (HD) facilities, HD facility

reimbursement as proportion of GDP per capita, and the number of prevalent dialysis patients per nephrologist were not associated with mortality on dialysis.

Incidence of Dialysis. Although the incidence rate of dialysis was associated with a higher mortality on dialysis in univariable analysis, there was no association after adjustment for healthcare expenditure as a percentage of GDP and the responsiveness index (Table 2).

Characteristics of the Incident Dialysis Population.

There was no association between the percentage of the incident dialysis population with diabetic nephropathy and mortality. There was, however, an association between the intrinsic age- and sex-related mortality risk of the dialysis population and mortality on dialysis in the univariable and multivariable analyses; in both models, each additional death per 10,000 person years corresponded with a 3.8% (95% CI=0.9%–6.9%) higher mortality risk.

Sensitivity Analyses

The models with 3-year mortality on dialysis ($n=20$) and 2-year mortality on dialysis for patients starting dialysis above the age of 65 years ($n=22$) as outcome measures provided similar results compared with the analyses of 2-year mortality on dialysis. However, in the subgroup of patients younger than 65 years, the determinants that were found to be associated with 2-year mortality on dialysis ($n=22$) lost their statistical significance.

The linear models with 2-year mortality on RRT as the outcome measure ($n=20$) showed similar results compared with the 2-year mortality on dialysis models, although GDP per capita was less clearly associated with 2-year mortality on RRT (per 1000 US dollar, HR=1.018, $P=0.12$).

Discussion

Using data from 22 countries across the globe, we explored whether *a priori*-selected national-level macroeconomic indicators were associated with the 2-year mortality of a country's incident dialysis population. Remarkably, our results showed that a higher GDP per capita and a higher healthcare expenditure as a percentage of GDP were associated with a higher 2-year mortality on dialysis. Secondary analyses showed that none of the renal service indicators and the percentage of diabetic nephropathy were associated with mortality on dialysis. However, a higher intrinsic mortality risk of the dialysis population was associated with a higher mortality on dialysis.

Macroeconomic Determinants

As shown in Figure 1, we hypothesized that GDP per capita and healthcare expenditure as a percentage of GDP were associated with mortality of a country's dialysis population through both an incidence of dialysis pathway and a quality of dialysis care pathway.

Association with Mortality on Dialysis through the Incidence of Dialysis Pathway. The first step on this pathway constitutes the association between macroeconomic indicators and the incidence of dialysis, either directly or through the health status of the general population. An earlier EVEREST paper (18) confirmed results from the ISHCOF study that higher values for

Table 1. Description and source of the available macroeconomic indicators, general population health indicators, renal service organization indicators, incidence of dialysis, and incident dialysis population characteristics

	Description	Source
Primary determinants		
Macroeconomics		
GDP per capita ppp	GDP per capita in US dollars (adjusted for ppp, which eliminates the differences in price levels between countries). Measure of national wealth.	WHO HFA database, OECD Health database, WHO SIS database
Healthcare expenditure as a percentage of GDP	Percentage of GDP (<i>i.e.</i> , national wealth) spent on healthcare.	WHO HFA database, OECD Health database, World Bank NHP Stats
Secondary determinants		
Renal service organization		
Private for-profit share of HD facilities	Percentage of chronic outpatient HD facilities owned by the private (nongovernmental) for-profit sector.	Expert questionnaire
HD facility reimbursement as proportion of GDP per capita	Average annual reimbursement rate for main center HD, including reimbursement of the nephrologist as a proportion of GDP per capita.	Expert questionnaire; not available for New Zealand
Prevalent dialysis patients per nephrologist	Average number of prevalent dialysis patients per nephrologist.	Expert questionnaire
Incidence of dialysis	Crude incidence rate of dialysis per million population at day 91.	Renal registry
Incident dialysis population characteristics		
Percentage diabetes as primary renal disease	Percentage of incident patients with diabetes mellitus as the cause of ESRD.	Renal registry
Intrinsic age- and sex-related mortality risk of incident dialysis population	Measure of the background mortality risk of the national dialysis population; based on the mortality of the general population and age and sex standardization (using 5-year age bands) of the incident dialysis population of that country. This intrinsic mortality risk has been identified as a determinant of mortality in RRT patients (6,7).	Registry data and WHO mortality tables. Not available for Taiwan
Additional possible confounders		
Macroeconomic		
Human development index	Combines indicators of life expectancy, education, and income to create a validated composite score of a nation's state of development (46).	Available from www.hdr.undp.org
Responsiveness index	Indicator of healthcare system performance, with elements capturing respect for dignity, confidentiality, autonomy, prompt attention, quality of amenities, incidence of social support networks, and choice of provider (47).	WHO
Public share of healthcare expenditure	Public expenditure as a percentage of total expenditure on healthcare.	WHO HFA database, OECD Health database, World Bank NHP Stats
General population health status indicators		
Cardiovascular mortality	Cardiovascular mortality rates for the general population.	WHO mortality tables; not available for Taiwan
Life expectancy at age 60 years	The number of years an individual at 60 years old would be expected to live.	Eurostat and OECD data; not available for Taiwan
Renal service organization indicators		
HD facility reimbursement method	Facility reimbursement method (activity based versus global budget).	Expert questionnaire
Prevalent dialysis patients per dialysis center	Average number of prevalent dialysis patients per dialysis center.	Expert questionnaire

Table 1. (Continued)

Description		Source
Incident dialysis population characteristics		
Mean age	Mean age of the incident dialysis population.	Renal registry
Percentage of males	Percentage of males of the incident dialysis population.	Renal registry

GDP, gross domestic product; ppp, purchasing power parity; WHO, World Health Organization; HFA, Health for All; OECD, Organization for Economic Cooperation and Development; SIS, Statistical Information System; NHP, National Health Policy; HD, hemodialysis; RRT, renal replacement therapy.

macroeconomic indicators were associated with a higher incidence of RRT (14). Both studies highlighted the differences between high- and low-income countries in the health status of their general populations and the availability of RRT as potential explanations.

Our univariable results showed that a 10 per million population increase in the incidence rate of dialysis was associated with a 2% increase in the 2-year mortality on dialysis. After adjustment for healthcare expenditure as a percentage of GDP and the responsiveness index, this association was no longer present, suggesting that incidence of dialysis may, indeed, act as an intermediate (24) in the pathway between macroeconomics and mortality on dialysis.

Furthermore, the incidence of dialysis in a country is associated with the characteristics of the dialysis population (25,26), which in turn, may be related to mortality on dialysis. Our results showed that a higher intrinsic age- and sex-related mortality risk of the incident dialysis population was associated with higher mortality on dialysis. For example, in this study, Romania, the country with the lowest mortality on dialysis, had the lowest incidence of dialysis, which went together with the lowest mean age, the lowest percentage of patients with diabetic nephropathy, and also, one of the lowest intrinsic mortality risks of the dialysis population. However, the United States, the country with the third highest mortality on dialysis, had the second highest incidence of dialysis, the highest percentage of patients with diabetes, and a very high percentage of comorbid diseases (3) as well as patients starting dialysis while living in a nursing home (27). A high incidence may, therefore, be a sign of a higher acceptance of patients with a poor health condition, with a low incidence raising the possibility that some of these higher-risk patients are opting not to have dialysis or are not being accepted for dialysis (28). This relation was seen with the introduction in Taiwan in 1995 of a national health insurance system (26,29). This introduction led to an abrupt increase of the incidence of dialysis as well as an increase in mortality on dialysis because of the acceptance of more patients with a poor health condition.

Our data did not show an association between the percentage of patients with diabetic nephropathy and mortality on dialysis. Although this failure to show an association could not be accounted for by differences in the percentage of patients with missing or unknown causes of ESRD, miscoding may have contributed to the dilution of an effect.

Finally, another country feature affecting dialysis patient characteristics is the kidney transplant rate. A high trans-

plant rate will leave the older and less healthy patients on dialysis and thus, result in a lower survival on dialysis. Information on transplant rates was unfortunately lacking for many participating countries, although this information has been published for some countries. Iceland and Norway are known to have relatively high pre-emptive transplant rates (11% and 13%, respectively) (30) compared with the rest of Europe (3%) (30) and the United States (2%) (31). If countries were to be reranked according to RRT mortality instead of dialysis mortality (Supplemental Table 1), Norway would shift from the 21st to the 13th position, whereas Iceland's position would not change. However, Japan, with the second lowest mortality on dialysis, is known to have a very low (pre-emptive) transplant rate (31), leaving all their relatively healthy patients on dialysis (25).

Association with Mortality on Dialysis through the Quality of Dialysis Care Pathway. Macroeconomic indicators may also be associated with the mortality of a country's dialysis population through the quality of dialysis care, either directly or through the organization of renal services.

Our analyses did not show an association between a country's private for-profit share of HD facilities and mortality on dialysis. Although others have reported a higher mortality in for-profit HD facilities (15,16), our results confirm the findings in the work by Foley *et al.* (17). Our analyses failed to show an association between the annual HD facility reimbursement rate as proportion of a country's GDP and mortality on dialysis. An earlier EVEREST paper (18) did show that higher levels of this determinant were associated with a lower incidence of RRT, but we found no studies relating this renal service indicator to mortality on dialysis. Furthermore, our results did not show an association between the number of prevalent patients per nephrologist and the mortality on dialysis. Although to our knowledge, this relationship has not previously been examined, there are two publications reporting the lack of a relationship between the frequency of patient-physician contact for dialysis care and mortality (32,33).

Although the EVEREST study could not collect comparable data on quality of care, such data are available for some participating countries from Dialysis Outcomes and Practice Patterns Study (DOPPS) analyses. Indeed, DOPPS reported a higher mortality on HD to be associated with lower average treatment time per HD session (34), lower rates of arteriovenous fistula use (8), lower rates of pre-nephrology visits (35), and lower percentages of patients

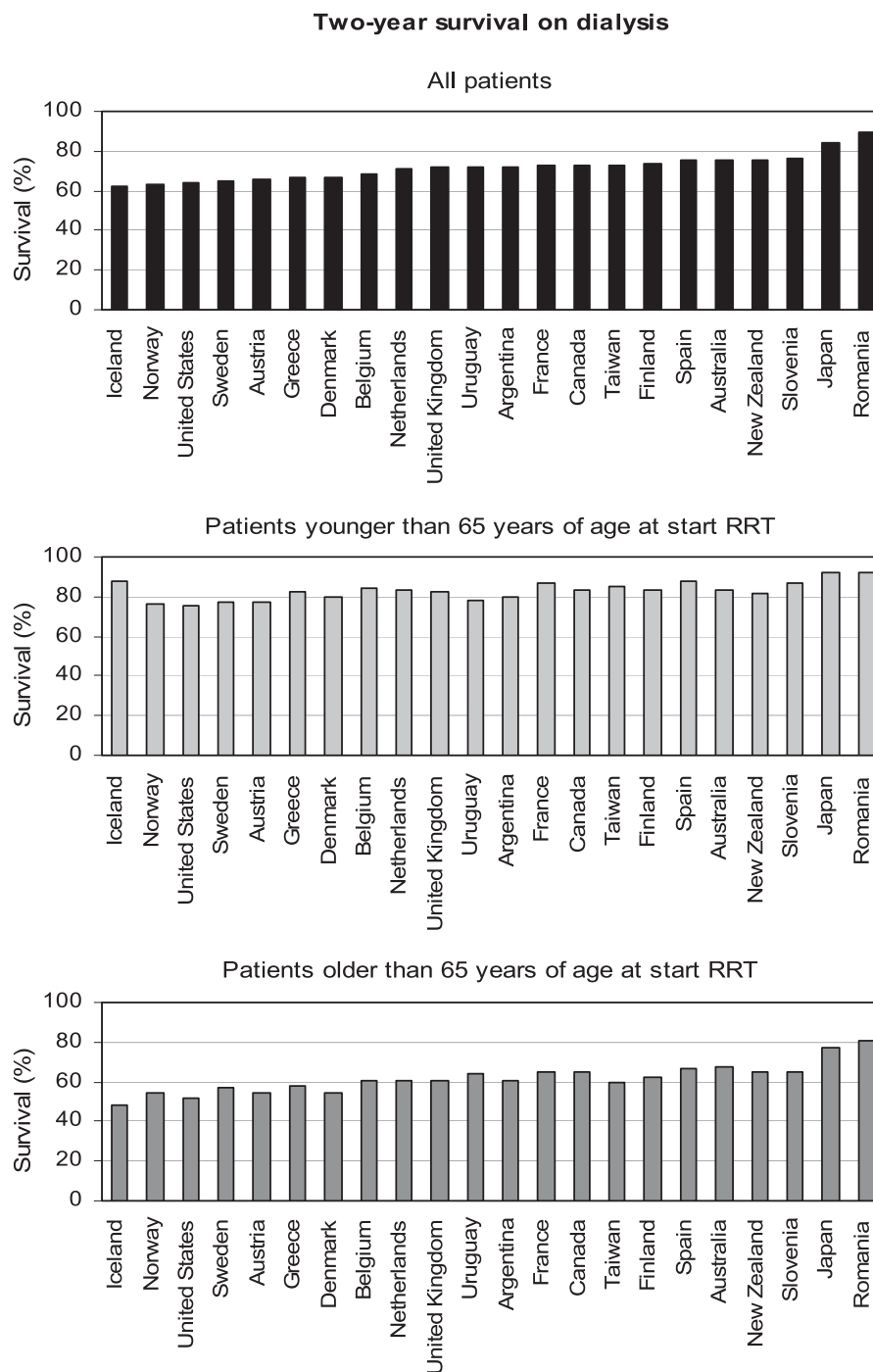


Figure 2. | Two-year mortality is widely distributed across the world. Distribution of 2-year dialysis survival probabilities for all patients (top panel), patients younger than 65 years at the start of dialysis as first renal replacement therapy (RRT; middle panel), and patients older than 65 years at the start of dialysis as first RRT (bottom panel).

within the guidelines for parathyroid hormone, serum phosphorus, serum calcium, and calcium-phosphorus product (36). These DOPPS publications also suggest that the United States (the country in EVEREST with the second highest GDP per capita and the highest healthcare expenditure as a percentage of GDP) provides lower quality of dialysis care (8,34,35) than other countries and that this quality is associated with higher mortality on dialysis. The apparently counterintuitive conclusion to be drawn

from both EVEREST and DOPPS, therefore, seems to be that higher spending on healthcare is associated with neither higher quality of dialysis care nor lower mortality on dialysis. Why might this be?

A potential explanation is that, in general, higher spending does not necessarily result in more effective care (37). The work by Wennberg *et al.* (38) examined why Medicare paid more than two times as much per person for healthcare in some US regions than other regions. He

Table 2. Hazard ratios (HRs) for 2-year mortality on dialysis (n=22)

	Univariable Model		Multivariable Model		
	Hazard Ratio ^a	P	Adjusted for Confounders ^b	Hazard Ratio ^a	P
Primary determinants					
Macroeconomic					
GDP per capita ppp (per 1000 USD)	1.021 (1.007–1.034)	0.007	Health expenditure percent GDP responsiveness index	1.023 (1.002–1.045)	0.05
Healthcare expenditure as percentage of GDP (per 1%)	1.129 (1.069–1.192)	0.001	HDI GDP per capita	1.103 (1.035–1.175)	0.007
Secondary determinants					
Renal service organization					
Private for profit share of HD facilities (per 1%)	0.997 (0.992–1.003)	0.35	None	NA	
HD facility reimbursement rate as proportion of GDP per capita (per year, per 1.0)	0.973 (0.762–1.243)	0.83	None	NA	
Prevalent dialysis patients per nephrologist (per 10)	0.996 (0.959–1.034)	0.83	None	NA	
Incidence of dialysis					
Incidence of dialysis (per 10 pmp)	1.023 (1.002–1.045)	0.04	Health expenditure percent GDP responsiveness index	0.976 (0.943–1.011)	0.19
Percentage diabetes as primary renal disease (per 1%)	1.002 (0.987–1.017)	0.83	Responsiveness index incidence of dialysis	0.985 (0.967–1.002)	0.10
Intrinsic age- and sex-related mortality risk of incident dialysis population (per 1 death/10,000 person years)	1.038 (1.009–1.069)	0.02	None	NA	

GDP, gross domestic product; ppp, purchasing power parity; HD, hemodialysis; NA, not applicable (because there were no variables qualifying as confounders; univariable relationships were, therefore, considered as independent); pmp, per million population.
^aBecause a log–log transformation was performed on the mortality probabilities, the exponent of the coefficients can be interpreted as hazard ratios.
^bThe variables listed comprise all of the confounders included in the model.

reported a strong association between higher spending and greater use of supply-sensitive care and a lack of association between more spending and more effective care (defined as services with use that is supported by well-articulated medical theory and strong evidence for efficacy). Another explanation may be provided in the work by Van Biesen *et al.* (39): in Belgium, higher spending on healthcare stimulates treatment of ESRD and discourages preventive strategies and early referral to the nephrology unit. In the DOPPS analyses that examined predialysis nephrology visits, Belgium was the only country with lower rates than the United States (35). The implication is that such countries might focus more on tertiary prevention (restoring function and alleviating symptoms) than primary or secondary prevention (avoiding disease or attempting to diagnose and treat it in its early stages). Finally, we wish to bring up another potential but more controversial explanation. Many of the current practice

guidelines stimulate higher spending, but in dialysis patients, adherence to such guidelines may not necessarily result in better outcomes. Although controversial, this explanation would be supported by the many negative trials conducted in dialysis patients that were published over the last decade (40–43).

Limitations of the Study

Although this study included all national renal registries in the world that had mortality data available, the country-level approach resulted in a maximum of 22 observations being available for analysis. As a consequence of the limited power, we may have missed real associations for some determinants. The study relied on existing general population, macroeconomic, and renal registry data. Where possible, internationally recognized secondary data sources, such as the World Health Organization and Organization for Economic Cooperation and Development,

were used, but in a small number of cases, national data (identified and approved by the national collaborator as best available) were accepted when these were not available (details in ref. 19). The difficulty to obtain standardized data restricted the number of variables that could be investigated. The potential for variation in definitions and data validation between renal registries also needs to be acknowledged, but again, every effort has been made to assess the quality of the data provided and exclude countries where data were considered unreliable. Prevalence of comorbid diseases among the dialysis population, a potential factor influencing mortality, was not available for a large number of countries. Also, kidney transplant rates were not available for all countries, and this rate is something that is likely to be an important factor affecting mortality of the dialysis population. However, sensitivity analyses using the 2-year mortality on RRT also showed an association for healthcare expenditure as a percentage of GDP with mortality on RRT.

National-level macroeconomic factors seem to be important determinants of international differences in mortality on dialysis. Potential complementary explanations include a more liberal acceptance policy among richer nations, perhaps mediated through reimbursement policies that favor high-technology treatments rather than preventive care. Furthermore, EVEREST data suggest the importance of taking into account the general population-derived intrinsic age- and sex-related mortality risk as a dialysis patient characteristic in survival comparisons across countries. Although the effect of national-level macroeconomic indicators on population health would be difficult for nephrologists to influence, a better understanding of how these indicators are associated with mortality of a country's dialysis population may guide future health policy to improve patient outcomes.

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Disclosures

None.

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