Greater First-Year Survival on Hemodialysis in Facilities in Which Patients Are Provided Earlier and More Frequent Pre-nephrology Visits

Takeshi Hasegawa,*†‡ Jennifer L. Bragg-Gresham,§ Shin Yamazaki,† Shunichi Fukuhara,† Tadao Akizawa,‖ Werner Kleophas,¶ Roger Greenwood,** and Ronald L. Pisoni§

*Division of Nephrology, Department of Internal Medicine, Fujiyoshida Municipal Hospital, Yamanashi, †Department of Epidemiology and Healthcare Research, Kyoto University Graduate School of Medicine and Public Health, Kyoto, ‡Division of Nephrology, Department of Internal Medicine, Showa University Fujigaoka Hospital, Yokohama, and ‖Department of Nephrology, Showa University School of Medicine, Tokyo, Japan; §Arbor Research Collaborative for Health, Ann Arbor, Michigan; ¶Dialysezentrum Karlstrasse, Dusseldorf, Germany; and **Department of Renal Medicine, Lister Hospital, Stevenage, United Kingdom*

Background and objectives: The aim of this study was to evaluate the relation between pre-nephrology visit (PNV) and 1-yr patient survival after hemodialysis (HD) induction.

Design, setting participants, & measurements: Data were analyzed from 8500 incident HD patients (on HD ≤30 d) in the Dialysis Outcomes and Practice Patterns Study (DOPPS) phases I and II. A visit to a nephrologist at least 1 mo before starting HD was regarded as PNV. Cox regression was used to estimate the adjusted hazard ratio (AHR) for mortality in the first year of HD in both patient- and facility-level analyses. All models were adjusted for age, sex, race, socioeconomic factors, cause of ESRD, 14 comorbid conditions, hemoglobin, serum albumin, and serum creatinine; accounted for facility clustering effects; and were stratified by country.

Results: In patient-level analysis, PNV was associated with significantly lower risk for death (AHR 0.57; $P < 0.0001$). Facility-level analysis also showed a significant lower risk for death in facilities with greater prevalence of PNV in both continuous models (AHR 0.92 per 10% greater facility mean %PNV; $P < 0.0004$) and in categorical models (AHR 0.71 for facilities with >90% of patients receiving PNV [first quartile] compared with facilities with <71% of patients receiving PNV [fourth quartile]; $P = 0.001$).

Conclusions: These results provide not only patient-level but also facility practice evidence that PNV is related to improved patient survival during the first year after initiation of HD, indicating the possible mortality benefits with more increased attention to PNV.

Clin J Am Soc Nephrol 4: 595–602, 2009. doi: 10.2215/CJN.03540708

Annual all-cause mortality adjusted for age, sex, and race among dialysis patients recently has been declining in some countries but still remains high, exceeding 20% in the United States (1). Numerous factors influence mortality of dialysis patients. The risk for death among dialysis patients is strongly associated with patient characteristics including age, sex, race, malnutrition, and nonrenal comorbidities (2–4). Such high mortality rates among dialysis patients have facilitated investigations on potentially modifiable factors related to higher risks for death. Consequently, it has been mentioned that inadequate dialysis has resulted in poorer patient survival (5–7). Furthermore, it has been noted in recent years that not only quality of dialysis but also the timing and quality of nephrology care before initiation of dialysis could affect outcomes in dialysis patients.

Early nephrology referral of patients with chronic kidney disease has been reported to reduce their mortality after initiation of dialysis, especially during the first year on dialysis (8–18); however, all of these findings were based on single-center or regional practices, thereby limiting generalizability of the findings. Indeed, some studies could not find the positive effect of early nephrology referral on patient survival (19,20). Thus, representative cohort studies estimating the effectiveness of early referral to a nephrologist on patient survival are lacking. Moreover, few investigations have evaluated the association of pre-nephrology visit (PNV) practice patterns with patient survival subsequent to initiation of dialysis; therefore, the aim of this study was to evaluate the relationship between PNV and 1-yr hemodialysis (HD) patient survival after HD induction in not only patient-level but also facility-level (facility practice patterns) analysis using the international representa-

Received July 17, 2008. Accepted November 18, 2008.

Published online ahead of print. Publication date available at www.cjasn.org.

Correspondence: Dr. Takeshi Hasegawa, Department of Epidemiology and Healthcare Research, Kyoto University Graduate School of Medicine and Public Health, Konoe-cho Yoshida, Sakyo-ku, Kyoto, 606-8501, Japan. Phone: +81-75-753-4646; Fax: +81-75-753-4644; E-mail: tahasegawa-npr@umin.net

ISSN: 1555-9041/403–0595

tive cohort, the Dialysis Outcomes and Practice Patterns Study (DOPPS).

Materials and Methods

Data Sources

We analyzed data of 8500 new HD patients (initiating dialysis ≤30 d before study enrollment) from DOPPS phases I and II. Prospective data were collected for maintenance HD patients who were randomly selected from 308 nationally representative dialysis facilities in seven countries (France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States) for DOPPS I (1996 through 2001) and from 322 facilities in DOPPS II (2002 through 2004) from 12 countries (DOPPS I countries plus Australia, Belgium, Canada, New Zealand, and Sweden). Details of the DOPPS sampling plan and study methods have been described elsewhere (21,22).

Data Collection

The main exposure to be tested was the presence or absence of PNV in both patient-level and facility-level analyses. A visit to a nephrologist at least 1 mo before the initiation of HD was regarded as PNV. The information about PNV was abstracted from patient medical records and self-reported patient questionnaires. When the medical record information and the patient questionnaire results contradicted or the questionnaire was not answered, we used the result from the medical records; the rate of contradiction was 5.1%. The secondary exposure to be tested was the number of PNV in both patient-level and facility-level analyses. Patients were asked the number of visits to a nephrologist in the year before starting dialysis (five or more visits, two to four visits, one visit, no visits, or not sure) in the patient questionnaire. All of these variables were collected at study enrollment.

The main outcome measure in this study was all-cause death within 1 yr after HD induction. Time at risk was defined as the period from study enrollment until all-cause death, departure from the study (as a result of the switch in treatment modality to peritoneal dialysis or transplantation or transfer to a non-DOPPS facility), or end of study follow-up. Other outcomes of interest were differences in PNV practice patterns by country and facility and the patient characteristics at study entry related to PNV practice. Patient characteristics that were examined at baseline included age; sex; race; socioeconomic factors; primary cause of ESRD; country of residence; and 14 summary comorbidities including coronary artery disease (CAD), congestive heart failure (CHF), cardiac disease other than CAD or CHF, hypertension, diabetes, cerebrovascular disease (CVD), peripheral arterial disease (PAD), cancer (other than skin), HIV/AIDS, lung disease, neurologic disorders, gastrointestinal (GI) bleeding, and recurrent cellulitis/gangrene. We also examined relationships with regard to baseline laboratory data including hemoglobin, serum albumin, and serum creatinine.

Statistical Analysis

We calculated descriptive statistics to describe patient characteristics by PNV group. We examined the adjusted odds ratio (AOR) of PNV by patient characteristics using multivariate logistic regression. We used Cox regression to estimate the hazard ratio of all-cause death within 1 yr after HD induction. Cox regression models were adjusted for age, sex, race, primary cause of ESRD, and the 14 summary comorbidities. These models were also stratified by country of residence and accounted for facility clustering effects using a sandwich estimator. All statistical analyses were performed with SAS 9.1 (SAS Institute, Cary, NC).

Ethical Consideration

Although this study was an observational study, institutional review boards approved the study in each country and facility as required. Informed consent was obtained for each sampled patient in accordance with the requirements of each country, institutional review board, and facility. Data collection was performed in a manner that maintained patient anonymity.

Results

Data were analyzed from 8500 new HD patients who had been on dialysis ≤30 d at time of enrollment in DOPPS. Table 1 shows the patient characteristics at study enrollment by PNV. Patients who had received PNV were more likely to have diabetes as cause of ESRD and comorbidities including hypertension and diabetes. In contrast, these patients were less likely to be of black race and have certain comorbidities such as CHF, lung disease, cancer, HIV/AIDS, GI bleeding, neurologic disease, and psychiatric disorder. The prevalence of some socioeconomic factors were slightly different by PNV. Patients who had seen a nephrologist before HD induction were more likely to be married, be employed, and have attended college. Patients with PNV *versus* without PNV displayed differences in laboratory values at study enrollment regarding hemoglobin (10.0 *versus* 9.8 g/dl), serum albumin (3.4 *versus* 3.2 g/dl), and serum creatinine (7.2 *versus* 7.6 mg/dl).

As shown in Figure 1, there were differences in PNV provided to HD patients across countries. The %PNV ranged from 70.1% in Belgium to 89.7% in Spain. Figure 2 illustrates the distribution of mean %PNV at the facility level. Wide variation was seen across facilities concerning the percentage of patients who received PNV in a facility (8.7 to 100%). In approximately three fourths of facilities, >70% of patients received nephrologist care at least 1 mo before HD induction. Mean and median facility %PNV was 80.1 and 82.1%, respectively.

Multivariate logistic regression models were used to examine the relationship of various patient factors with the AOR of PNV (Table 2). A greater odds of receiving PNV was seen for patients who had diabetes as ESRD cause (AOR 1.44; $P = 0.001$) and for patients with hypertension (AOR 1.45; $P < 0.0001$). Conversely, comorbidities such as CHF (AOR 0.78; $P < 0.0001$), lung disease (AOR 0.77; $P = 0.001$), neurologic disease (AOR 0.75; $P = 0.002$), and psychiatric disorder (AOR 0.87; $P = 0.04$) were negatively associated with receiving PNV. Patients who received PNV had significantly higher hemoglobin (AOR 1.07 per 1 g/dl higher; $P = 0.001$) and serum albumin (AOR 1.46 per 1 g/dl higher; $P < 0.0001$) but lower serum creatinine (AOR 0.94 per 1 mg/dl higher; $P < 0.0001$) at study enrollment. When the odds of PNV by country of residence were compared with that of the United States, patients in Australia/New Zealand (AOR 1.85; $P = 0.07$), France (AOR 2.60; $P < 0.0001$), Italy (AOR 2.37; $P < 0.0001$), Japan (AOR 3.55; $P < 0.0001$), Spain (AOR 2.85; $P < 0.0001$), Sweden (AOR 2.20; $P = 0.0001$), and the United Kingdom (AOR 1.75; $P = 0.005$) had a higher likelihood of receiving PNV. Patients with certain socioeconomic factors including living alone (AOR 1.24; $P = 0.03$), being married (AOR 1.24; $P = 0.001$), and having attended college (AOR 1.35; $P < 0.0001$) were also more likely to have received PNV.

Table 1. Patient characteristics by PNV[a]

Characteristic	PNV (n = 6836)	No PNV (n = 1664)
Demographics		
Age (yr; mean ± SD)	62.7 ± 14.9	62.9 ± 16.3
Male (%)	60.1	58.4
Race (%)		
white	72.5	68.1
black	13.8	19.1
Asian	10.4	7.8
other	3.3	5.0
Socioeconomic factors (%)		
live alone	14.8	14.4
married	59.6	52.0
attended college	17.1	13.6
employed	14.0	10.5
Diabetes as cause of ESRD (%)	37.5	31.0
Comorbidities (%)		
CAD	42.7	44.6
CHF	36.2	43.2
other cardiac disease	28.0	30.7
hypertension	83.2	77.9
CVD	15.9	16.5
PAD	24.3	24.1
diabetes	45.3	40.2
lung disease	11.2	16.4
cancer (other than skin)	12.0	14.1
HIV/AIDS	0.4	1.4
gastrointestinal bleeding	6.2	8.2
neurologic disease	7.5	11.3
psychiatric disorder	21.1	25.7
recurrent cellulitis/gangrene	6.6	6.0
Laboratory data		
hemoglobin (g/dl; mean ± SEM)	10.00 ± 0.02	9.80 ± 0.05
serum albumin (g/dl; mean ± SEM)	3.40 ± 0.01	3.20 ± 0.02
serum creatinine (mg/dl; mean ± SEM)	7.20 ± 0.04	7.60 ± 0.10

[a]A visit to a nephrologist at least 1 mo before the initiation of hemodialysis (HD) was regarded as a pre-nephrology visit (PNV). CAD, coronary artery disease; CHF, congestive heart failure; CVD, cerebrovascular disease; PAD, peripheral arterial disease.

During 2,336,822 person-days of follow-up (n = 8500 patients), the mean and median follow-up period were 275 d and 365 d, respectively, with 1065 (12.5%) deaths recorded. Figure 3 shows that the cumulative mortality during the first year after the initiation of HD was significantly lower in patients who received PNV than in patients who did not. The adjusted hazard ratio (AHR) of all-cause death was 0.57 (95% confidence interval [CI] 0.50 to 0.66; $P < 0.0001$) for patients who received PNV *versus* those who did not.

The AHR of all-cause death by facility %PNV is shown in Figure 4. Facility-level analysis showed a significantly lower risk for all-cause death with a greater proportion of patients who were provided PNV in a facility in both a continuous model (AHR 0.92 per 10% greater mean facility %PNV; 95% CI 0.88 to 0.96; $P = 0.0004$) and a categorical model (AHR 0.71, facilities with >90% of patients receiving PNV (75th percentile) *versus* facilities with <71% of patients receiving PNV (25th percentile); 95% CI 0.57 to 0.87; $P = 0.001$).

Figure 5 shows the AHR of all-cause death by a patient's number of PNV. Patients who saw a nephrologist five or more times in the year before HD induction displayed a 28% lower risk for all-cause death compared with those who had one or no nephrologist visits (AHR 0.72; 95% CI 0.56 to 0.93; $P = 0.01$). There was also significant association for a reduced risk for all-cause death with greater facility proportion of PNV (Table 3). For facilities that had 20% more patients receiving five or more PNV, patients in those facilities displayed lower mortality risk during the first year after HD induction (AHR 0.91; 95% CI 0.83 to 0.99; $P = 0.048$).

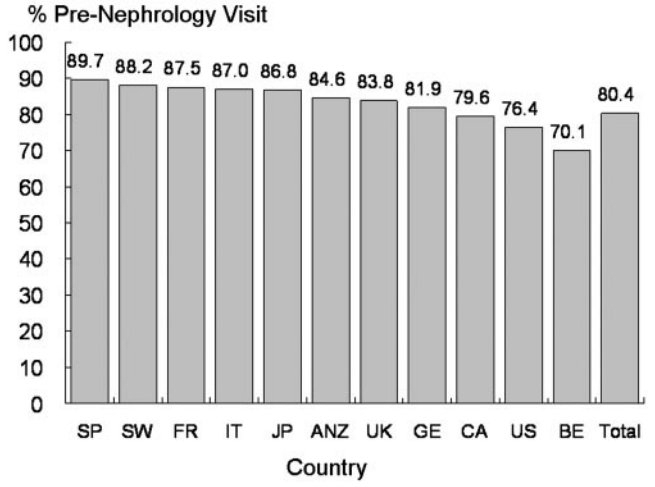

Figure 1. Percentage of pre-nephrology visit (%PNV; a visit to a nephrologist at least 1 mo before the initiation of HD was regarded as PNV) in patient level by country. Based on a point prevalent cross-section at study enrollment of patients who had been on hemodialysis (HD) ≤30 d; $n = 182$ in Australia/New Zealand (ANZ), $n = 264$ in Belgium (BE), $n = 225$ in Canada (CA), $n = 478$ in France (FR), $n = 504$ in Germany (GE), $n = 494$ in Italy (IT), $n = 698$ in Japan (JP), $n = 571$ in Spain (SP), $n = 245$ in Sweden (SW), $n = 346$ in the United Kingdom (UK), $n = 4493$ in the United States (US), and $n = 8500$ in total.

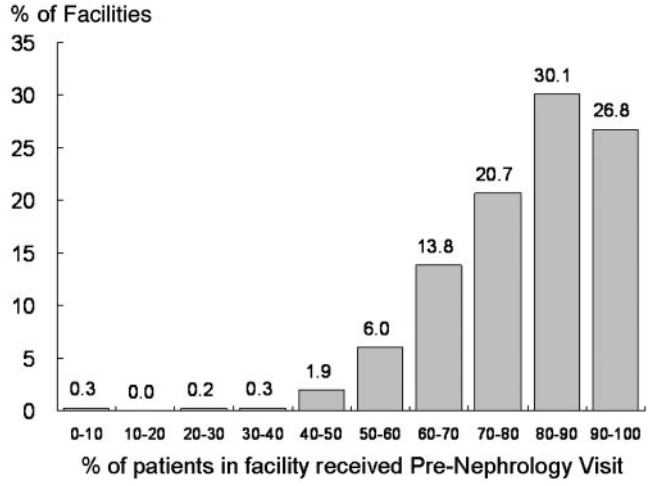

Figure 2. Distribution of mean facility %PNV, restricting to facilities that had at least five patients with PNV information (510 facilities, $n = 8298$).

Discussion

We investigated nationally representative incident HD patients (initiating dialysis ≤30 d at study enrollment) in 12 countries. Our study indicated that PNV, defined as having seen a nephrologist at least 1 mo before ESRD, was associated with lower risk for all-cause death during the first year after HD induction. We also evaluated the association of greater PNV as a facility practice pattern with 1-yr patient survival subsequent to HD induction. As a result, a graded relationship was seen between practice patterns of PNV and mortality, in which risk for death was lower with a greater prevalence of facility patients receiving PNV.

In this study, the primary cause of ESRD (diabetes) was related to receiving PNV, and similar results were reported in previous investigations (13,14,17,23). Hypertension was the most common comorbid condition (83.2% in PNV group, 77.9% in no PNV group) and was associated with receiving PNV in this study. Other studies have also shown that patients with hypertension were more likely to receive PNV (15,23). In contrast, patients with certain comorbidities such as CHF, lung disease, neurologic disease, and psychiatric disorder were less likely to receive PNV in this study. Winkelmayer *et al.* (15) also reported that patients without PNV were more likely to have CHF at the initiation of dialysis, which may be a consequence of these patients' possibly requiring urgent HD induction more often than patients with other types of comorbidities. In this study, the patients who were referred late to a nephrologist presented with slightly higher serum creatinine but marginally lower hemoglobin and serum albumin compared with early referral patients. This observation was also addressed in several previous studies (24–26). Lower hemoglobin and serum albumin levels at dialysis induction may reflect suboptimal pre-ESRD care. Patients without PNV may be exposed to poorer conditions, leading to initiation of HD at a more advanced stage, reflected by higher serum creatinine concentrations at ESRD onset. It is possible that sicker patients are less likely to be referred earlier, but delay in PNV itself may contribute to poor health through inattention to modifiable risk factors.

In this study, %PNV was 80.4% in total and varied by country. Other studies that used the same definition of PNV as this study (visit to a nephrologist at least 1 mo before the initiation of dialysis) reported that the proportion of PNV was 50 to 75% in the United States (17,19,27), 70 to 77% in France (13,24), and 67% in the United Kingdom (12). The proportion of PNV in each country is somewhat different from this study (76.4% in the United States, 87.5% in France, and 83.8% in the United Kingdom); however the past studies were based on regional or single-center data, so our results may have the strongest generalizability because the patients were randomly collected from nationally representative dialysis facilities in each country. We also examined the likelihood of PNV by country of residence; the patients in all countries except Belgium were more likely to receive PNV than HD patients who lived in the United States.

There was also wide variation in the distribution of %PNV at the facility level in this study. This result may suggest the large difference in the practice pattern of PNV across facilities. We could not find a similar descriptive analysis in previous investigations.

According to the results from this research, PNV was associated with significantly lower all-cause mortality risk within 1 yr after HD induction. For multivariate analysis, we found that patients who saw a nephrologist at least 1 mo before initiation of HD had a 43% lower likelihood of all-cause death in the first year of HD compared with patients with late referral. Other studies have examined whether PNV is beneficial for dialysis patient survival. Most previous investigations also found substantially lower 1-yr mortality

Table 2. AOR of PNV[a]

Characteristic	AOR	95% CI	*P*
Age (per 10 yr)	0.98	0.93 to 1.02	0.3400
Male (*versus* female)	1.00	0.89 to 1.12	0.9700
Race (*versus* white)			
black	0.97	0.82 to 1.16	0.7600
Asian	0.67	0.44 to 1.04	0.0800
other	0.68	0.51 to 0.91	0.0100
Socioeconomic factors			
live alone (*versus* not alone)	1.24	1.03 to 1.49	0.0300
married (*versus* not married)	1.24	1.09 to 1.40	0.0010
attended college (*versus* no college)	1.35	1.15 to 1.58	<0.0001
employed (*versus* not employed)	1.04	0.86 to 1.26	0.6900
Diabetes as cause of ESRD (yes *versus* no)	1.44	1.17 to 1.77	0.0010
Comorbidities (yes *versus* no)			
CAD	1.01	0.89 to 1.15	0.8600
CHF	0.78	0.69 to 0.89	<0.0001
other cardiac disease	0.94	0.83 to 1.07	0.3700
hypertension	1.45	1.25 to 1.70	<0.0001
CVD	1.06	0.90 to 1.24	0.5100
PAD	0.99	0.85 to 1.16	0.9300
diabetes	1.09	0.92 to 1.30	0.3300
lung disease	0.77	0.66 to 0.90	0.0010
cancer (other than skin)	0.90	0.77 to 1.06	0.2000
HIV/AIDS	0.73	0.42 to 1.27	0.2700
gastrointestinal bleeding	0.87	0.71 to 1.08	0.2100
neurologic disease	0.75	0.62 to 0.90	0.0020
psychiatric disorder	0.87	0.76 to 0.99	0.0400
recurrent cellulitis/gangrene	1.21	0.94 to 1.55	0.1500
Laboratory data			
hemoglobin (per 1 g/dl higher)	1.07	1.03 to 1.12	0.0010
serum albumin (per 1 g/dl higher)	1.46	1.28 to 1.66	<0.0001
serum creatinine (per 1 mg/dl higher)	0.94	0.92 to 0.97	<0.0001
Country of residence (*versus* United States)			
Australia/New Zealand	1.85	0.96 to 3.57	0.0700
Belgium	0.75	0.53 to 1.11	0.1600
Canada	1.14	0.77 to 1.70	0.5200
France	2.60	1.79 to 3.79	<0.0001
Germany	1.40	0.97 to 2.01	0.0800
Italy	2.37	1.53 to 3.65	<0.0001
Japan	3.55	2.04 to 6.18	<0.0001
Spain	2.85	2.05 to 3.96	<0.0001
Sweden	2.20	1.39 to 3.36	0.0010
United Kingdom	1.75	1.19 to 2.57	0.0050

[a]$n = 8500$. The results are from a multivariate analysis adjusting for all factors shown. A visit to a nephrologist at least one month before the initiation of HD was regarded as PNV. AOR, adjusted odds ratio; CI, confidence interval; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cerebrovascular disease; PAD, peripheral arterial disease.

among early referral *versus* late referral patients (8–18). In contrast, some of these studies did not find a positive effect of early referral on patient survival (19,20). These conflicting outcomes could be partly explained by inconsistencies in the definition of PNV. Furthermore, these negative results were based on single-center settings and relatively small numbers of patients; therefore, the failure to find a difference in patient survival between early referral *versus* late referral in these investigations may be attributable to sample size limitations and selection bias.

We evaluated PNV using two different PNV measures: Whether the patient saw a nephrologist before ESRD and the frequency of nephrologist care in the year before starting HD. This latter measure may be a more representative indicator of

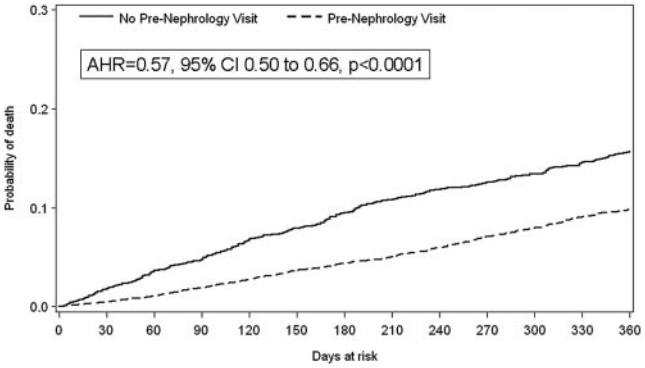

Figure 3. Cumulative hazard of all-cause death by PNV in patient level analyses. Adjusted hazard ratios (AHRs) of all-cause death were adjusted for age, sex, race, primary cause of ESRD, 14 summary comorbidities (coronary artery disease [CAD], congestive heart failure [CHF], cardiac disease other than CAD or CHF, hypertension, diabetes, cerebrovascular disease [CVD], peripheral arterial disease [PAD], cancer [other than skin], HIV/AIDS, lung disease, neurologic disorders, GI bleeding, and recurrent cellulitis/gangrene); were stratified by country; and accounted for facility clustering effects (n = 8500).

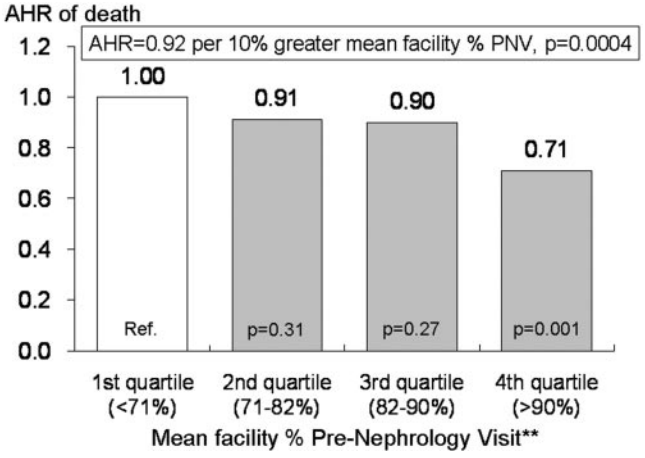

Figure 4. Lower risk for all-cause death for greater mean facility %PNV, restricting to facilities that had at least five patients with PNV information (510 facilities, n = 8298). AHRs of all-cause death were adjusted for age, sex, race, primary cause of ESRD, 14 summary comorbidities (CAD, CHF, cardiac disease other than CAD or CHF, hypertension, diabetes, CVD, PAD, cancer [other than skin], HIV/AIDS, lung disease, neurologic disorders, GI bleeding, and recurrent cellulitis/gangrene); were stratified by country; and accounted for facility clustering effects. **The 75th percentile of mean facility PNV was 90% of patients in a facility receiving PNV.

exposure to consistent care by a nephrologist. A graded relationship between the number of PNV and all-cause mortality was observed. Those who saw a nephrologist on five or more occasions in the year before HD had a 28% lower all-cause mortality risk in the first year of HD compared with those who had one or no nephrologist visits. Our result that frequent PNV was independently associated with improved patient survival

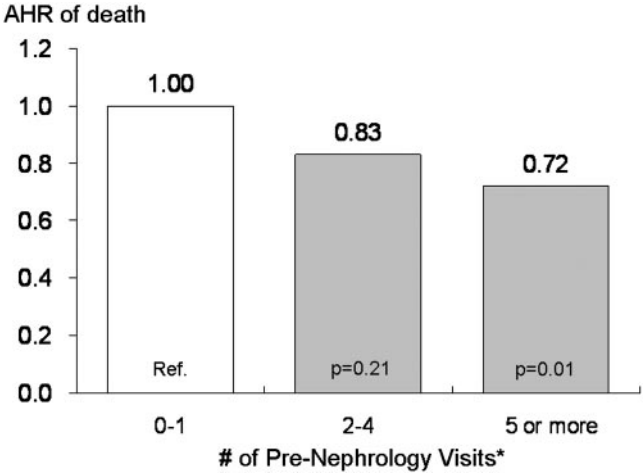

Figure 5. Lower risk for all-cause death for patients who saw a nephrologist more often (greater number of PNV) in the year before HD induction, restricting to patients with PNV information (n = 4270). AHRs of all-cause death were adjusted for age, sex, race, primary cause of ESRD, 14 summary comorbidities (CAD, CHF, cardiac disease other than CAD or CHF, hypertension, diabetes, CVD, PAD, cancer [other than skin], HIV/AIDS, lung disease, neurologic disorders, GI bleeding, and recurrent cellulitis/gangrene); were stratified by country; and accounted for facility clustering effects. *The number of visits to a nephrologist in the year before starting dialysis.

agrees with the findings from previous studies (17,23). These studies investigated only vulnerable patients from the Centers for Medicare & Medicaid Services in the United States (*i.e.*, older or indigent patients), so we could confirm similar association in a more representative HD population in this study.

We also assessed the association of facility practice patterns concerning PNV with all-cause mortality in the first year of HD. After adjustment for potential confounders, there was the association between greater proportion of patients who were provided PNV in a facility and improved patient survival within 1 yr after HD induction, and this relationship was graded. According to our result, patients displayed a 29% lower mortality risk during the first year of HD when treated in facilities that had at least 90% of patients receiving PNV (75th percentile), compared with patients in facilities in which ≤71% of patients received PNV (25th percentile). There was a similar graded and significant association between a greater percentage of facility patients with more frequent PNV and a lower risk for all-cause death within 1 yr after HD induction. It is probably impossible to conduct randomized, controlled trials to determine the impact of early referral to a nephrologist on patient survival. Consequently, analyses such as ours that evaluate the relationship between a facility practice pattern for PNV and mortality may suggest some benefit.

A strength of this study is that identical questionnaires are used in 12 countries to collect detailed data from a large number of patients. A two-stage random sampling method was used to prospectively collect data in these 12 developed countries. These data contain expected confounding factors, which

Table 3. AHR for all-cause death by facility prevalence of PNV[a]

Facility Prevalence of PNV	AHR[b]	95% CI	*P*
Per 20% more patients having 2 to 4 PNVs	0.97	0.88 to 1.08	0.620
Per 20% more patients having ≥5 PNVs	0.91	0.83 to 0.99	0.048

[a]A visit to a nephrologist at least one month before the initiation of HD was regarded as PNV. Restricted to facilities that had at least five patients with PNV information (359 facilities, $n = 3774$). AHR, adjusted hazard ratio
[b]Compared with having one or no PNVs.

could make the results more appropriate; their representative nature makes our findings more broadly applicable. Stratification by country and accounting for facility clustering effects served to adjust the differential impact of PNV on first-year mortality in HD patients by geographic region. We carried out a facility-level analysis to evaluate the association of PNV practice patterns with the mortality outcome. The results from the facility-level analysis also provide some benefit for interpretation.

Our findings must be interpreted with certain limitations in mind. The possibility of confounding as a result of healthier patients seeing nephrologists before starting dialysis should be mentioned as a limitation. The information on the number of PNV was collected only from the patient questionnaire, so there is some bias, such as sicker patients are less likely to answer the questions; however, we verified the information of PNV, the main exposure to be tested in this study, by not only the patient questionnaire but also the patient's medical record information. It is necessary to consider that the investigations concerning mortality may suffer from lead-time bias. Patients who received PNV may start HD earlier (*i.e.*, at lower serum creatinine levels and with preserved residual renal function [RRF]) than those who did not. In our findings, serum creatinine level at study enrollment was slightly lower in the PNV group than in the no PNV group (7.2 *versus* 7.6 mg/dl), but how this difference would affect clinical outcomes is uncertain. Recent studies described the data on serum creatinine level and RRF at the start of dialysis. In these investigations, RRF was nearly identical in the early and late referral groups (13,14). Kinchen *et al.* (11) found that the proportion of patients with a serum creatinine concentration ≥10 mg/dl was not different among early, intermediate, or late referral groups. Furthermore, Kazmi *et al.* (28) reported patients who initiate dialysis therapy at greater RRF have an increased risk for death not fully explained by comorbidity. Finally, this is an observational study that can only infer association between exposures to be tested and outcomes and not causality.

Conclusions

In representative incident HD patients from the countries that participated in DOPPS, PNV was related to better first-year HD patient survival on the basis of not only patient-level but also facility-level analyses (*i.e.*, greater survival in the first year of HD was observed in facilities in which patients were provided earlier and more frequent PNV). Practice patterns of PNV varied by country and facility. These findings indicate a need for increased attention to PNV to improve HD patient outcomes.

Acknowledgments

The DOPPS is supported by research grants from Amgen Inc. and Kirin Pharma Co., Ltd., without restrictions on publications.

Disclosures

The DOPPS is administered by Arbor Research Collaborative for Health.

References

1. US Renal Data System: *USRDS 2004 Annual Data Report*, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2005
2. Owen WF Jr, Lew NL, Liu Y, Lowrie EG, Lazarus JM: The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. *N Engl J Med* 329: 1001–1006, 1993
3. Keane WF, Collins AJ: Influence of co-morbidity on mortality and morbidity in patients treated with hemodialysis. *Am J Kidney Dis* 24: 1010–1018, 1994
4. Port FK: Morbidity and mortality in dialysis patients. *Kidney Int* 46: 1728–1737, 1994
5. Hakim RM, Held PJ, Stannard DC, Wolfe RA, Port FK, Daugirdas JT, Agodoa L: Effect of the dialysis membrane on mortality of chronic hemodialysis patients. *Kidney Int* 50: 566–570, 1996
6. Held PJ, Port FK, Wolfe RA, Stannard DC, Carroll CE, Daugirdas JT, Bloembergen WE, Greer JW, Hakim RM: The dose of hemodialysis and patient mortality. *Kidney Int* 50: 550–556, 1996
7. Feldman HI, Kinosian M, Bilker WB, Simmons C, Holmes JH, Pauly MV, Escarce JJ: Effect of dialyzer reuse on survival of patients treated with hemodialysis. *JAMA* 276: 620–625, 1996
8. Innes A, Rowe PA, Burden RP, Morgan AG: Early deaths on renal replacement therapy: The need for early nephrological referral. *Nephrol Dial Transplant* 7: 467–471, 1992
9. Sesso R, Belasco AG: Late diagnosis of chronic renal failure and mortality on maintenance dialysis. *Nephrol Dial Transplant* 11: 2417–2420, 1996
10. Jungers P, Massy ZA, Nguyen-Khoa T, Choukroun G, Robino C, Fakhouri F, Touam M, Nguyen AT, Grunfeld JP: Longer duration of predialysis nephrological care is associated with improved long-term survival of dialysis patients. *Nephrol Dial Transplant* 16: 2357–2364, 2001
11. Kinchen KS, Sadler J, Fink N, Brookmeyer R, Klag MJ,

Levey AS, Powe NR: The timing of specialist evaluation in chronic kidney disease and mortality. *Ann Intern Med* 137: 479–486, 2002
12. Roderick P, Jones C, Drey N, Blakeley S, Webster P, Goddard J, Garland S, Bourton L, Mason J, Tomson C: Late referral for end-stage renal disease: A region-wide survey in the south west of England. *Nephrol Dial Transplant* 17: 1252–1259, 2002
13. Kessler M, Frimat L, Panescu V, Briancon S: Impact of nephrology referral on early and midterm outcomes in ESRD: EPidemiologie de l'Insuffisance REnale chronique terminale en Lorraine (EPIREL)—Results of a 2-year, prospective, community-based study. *Am J Kidney Dis* 42: 474–485, 2003
14. Stack AG: Impact of timing of nephrology referral and pre-ESRD care on mortality risk among new ESRD patients in the United States. *Am J Kidney Dis* 41: 310–318, 2003
15. Winkelmayer WC, Owen WF Jr, Levin R, Avorn J: A propensity analysis of late versus early nephrologist referral and mortality on dialysis. *J Am Soc Nephrol* 14: 486–492, 2003
16. Kazmi WH, Obrador GT, Khan SS, Pereira BJ, Kausz AT: Late nephrology referral and mortality among patients with end-stage renal disease: A propensity score analysis. *Nephrol Dial Transplant* 19: 1808–1814, 2004
17. Khan SS, Xue JL, Kazmi WH, Gilbertson DT, Obrador GT, Pereira BJ, Collins AJ: Does predialysis nephrology care influence patient survival after initiation of dialysis? *Kidney Int* 67: 1038–1046, 2005
18. Schwenger V, Morath C, Hofmann A, Hoffmann O, Zeier M, Ritz E: Late referral: A major cause of poor outcome in the very elderly dialysis patient. *Nephrol Dial Transplant* 21: 962–967, 2006
19. Schmidt RJ, Domico JR, Sorkin MI, Hobbs G: Early referral and its impact on emergent first dialyses, health care costs, and outcome. *Am J Kidney Dis* 32: 278–283, 1998
20. Roubicek C, Brunet P, Huiart L, Thirion X, Leonetti F, Dussol B, Jaber K, Andrieu D, Ramananarivo P, Berland Y: Timing of nephrology referral: Influence on mortality and morbidity. *Am J Kidney Dis* 36: 35–41, 2000
21. Young EW, Goodkin DA, Mapes DL, Port FK, Keen ML, Chen K, Maroni BL, Wolfe RA, Held PJ: The Dialysis Outcomes and Practice Patterns Study (DOPPS): An international hemodialysis study. *Kidney Int* 57: S74–S81, 2000
22. Pisoni RL, Gillespie BW, Dickinson DM, Chen K, Kutner MH, Wolfe RA: The Dialysis Outcomes and Practice Patterns Study (DOPPS): Design, data elements, and methodology. *Am J Kidney Dis* 44: 7–15, 2004
23. Avorn J, Bohn RL, Levy E, Levin R, Owen WF Jr, Winkelmayer WC, Glynn RJ: Nephrologist care and mortality in patients with chronic renal insufficiency. *Arch Intern Med* 162: 2002–2006, 2002
24. Jungers P, Zingraff J, Albouze G, Chauveau P, Page B, Hannedouche T, Man NK: Late referral to maintenance dialysis: Detrimental consequences. *Nephrol Dial Transplant* 8: 1089–1093, 1993
25. Obrador GT, Pereira BJ: Early referral to the nephrologist and timely initiation of renal replacement therapy: A paradigm shift in the management of patients with chronic renal failure. *Am J Kidney Dis* 31: 398–417, 1998
26. Arora P, Obrador GT, Ruthazer R, Kausz AT, Meyer KB, Jenuleson CS, Pereira BJ: Prevalence, predictors, and consequences of late nephrology referral at a tertiary care center. *J Am Soc Nephrol* 10: 1281–1286, 1999
27. Pisoni RL, Young EW, Dyksta DM, Greenwood RN, Hecking E, Gillespie B, Wolfe RA, Goodkin DA, Held PJ: Vascular access use in Europe and the United States: Results from the DOPPS. *Kidney Int* 61: 305–316, 2002
28. Kazmi WH, Gilbertson DT, Obrador GT, Guo H, Pereira BJ, Collins AJ, Kausz AT: Effect of comorbidity on the increased mortality associated with early initiation of dialysis. *Am J Kidney Dis* 46: 887–896, 2005