C-Reactive Protein and Prediction of 1-Year Mortality in Prevalent Hemodialysis Patients

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Summary

Background and objectives Measurement of C-reactive protein (CRP) levels remains uncommon in North America, although it is now routine in many countries. Using Dialysis Outcomes and Practice Patterns Study data, our primary aim was to evaluate the value of CRP for predicting mortality when measured along with other common inflammatory biomarkers.

Design, setting, participants, & measurements We studied 5061 prevalent hemodialysis patients from 2005 to 2008 in 140 facilities routinely measuring CRP in 10 countries. The association of CRP with mortality was evaluated using Cox regression. Prediction of 1-year mortality was assessed in logistic regression models with differing adjustment variables.

Results Median baseline CRP was lower in Japan (1.0 mg/L) than other countries (6.0 mg/L). CRP was positively, monotonically associated with mortality. No threshold below which mortality rate leveled off was identified. In prediction models, CRP performance was comparable with albumin and exceeded ferritin and white blood cell (WBC) count based on measures of model discrimination (c-statistics, net reclassification improvement [NRI]) and global model fit (generalized R^2). The primary analysis included age, gender, diabetes, catheter use, and the four inflammatory markers (omitting one at a time). Specifying NRI ≥5% as appropriate reclassification of predicted mortality risk, NRI for CRP was 12.8% compared with 10.3% for albumin, 0.8% for ferritin, and <0.1% for WBC.

Conclusions These findings demonstrate the value of measuring CRP in addition to standard inflammatory biomarkers to improve mortality prediction in hemodialysis patients. Future studies are indicated to identify interventions that lower CRP and to identify whether they improve clinical outcomes.

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Introduction

Mortality rates among hemodialysis (HD) patients remain exceptionally high, at levels six to eight times those of the general population (1). Effective means to identify patients at greatest risk, as well as interventions to improve outcomes, are urgently needed.

C-reactive protein (CRP) is an inflammatory biomarker associated with infection, cardiovascular events, and mortality in dialysis patients (2–8). Despite increasingly routine CRP measurement in dialysis units in Japan and Europe (9), controversy over what might be gained by this practice has impeded its adoption in the United States and Canada (10,11). Furthermore, previous studies have had few patients with low CRP levels, calling into question the interpretation of modest elevations in CRP. For this reason, determining a clinically meaningful CRP "cutoff point" is a research priority identified by the National Kidney Foundation's Kidney Disease Outcomes and Quality Initiative (KDOQI) (12).

The Dialysis Outcomes and Practice Patterns Study (DOPPS) is an international prospective cohort study of adult HD patients and practices. Using data from this sample with several thousand patients, the primary aim of this study was to test the hypothesis that CRP improves the prediction of mortality when measured in conjunction with standard inflammatory biomarkers. An additional aim was to more completely characterize the association of CRP with mortality, especially at low CRP levels.

Materials and Methods

Data Source and Study Patients

Data were from phase 3 (2005 to 2008) of the DOPPS, involving prevalent HD patients ≥18 years old from 300 randomly selected facilities in 12 countries (Australia, Belgium, Canada, France, Germany, Italy, Japan, New Zealand, Spain, Sweden, the United Kingdom, and the United States). Study approval was obtained by a central institutional review board. Additional study approval and patient consent were ob-

tained as required by national and local ethics committee regulations.

Demographics, comorbidities, and laboratory values measured during the course of routine clinical care were recorded (13,14).

To reduce selection bias for patients with suspected acute infections, analyses were restricted to patients in facilities that measure CRP routinely (at least quarterly on ≥75% of patients) and on maintenance HD >90 days with recorded baseline CRP values (5061 patients from 140 facilities in 10 countries; no facilities in Canada or the United States measured CRP routinely). All analyses were restricted to baseline CRP values, which were highly skewed. Extreme values were capped at the 99th percentile (172 mg/L).

Statistical Methods

CRP was categorized into groups using typical clinical thresholds with similar numbers of patients. CRP categories were treated as a set of indicator variables to estimate hazard (rate) ratios for the nonreference categories. To assess the association between CRP and overall and cause-specific mortality, we used Cox regression, stratified by country and accounting for facility clustering. Baseline covariates included in the Cox model are listed in Figure 3. Time-at-risk started at study entry for each patient. Analyzed deaths occurred during study follow-up or within 7 days after study departure. The proportional hazards assumption was confirmed for CRP and the majority of the covariates. For a few covariates that violated the assumption, we either stratified the model by these covariates or added interactions between them and time, as appropriate.

To examine the predictive characteristics of CRP, we used generalized estimation equations (GEE) with logit link functions to construct a prediction model for 1-year mortality. These models were used because the tests of prediction model performance were more easily applied to logistic than Cox regression, and because the censoring mechanism did not seem to be informative (confirmed by the similarity between the GEE and Cox model estimates). GEE was selected to deal with within-facility correlation of the outcome. In these regression analyses, CRP values were transformed by taking the natural logarithm of measured CRP + 0.1 mg/L.

We evaluated demographics, comorbidities, laboratory values, and other patient characteristics for inclusion in the prediction model. To achieve a parsimonious model for the purpose of mortality prediction without overfitting (15), we restricted to predictors that are routinely and relatively easily assessed and that had significant statistical associations with mortality. After examining their functional forms, white blood cell (WBC) count was modeled as a step-function (WBC $>8 \times 10^3$ *versus* $\leq 8 \times 10^3$ cells/dl), while albumin, ln (CRP + 0.1), and ferritin were modeled as continuous variables.

We assessed the markers' discrimination capacity using the c-statistic or the area under the receiver operating characteristic (ROC) curve. The c-statistic measures the model's ability to discriminate people who will have died by 1 year from those who will not. Higher values denote better discrimination. In addition, we assessed global model fit using the generalized R^2 statistic and the quasi-likelihood information criterion (QICu) (16). We first assessed the effects of adding single markers (not sequentially) to a limited risk prediction model without other inflammatory markers. Next, we tested the effect of removing single markers from the full model with all four markers.

Since the c-statistic may not be sensitive to differences in risk prediction (17), risk reclassification plotting was used to quantify the number of patients whose outcome prediction was improved by addition of each inflammatory marker to the prediction model. As a summary statistic, we used net reclassification improvement (NRI) (18). The NRI is the difference in proportion of patients whose predicted risk is reclassified up or down among patients who died within 1 year compared with patients who survived 1 year. It is calculated by counting how many patients are more accurately reclassified in terms of risk for 1-year mortality with the addition of each biomarker. Because treatment recommendations based on predicted risk are unavailable for this population, we chose to study 2%, 5%, and 10% as a minimum significant change in risk.

For missing data, we used the Sequential Regression Multiple Imputation Method implemented by IVEware (19). All analyses used SAS 9.2.

Results

CRP Measurement and Distribution of CRP Levels

Routine measurement of CRP (quarterly or more often in ≥75% of patients) ranged from 0% of facilities in Canada and the United States to 90% of facilities in Sweden (Figure 1). In facilities that measured CRP routinely, median CRP levels were notably lower in Japan (1.0 mg/L; interquartile range [IQR], 0.5 to 3.1) than in Europe and Australia-New Zealand (ANZ; 6.0 mg/L; IQR 3.0 to 14.0; Figure 2). In general, CRP was positively associated with male gender, age, body mass index (BMI), catheter use, and all comorbid conditions except diagnosis of hypertension (Table 1; see footnote regarding missing data). CRP was positively associated with ferritin and WBC count, and inversely associated with albumin.

Association of CRP with Mortality

CRP was positively and monotonically associated with mortality (Figure 3), even when adjusting for comorbidities and laboratory values. The interaction between being from Japan and CRP was nonsignificant ($P = 0.62$). Furthermore, plotting Japan and Europe/ANZ separately with the same CRP categories resulted in similar curves (not shown). When considering cause-specific death (Figure 4), the positive association with CRP was strongest for infection-related death, and evident for cardiovascular death at levels >10 mg/L.

Model for Prediction of 1-Year Mortality

After evaluating 30 patient variables for the logistic model of 1-year mortality, including 13 comorbidities, four covariates besides the prerequisite four inflammatory markers were selected, as listed in Table 2. After adjustment for other inflammatory markers, the 95% confidence interval (CI) of the OR for ferritin crossed 1.0. The association of WBC count with mortality was substantially at-

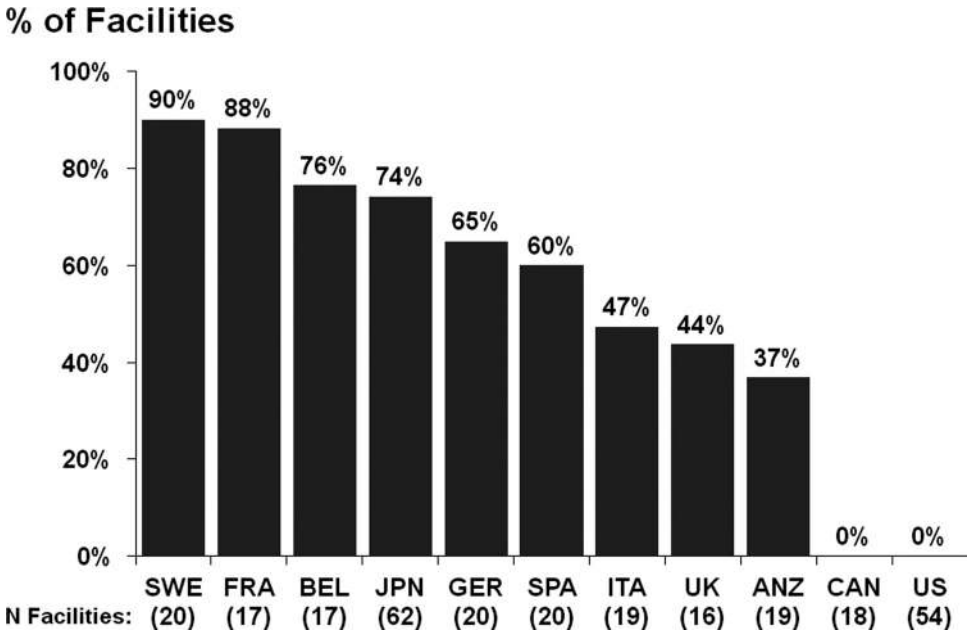

Figure 1. | Percent of facilities by country that routinely measured C-reactive protein (CRP) (2005 to 2006), routinely defined as at least quarterly on ≥75% of patients. Other than Canada and US, 67% of facilities measured CRP routinely. SWE, Sweden; FRA, France; BEL, Belgium; JPN, Japan; GER, Germany; SPA, Spain; ITA, Italy; UK, United Kingdom; ANZ, Australia-New Zealand; CAN, Canada; US, United States.

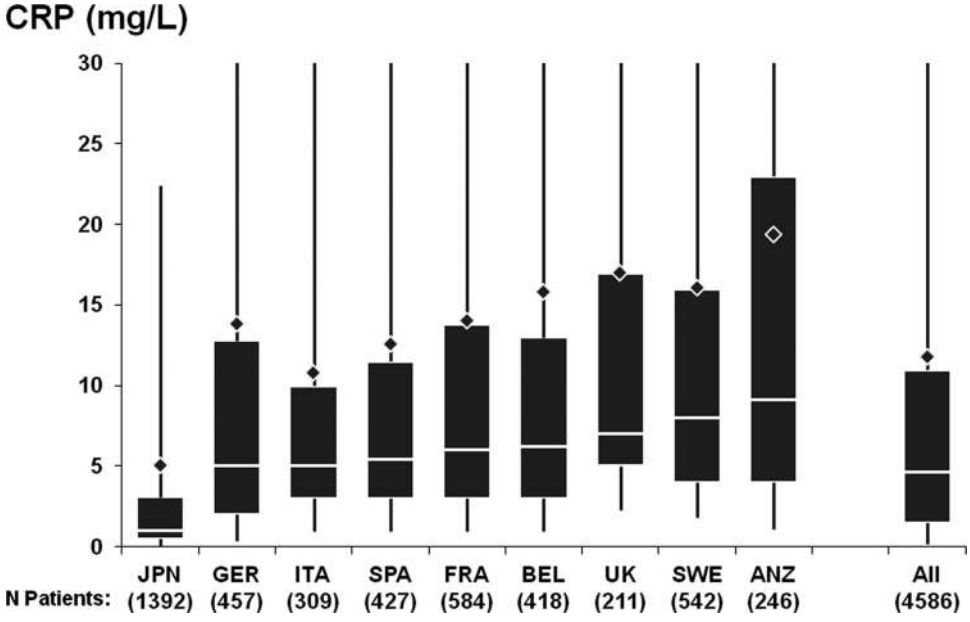

Figure 2. | Distribution of C-reactive protein (CRP) by country, restricted to patients on dialysis >90 days in facilities that routinely measure CRP (n = 4586). The top and bottom of the boxes indicate the 25th and 75th percentiles of the distribution. The horizontal line within the box indicates the median (50th percentile), and the diamond indicates the mean. Vertical lines extend to the 5th and 95th percentiles. The line extending to the 95th percentile was truncated at 30 mg/L. Outside of Japan, the 95th percentile ranged from 37 mg/L in Italy to 75 mg/L in Australia-New Zealand. JPN, Japan; GER, Germany; ITA, Italy; SPA, Spain; FRA, France; BEL, Belgium; UK, United Kingdom; SWE, Sweden; ANZ, Australia-New Zealand.

tenuated but still significant after adjustment, whereas albumin and CRP remained strongly and independently associated with mortality. An interaction with CRP and albumin was nonsignificant (NS) in the models for Table 2 (P = 0.99).

Prediction Model: Overall Model Fit and Discrimination

Effects on measures of model fit that resulted from inclusion or removal of each inflammatory marker in predictive models were assessed. Adding CRP to a limited model, which did not include other markers of inflammation, im-

Table 1. Median CRP (mg/L) and interquartile range by region (Europe/ANZ *versus* Japan) and patient characteristics

Patient Characteristics[a,b]	Europe/ANZ (n = 3194)		Japan (n = 1392)	
	Percent	CRP Median (IQR)	Percent	CRP Median (IQR)
Overall	100%	6.0 (3.0 to 14.0)	100%	1.0 (0.5 to 3.1)
Sex				
female	40.3%	5.6 (3.0 to 12.1)	40.2%	1.0 (0.4 to 3.0)
male	59.7%	7.0 (3.1 to 15.0)	59.8%	1.3 (0.7 to 4.0)
Age (years)				
18 to 54	23.9%	5.0 (3.0 to 11.0)	21.0%	1.0 (0.5 to 2.5)
54 to 64	19.7%	6.0 (3.0 to 13.0)	31.7%	1.1 (0.5 to 3.0)
65 to 74	27.8%	6.6 (3.1 to 14.8)	27.2%	1.1 (0.5 to 3.1)
≥ 75	28.7%	7.0 (4.0 to 16.0)	20.0%	1.4 (0.6 to 4.1)
Time on ESRD				
<1 year	29.5%	5.4 (3.0 to 12.0)	19.0%	1.0 (0.5 to 3.0)
≥1 year	70.5%	6.7 (3.1 to 14.0)	81.0%	1.1 (0.5 to 3.3)
BMI (kg/m^2)				
<20	13.1%	6.0 (3.0 to 15.2)	40.0%	1.0 (0.4 to 3.4)
20 to 29.9	71.0%	6.0 (3.0 to 13.0)	58.8%	1.1 (0.6 to 3.0)
≥ 30	15.9%	7.4 (4.0 to 15.0)	1.2%	4.1 (1.6 to 7.0)
Baseline vascular access				
fistula	70.9%	5.9 (3.0 to 13.0)	91.1%	1.0 (0.5 to 3.0)
graft	7.8%	7.0 (3.0 to 12.0)	6.9%	1.7 (0.7 to 4.0)
catheter	21.2%	8.0 (4.0 to 18.2)	2.0%	1.6 (0.7 to 3.4)
Coronary heart disease				
no	49.1%	5.3 (3.0 to 12.0)	56.8%	1.0 (0.5 to 3.0)
yes	50.9%	7.0 (3.5 to 16.1)	43.2%	1.5 (0.6 to 4.0)
Cancer (other than skin)				
no	84.5%	6.0 (3.0 to 13.4)	88.9%	1.0 (0.5 to 3.0)
yes	15.5%	7.0 (3.1 to 15.7)	11.1%	2.0 (0.6 to 6.5)
Other cardiovascular disease				
no	56.8%	5.5 (3.0 to 12.5)	67.3%	1.0 (0.5 to 3.0)
yes	43.2%	7.0 (3.5 to 16.3)	32.7%	1.5 (0.6 to 4.0)
Cerebrovascular disease				
no	80.9%	6.0 (3.0 to 13.0)	85.4%	1.0 (0.5 to 3.0)
yes	19.1%	8.0 (3.3 to 17.0)	14.6%	1.7 (0.6 to 4.0)
Congestive heart failure				
no	55.7%	5.8 (3.0 to 12.0)	72.8%	1.0 (0.5 to 3.0)
yes	44.3%	7.0 (3.3 to 17.0)	27.2%	1.8 (0.7 to 4.1)
Diabetes				
no	65.0%	6.0 (3.0 to 13.0)	62.4%	1.0 (0.5 to 3.0)
yes	35.0%	7.0 (3.1 to 15.0)	37.6%	1.2 (0.6 to 3.6)
Hypertension				
no	17.9%	6.4 (4.0 to 14.0)	23.2%	1.0 (0.5 to 3.6)
yes	82.1%	6.0 (3.0 to 14.0)	76.8%	1.0 (0.5 to 3.0)
Neurologic disease				
no	88.2%	6.0 (3.0 to 13.0)	89.9%	1.0 (0.5 to 3.0)
yes	11.8%	7.3 (3.0 to 18.2)	10.1%	2.2 (0.8 to 6.1)
Psychiatric disorder				
no	87.8%	6.0 (3.0 to 13.0)	96.0%	1.0 (0.5 to 3.1)
yes	12.2%	7.0 (3.0 to 18.0)	4.0%	1.6 (0.5 to 5.4)
Peripheral vascular disease				
no	66.5%	5.6 (3.0 to 12.0)	79.9%	1.0 (0.5 to 3.0)
yes	33.5%	8.0 (4.0 to 18.0)	20.1%	2.0 (1.0 to 5.4)
Albumin (g/dl)				
<3.5	26.4%	10.0 (5.0 to 28.0)	16.7%	2.3 (1.0 to 10.0)
3.5 to 3.9	41.5%	6.5 (3.0 to 13.0)	45.9%	1.2 (0.6 to 3.2)
≥4.0	32.2%	5.0 (2.4 to 10.0)	37.4%	1.0 (0.3 to 2.0)
Ferritin (ng/ml)				
<500	64.3%	5.1 (3.0 to 11.5)	92.8%	1.0 (0.5 to 3.0)
500 to 799	21.3%	7.0 (3.3 to 17.6)	4.4%	2.0 (1.0 to 5.3)
≥ 800	14.4%	10.0 (4.2 to 26.0)	2.9%	2.3 (1.0 to 8.9)

Table 1. (Continued)

Patient Characteristics[a,b]	Europe/ANZ (n = 3194)		Japan (n = 1392)	
	Percent	CRP Median (IQR)	Percent	CRP Median (IQR)
WBC count ($\times 10^3$ cells/dl)				
<8.0	69.3%	5.0 (3.0 to 11.2)	85.8%	1.0 (0.5 to 3.0)
8.0 to 10.9	24.3%	8.0 (4.0 to 18.6)	12.6%	3.0 (1.0 to 10.5)
≥11.0	6.4%	15.6 (6.0 to 40.0)	1.6%	5.0 (2.1 to 15.2)

ANZ, Australia-New Zealand; CRP, C-reactive protein; IQR, interquartile range; WBC, white blood cell; BMI, body mass index.
[a]Among patients with non-missing CRP values. Missing values <10% except for the following: BMI in Europe/ANZ (10.6%), albumin in Europe/ANZ (11.3%), and ferritin in Japan (24.5%).
[b]Nonparametric tests on the median scores tested the associations between patient characteristics and CRP within each region. $P < 0.01$ for all except in Europe/ANZ, cancer (0.08), hypertension (0.26), neurologic disease (0.13), psychiatric disorder (0.39); in Japan, time on ESRD (0.08), baseline vascular access (0.19), diabetes (0.02), hypertension (0.40), psychiatric disorder (0.41), and ferritin (0.04).

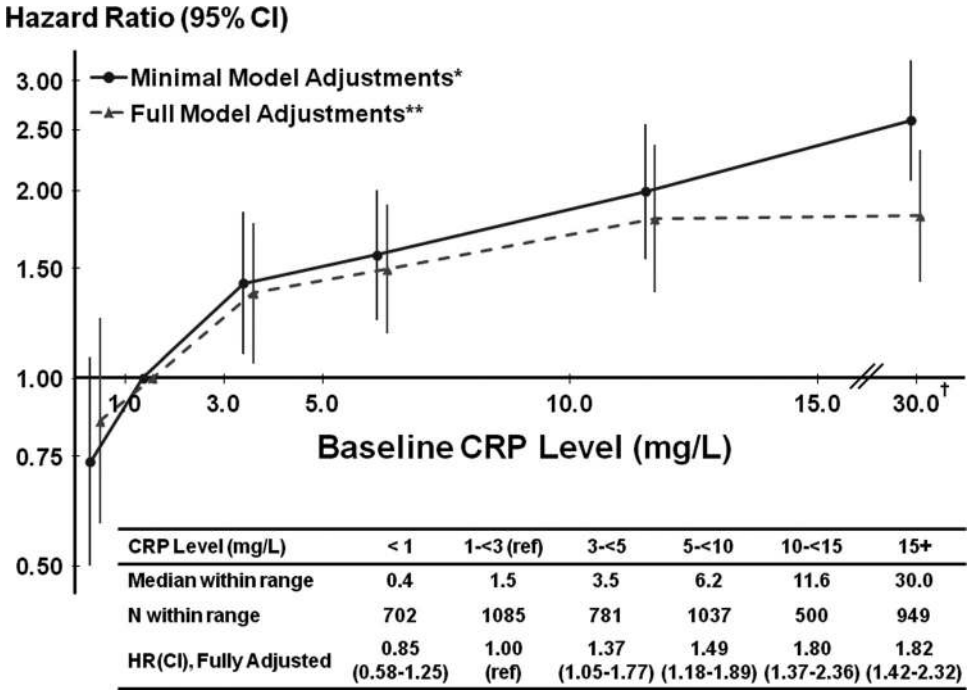

Figure 3. | Hazard ratio (HR) for mortality by baseline C-reactive protein (CRP) among 5054 patients (1105 deaths) from 10 countries with vintage (total time on dialysis) >90 days. *Adjusted for age, gender, ln (vintage), stratified by country, and accounting for facility clustering. **Additionally adjusted for body mass index, smoking, residual kidney function, 13 summary comorbid conditions, baseline laboratory values (albumin, calcium, creatinine, ferritin, hemoglobin, phosphate, BUN, total cholesterol, uric acid, and WBC), and catheter use. HRs are plotted at the median of each category. †30.0 = Median of the 15+ mg/dl category. CI, confidence interval; BUN, blood urea nitrogen; WBC, white blood cell.

proved the c-statistic from 0.681 to 0.731, approximately the same magnitude as adding albumin (0.715), whereas ferritin and WBC had much smaller effects (0.693 and 0.697, respectively). The full model (c-statistic = 0.747) consisted of the limited model plus all four of the inflammatory markers, and we omitted one marker at a time (nonsequentially). Removal of either WBC or ferritin made little difference (c-statistic = 0.745 for both), whereas omission of either CRP or albumin yielded similar reductions in the c-statistic (0.731 and 0.735, respectively). Similar relative effects of adding and removing each marker were observed on measures of overall model fit, the generalized R^2 and QICu. Overall, these findings suggest both albumin and CRP were important in improving model fit and discrimination. Sensitivity analyses using models with up to 30 variables (including residual renal function and dialysis vintage), or models parsimoniously selected by backward and score-based methods, yielded similar predictive capacity for CRP and other inflammatory markers.

Prediction Model: Risk Reclassification

Risk reclassification is represented graphically in Figure 5. CRP and albumin reclassified the outcome cor-

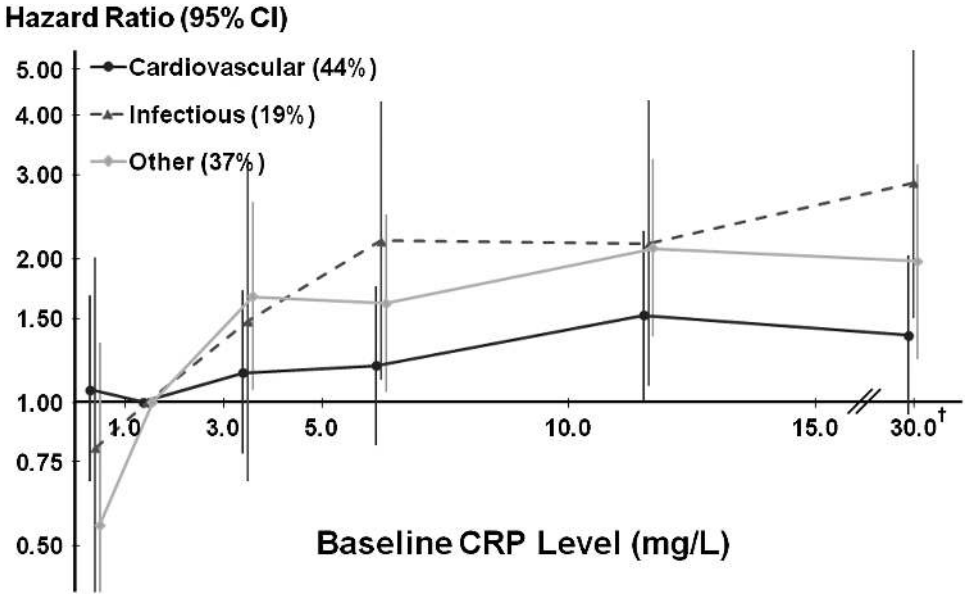

Figure 4. | Hazard ratio for cause-specific mortality by baseline C-reactive protein (CRP) among 5054 patients (939 deaths) with vintage >90 days and recorded cause of death. Deaths with missing cause of death ($n = 166$) were treated as censoring events. Stratified by country and accounting for facility clustering. Adjusted for age, gender, ln (vintage), body mass index, smoking, residual kidney function, 13 summary comorbid conditions, baseline laboratory values (albumin, calcium, creatinine, ferritin, hemoglobin, phosphate, BUN, total cholesterol, uric acid, and WBC), and catheter use. HRs for each cause of death calculated in separate models with alternative causes of death as censoring events. HRs are plotted at the median of each category. †Median of the 15+ mg/dl category. BUN, blood urea nitrogen; WBC, white blood cell.

Table 2. Final "full" prediction model: Included predictors are listed in the left column

Variable[a]	Odds Ratio of 1-Year Mortality (95% CI)	*P* Value
Age (per 10 Years)	1.47 (1.33 to 1.62)	<0.01
Male *versus* female	1.64 (1.33 to 2.01)	<0.01
Diabetes vs. no	1.17 (0.98 to 1.41)	0.09
Catheter vs. all other	1.53 (1.18 to 1.99)	0.01
Albumin (per 1 g/dl)	0.49 (0.39 to 0.62)	<0.01
Ln (CRP + 0.1) [mg/L]	1.32 (1.20 to 1.45)	<0.01
Ferritin (per 250 ng/ml)	1.04 (0.99 to 1.11)	0.14
WBC $>8\times10^3$ cells/dl vs. less	1.29 (1.02 to 1.64)	0.04

CRP, C-reactive protein; WBC, white blood cell count; CI, confidence interval.
[a]Variables excluded during the selection process included residual kidney function, body mass index, Japanese origin, creatinine, smoking status, phosphorus, hemoglobin, calcium, predialysis blood urea nitrogen, total cholesterol, and uric acid.

rectly in many more patients than ferritin and WBC. The NRI can summarize this graphical information at different thresholds (Table 3). Using a threshold of ≥5%, NRI was 12.8% for CRP, 10.3% for albumin, 0.8% for ferritin, and <0.1% for WBC. Alternative thresholds produced comparable results (Table 3).

Discussion

The Practice of CRP Measurement

Uncertainty surrounding the usefulness of routine CRP measurement is highlighted by the wide variation in practice across DOPPS countries (9). Whether the practice of measuring CRP improves outcomes has not been rigorously evaluated, but this has not impeded its rapid spread across many industrialized countries outside of North America (Figure 1). While CRP had historically been measured on the basis of clinical triggers, the shift to routine measurement suggests a significant change in practice.

Regional Differences in CRP Levels

Our finding of a large difference in median CRP between the Japanese (1.0 mg/L) HD patients and those of other DOPPS countries (6.0 mg/L) agrees with findings in general populations. A three- to tenfold difference in CRP levels between patients of European *versus* Japanese or Chinese ancestry was demonstrated previously (20–23). Although differences in liver production are thought to account for underlying variation in serum CRP levels, the specific biologic basis underlying differences by race and ethnicity is unclear (20).

Association of CRP Levels with Mortality

The present study adds to earlier studies in dialysis patients that demonstrated a positive association between CRP and mortality (2–4). Our data, illustrated in Figure 3, do not identify a specific inflection point below which the hazard ratio levels off. Although prior studies have reported increased mortality above various CRP thresholds (2.6 (3), 7.4 (4), and 8.15 mg/L (5) in studies of 91, 280, and 224 patients, respectively), all were limited by having few patients with normal or near-normal CRP levels. For example, the study evaluating a CRP cut point of 2.6 mg/L had only 23 patients in the <2.6-mg/L quartile. In contrast,

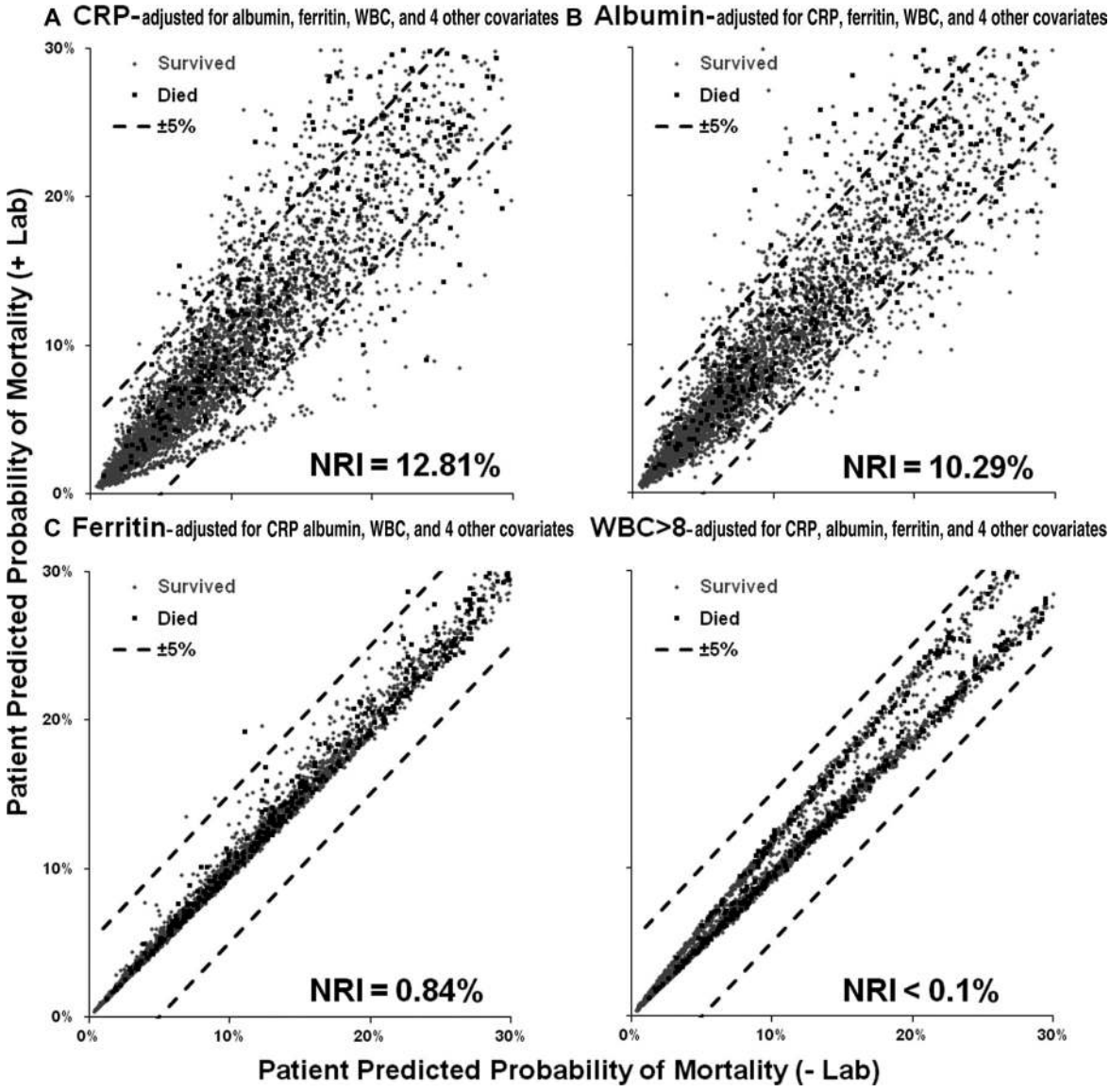

Figure 5. | Predicted 1-year risk of mortality from models with and without (A) C-reactive protein (CRP), (B) albumin, (C) ferritin, and (D) White blood cells (WBC) count. Models are adjusted for indicated variables, the other three inflammatory markers, and age, gender, diabetes, and catheter use. Dotted lines indicate ± 5% from the line of unity (The line of unity indicating no additional predictive risk value associated with addition of the variable to the model). The Net Reclassification Improvement (NRI) summarizes the number of patients who were correctly moved across the 5% threshold after the addition of each inflammatory marker (up for patients who died; down for patients who survived), minus those who were reclassified incorrectly (down for patients who died; up for patients who survived). Graphs are truncated at 30% predicted risk.

our study has 1787 patients with CRP <3 mg/L. Thus, the call by the KDOQI guidelines for research to identify "the optimal cut-off point at which CRP predicts outcome" in chronic kidney disease patients (12) can be answered for the first time in this study, by demonstrating that the lower the CRP in HD patients the better. This finding is consistent with the positive and monotonic association of CRP levels and cardiovascular risk in the general population (24). However, because HD patients have much higher CRP levels, on average, than the general population, this finding identifies a substantial majority of HD patients as having increased mortality relative to those with very low CRP levels. While one may speculate that there could be different mortality risk by CRP level in Japan *versus* elsewhere, our data suggest simply a monotonic relationship of CRP with mortality across all studied countries. Our finding of a positive association of CRP >10 mg/L with cardiovascular death (Figure 4) agrees with previous reports of a strong relationship between CRP levels and cardiovascular mortality, at levels above 5 mg/L (3,4). For infectious deaths, we found the association of CRP to be strong across all CRP ranges.

CRP and Risk Prediction

Improvement in prediction resulting from addition of novel biomarkers such as CRP to a prediction model has

Table 3. Net reclassification improvement of 1-year mortality risk for inflammatory markers at different thresholds of risk reclassification

	NRI by Risk Reclassification Threshold		
	2%	5%	10%
Albumin	14.8%	10.3%	6.3%
Ln (CRP)	20.1%	12.8%	2.4%
Ferritin	1.6%	0.8%	<0.1%
WBC $>8\times10^3$ cells/dl	8.5%	<0.1%	<0.1%

NRI, net reclassification improvement; CRP, C-reactive protein; WBC, white blood cell count.

been studied in the general population using the Framingham Risk Index (25–27). The ROC curve is used to evaluate diagnostic test performance against a gold standard, but it is often insensitive when evaluating the effect of a variable on risk prediction (17). Given this limitation, we also applied risk reclassification to quantify the extent to which risk classification is improved with the addition of the marker of interest (17,18,25,27).

Since albumin is an established strong predictor of mortality in HD patients (28,29), we used the effect of albumin in all analyses as the standard of comparison for CRP and other markers. By each approach used to compare risk prediction, we found that albumin and CRP improve prediction of 1-year mortality to a similar degree. In contrast, WBC count and ferritin had minimal effect while controlling for the other three markers (Figure 5). These findings were robust to a variety of assumptions.

Clinical Implications

Having demonstrated that CRP levels are useful to inform prognosis for HD patients, the clinical implications merit discussion. Although most evidence does not support a causal relationship between CRP and mortality (30), CRP has gained acceptance as a marker to characterize risk (*e.g.*, for secondary cardiovascular prevention) (24). A marker that improves risk reclassification can be especially useful in clinical contexts where treatment recommendations vary according to predicted risk. For example, in the general population, the LDL target for cholesterol-lowering therapy varies according to Framingham risk category. Although treatment recommendations in current dialysis practice are not based on predicted risk, risk reclassification is probably useful nonetheless because it informs prognosis, and this may influence patient counseling and treatment choices (*e.g.*, intensity of treatment, additional diagnostic testing) in some cases. Furthermore, risk reclassification may gain utility for recommendations based on evidence-based treatment algorithms in the future.

Although our study addressed prognosis, it did not address treatment in response to CRP levels. Increasingly routine measurement supports the impression that many physicians incorporate CRP levels into clinical decisions. An otherwise unexplained acute elevation in CRP typically prompts a search for infection and antibiotic treatment, if found. Alternatively, elevated CRP levels may provide the impetus to detect and address diverse inflammatory stimuli including tunneled catheters (31,32), failed allografts (33), water impurities (34), more subtle infections, including periodontitis (35), and those involving a diabetic foot or obsolete vascular accesses (36). Recent unpublished data from the DOPPS show that many clinicians report ordering chest radiographs, blood cultures, or electrocardiograms "usually or always" in response to elevated CRP in asymptomatic patients. In the absence of an identifiable cause for CRP elevation, uncertainty exists about options to treat inflammation directly in HD patients (as in the general population) (24,37–45). For example, statins lower CRP in dialysis and nondialysis populations but have not been shown to improve survival in dialysis patients (37–42). Identification of effective responses to elevated CRP levels (both diagnostic evaluations to identify an inflammatory source and treatments that improve outcomes) warrants further study. Of note, CRP assays have now become inexpensive in many health systems (46).

Additional Considerations

Assay methods were not recorded in the DOPPS. Although it is unclear whether high-sensitivity CRP (hsCRP) or conventional CRP assays were used by the local laboratories contributing data, several studies have found good concordance between hsCRP and conventional CRP assays (47,48). In addition, because our findings suggest that CRP predicts risk at very low levels, the data in this range are carrying useful information despite the lower sensitivity of conventional CRP assays at <3 mg/L. If anything, the association with hsCRP would be stronger because we would have more precise CRP values between 0.1 and 3.0 mg/L.

The international breadth of our sample raises the likelihood that our findings are generalizable to other settings. Levels of CRP in the United States appear to be comparable to those in Europe/ANZ, based on a cohort of incident US dialysis patients with a median of 3.8 mg/L (IQR 1.6 to 9.5) (49). However, because the United states and Canada have different racial and ethnic composition than the countries studied, the applicability of these findings to North America merits further study.

Conclusions

We studied CRP in a large international HD patient sample in facilities with routine CRP measurement and made several new observations. First, CRP levels were notably lower in Japan than other regions. Second, we have demonstrated, more clearly than prior studies, that the lower the CRP level, the lower the mortality risk. No threshold level below which the risk levels off was apparent. Third, when measured in conjunction with other inflammatory markers (albumin, WBC, ferritin), CRP improves prediction of 1-year mortality—and to an extent comparable to albumin. While many dialysis providers worldwide already measure CRP, its role in guiding individual patient decision making and treatment needs further study.

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Disclosures

None.

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