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The prevalence of hematologic and metabolic abnormalities during chronic kidney disease stages in different ethnic groups

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We conducted an observational cross-sectional study to determine if the prevalence of hematologic and metabolic abnormalities in chronic kidney disease (CKD) varied in different ethnic groups. We used a CKD provincial database where a complete data set at the time of registration was available as well as an estimated glomerular filtration rate (eGFR), which showed using the abbreviated MDRD formula that the patients had CKD of stages 3–5. We included patients with self-reported race of Caucasian, Oriental Asian, or South Asian. Primary outcomes were the prevalence of at least one of the following: anemia, hypocalcemia, hyperphosphatemia, hyperparathyroidism, hypoalbuminemia, and three or more laboratory abnormalities. All definitions were consistent with K/DOQI guidelines. When compared with Caucasians, Oriental Asians and South Asians had a higher prevalence of many of the metabolic abnormalities during most stages of CKD and were more likely to have any abnormality at all levels of eGFR. The prevalence of three or more laboratory abnormalities was higher in Oriental Asians at all stages and in South Asians at some levels of eGFR. These results were unchanged or exaggerated when controlled for age, gender, diabetes, and a primary diagnosis of renal disease. Hence, it appears that South Asians and Oriental Asians have more laboratory abnormalities compared with Caucasians at most levels of eGFR.

Kidney International (2008) **74,** 108–114; doi:10.1038/ki.2008.151; published online 23 April 2008

KEYWORDS: chronic kidney disease; ethnic differences; hyperparathyroidism; anemia; staging; cohort study

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Received 24 July 2007; revised 14 January 2008; accepted 6 February 2008; published online 23 April 2008

Chronic kidney disease (CKD) is associated with increased morbidity and mortality.[1] The majority of deaths, both in patients on renal replacement therapy and in pre-dialysis patients, are due to cardiovascular events.[2] The presence of CKD has been shown to be a strong predictor of future cardiovascular events, independent of traditional risk factors.[2–4] It is not clear what accounts for this increased risk. There are many metabolic abnormalities that develop with progressive renal parenchymal damage, including calcium, phosphate, parathyroid hormone, albumin, and hemoglobin disturbances. It is not known which, if any, of these abnormalities accounts for the increased cardiovascular disease risk, or whether treating these abnormalities can alter morbidity and mortality rates.

The metabolic abnormalities related to CKD (including anemia, hypocalcemia, hyperphosphatemia, and hyperparathyroidism) are associated with increased risk to the patient.[4–10] These risks are for the development of other conditions (cardiovascular disease, susceptibility to infection, bone disease), as well as progression of kidney disease to end stage. However, at any given level of eGFR, there is much heterogeneity in the severity of metabolic abnormalities. For example, in CKD stage 5, 25% of patients have a hemoglobin level above $110\,g\,l^{-1}$ (the recommended lower limit of the target hemoglobin level).[6,11] In end-stage renal disease patients, 15% have normal bone biopsies with no evidence of osteitis fibrosa cystica, aplastic bone disease, or osteomalacia.[12] These observations suggest a disconnect between the filtration function of the kidney (as measured by GFR) and the hormonal function of the kidney (as measured by various metabolic abnormalities).

One possible explanation for such heterogeneity might be ethnicity, which has been shown to affect various outcomes in renal disease. Among peritoneal dialysis patients, Blacks have significantly lower hemoglobin levels compared to nonblacks despite receiving more treatment for anemia.[13] At each of CKD stages 3–5, anemic patients (defined as hemoglobin $<110\,g\,l^{-1}$) are more likely to be Caucasian than they are Asian, with the majority of anemic patients

being Caucasian.[6] Furthermore, the long-term outcome of patients on dialysis has been shown to be impacted by ethnicity, with Asians having the best outcomes when compared with age- and gender-matched controls on dialysis.[14,15]

As metabolic abnormalities are associated with poor outcomes, and ethnicity is known to predict survival, we hypothesize that the number of metabolic abnormalities at each stage of CKD may vary by ethnicity. We sought to investigate this further by describing the metabolic abnormalities in Asians and Caucasians at each stage of CKD, a relationship that has yet to be reported in the literature.

RESULTS

Derivation of the cohort and characteristics

The entire database contains 15 346 registered patients. The primary criteria for establishment of the cohort were the availability of self-reported race (SRR), complete laboratory data, and eGFR <60 ml per min per 1.73 m^2 within the prespecified date range, which were available for 5536 patients. Figure 1 describes the final derivation of the analytical cohort, which excluded patients with SRR other than Asian Orientals, South Asians, and Caucasians (e.g. Filipino and First Nations); thus a total of 5322 patients were available for analysis. Of note, analyses that included patients without an available SRR were not significantly different than those that excluded them; thus concerns about biased sample are relatively minor. This is addressed further in the discussion. The final cohort thus included 4047 Caucasians, 763 Oriental Asians, and 512 South Asians. The baseline characteristics of the different SRR groups are shown in Table 1. There are statistical differences between SRR for baseline eGFR, age, sex, diabetes, and primary diagnosis of kidney disease. The absolute differences in eGFR were small, so we examined the ethnic mix at each level of eGFR. Figure 2 shows that the relative proportion of each SRR across levels of eGFR is similar.

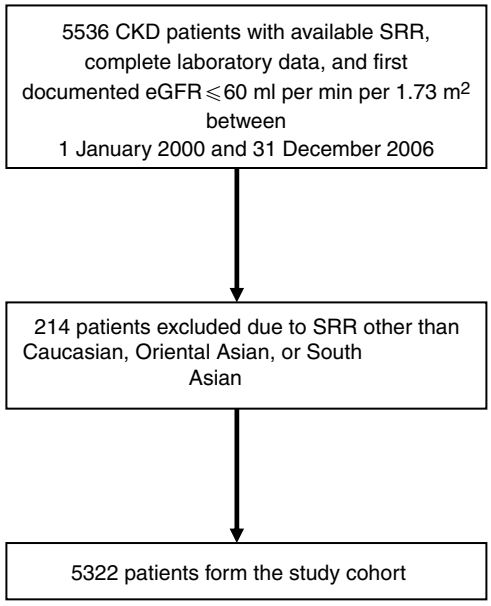

Figure 1 | Analytical cohort derivation from the Provincial Registry of all CKD patients. SRR, self-reported race.

Laboratory abnormalities

The data describing the median values for calcium, phosphate, parathyroid hormone, hemoglobin, and albumin are shown in Table 2; Figure 3 displays similar data graphically, using the prevalence of abnormalities as defined by K/DQOI cut-offs, in percentages. The interaction terms for SRR and eGFR were significant for PO_4 and Alb (both P-values <0.03) but not for Hb, Ca, and intact parathyroid hormone (iPTH); that is, the effect that race has on Hb, Ca, and iPTH holds true at all levels of eGFR. The percentage of patients who are anemic was significantly different across SRR ($P<0.01$); Oriental Asians were 1.4 times more likely to be anemic than Caucasians (95% confidence interval (CI) for odds ratio (OR): 1.2–1.7), with no difference between South Asians and Caucasians (OR: 1.0, 95% CI for OR: 0.8–1.3). The results for hypocalcemia follow the same pattern as those for anemia; the odds for hypocalcemia in Oriental Asians were almost two times the odds in Caucasians (95% CI for OR: 1.4–2.6). Hyperparathyroidism was also statistically different between SRR ($P<0.01$), with both South Asians (OR: 1.5, 95% CI for OR: 1.3–1.8) and Oriental Asians (OR: 2.2, 95% CI for OR: 1.8–2.7) more likely to be hyperparathyroid than Caucasians.

The interaction terms for SRR and eGFR were significant for hyperphosphatemia and hypoalbuminemia, suggesting that the effect of SRR on these metabolic abnormalities may vary at some levels of eGFR. The percentage of patients with hyperphosphatemia was found to be different by SRR only at eGFR levels of 15–30 and 30–45 ml per min per 1.73 m^2 (both P-values for SRR <0.01). For an eGFR of 15–30 ml per min per 1.73 m^2, South Asians were more likely to be hyperphosphatemia than Caucasians (OR: 1.8, 95% CI for OR: 1.2–2.7), with no difference between Oriental Asians and Caucasians. For an eGFR of 30–45 ml per min per 1.73 m^2, Oriental Asians had higher odds of being hyperphosphatemia than Caucasians (OR: 2.5, 95% CI for OR: 1.4–4.5), with no difference between South Asians and Caucasians. The percentage of patients with hypoalbuminemia was significantly different by SRR only at eGFR levels of <15 and 15–30 ml per min per 1.73 m^2 (both P-values for SRR <0.01). For an eGFR of 15–30 ml per min per 1.73 m^2, both Oriental Asians and South Asians were 1.5 times more likely hypoalbuminemia than Caucasians (95% CI for OR: 1.2–2.0), whereas for an eGFR of <15 ml per min per 1.73 m^2, the odds were much lower in South Asians (OR: 0.4, 95% CI for OR: 0.3–0.7).

The association between the presence of 'any laboratory abnormality' and SRR did not vary by eGFR levels (P-value for the SRR/eGFR interaction $=0.24$). The proportions were found to be different by SRR ($P<0.01$); specifically, both Oriental Asians and South Asians were more likely to have

Table 1 | Baseline characteristics of Caucasians, South Asians, and Oriental Asians

	Overall	Ethnicity			*P*-value
		Caucasians	Oriental Asians	South Asians	
N	5322	4047	763	512	
eGFR (mean ± SD)	26.5 ± 12.7	27.3 ± 12.8	23.5 ± 11.7	24.7 ± 12.8	<0.01
eGFR level (%)					<0.01
45–60	10	11	6	9	
30–45	27	28	22	21	
15–30	43	42	46	46	
<15	20	19	26	24	
Age (mean ± SD)	67 ± 15.2	67 ± 14.9	68 ± 15.4	61 ± 16.7	<0.01
Male (%)	57	59	53	54	<0.01
Diabetes (%)	37	38	28	48	<0.01
Primary diagnosis					<0.01
HTN	19	21	8	13	
DM	24	25	14	30	
GN	8	8	8	9	
PCKD	3	4	1	2	
Other	30	30	35	23	
Unknown	16	11	34	23	

DM, diabetes; GN, glomerulonephritis; HTN, hypertension; PCKD, polycystic kidney disease.
eGFR in ml per min per 1.73 m^2, age in years.

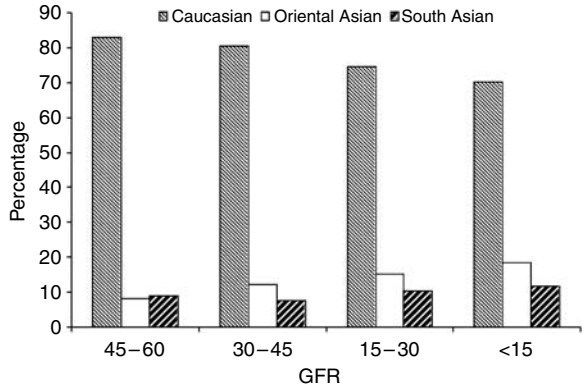

Figure 2 | Percentage of Oriental Asians, South Asians, and Caucasians at each level of eGFR (ml per min per 1.73 m^2).

'any laboratory abnormality' compared with Caucasians (OR for Oriental Asians: 1.5 (95% CI: 1.3–1.9); OR for South Asians: 1.9 (95% CI: 1.5–2.3)). For the presence of ⩾3 metabolic abnormalities, our data suggested that its relationship with SRR might differ at some levels of eGFR (*P*-value for the SRR/eGFR interaction <0.01). For eGFR levels of <15 and 45–60 ml per min per 1.73 m^2, only Oriental Asians were more likely to have ⩾3 abnormalities than Caucasians (OR at eGFR <15: 1.6 (95% CI: 1.1–2.4); OR at eGFR 45–60: 6.4 (95% CI: 2.5–16.2)). For an eGFR level of 15–30 and 30–45 ml per min per 1.73 m^2, both South Asians and Oriental Asians were more likely to have ⩾3 metabolic abnormalities than Caucasians. More specifically, at an eGFR level of 15–30 ml per min per 1.73 m^2, the OR for South Asians was 1.7 (95% CI for OR: 1.1–2.5), and the OR for Oriental Asians was 1.6 (95% CI for OR: 1.2–2.3). As for eGFR level of 30–45 ml per min per 1.73 m^2, the OR for South Asians and Oriental Asians were 2.5 (95% CI for OR: 1.2–5.3) and 3.4 (95% CI for OR: 1.9–6.0), respectively (see Figure 4).

Multivariate analysis

We also performed multivariate analyses (controlling for age, sex, and the presence of diabetes) for each of the primary outcomes described above. All of the above results held true for these adjusted analyses. In addition, we controlled for the primary diagnosis of renal disease, which resulted in the same results except that at an eGFR of 15–30 ml per min per 1.73 m^2, both Oriental and South Asians were more hyperphosphatemic compared with Caucasians (as opposed to South Asians alone in the unadjusted analysis).

DISCUSSION

This large cohort analysis of patients referred to nephrologists demonstrates that at the time of referral to a nephrologist, at most levels of GFR, Oriental Asians and South Asians have more observed laboratory abnormalities than comparable Caucasians. The prevalence of these abnormalities among different SRR in CKD patients has not previously been described. Studies examining kidney disease in Asian populations have been smaller than the current analysis. To the extent that Asians have been shown to have better outcomes on dialysis, and that laboratory parameters selected here are associated with poor outcomes, one might have assumed that Asians would also have better laboratory parameters at each stage of CKD. Thus, the results of this analysis in a referred cohort are unexpected.

As in all cohort studies, there are weaknesses. The link between association and causation is difficult: Specifically, we describe here an association of SRR with a different prevalence of laboratory abnormalities by CKD stage, but we cannot ascribe SRR as the sole cause of these differences.

Table 2 | The levels of Hb (g l^{-1}), Ca (mmol l^{-1}), PO_4 (mmol l^{-1}), iPTH (pmol l^{-1}), and Alb (g l^{-1}) by eGFR level among Caucasians, Oriental Asians, and South Asians with CKD, reported as median values with interquartile range

	Ethnicity		
	Caucasians	Oriental Asians	South Asians
Hb			
Overall	120 (107–132)	116 (102–129)	117 (106–128)
eGFR: (45–60)	128 (114–140)	118 (109–138)	125 (115–140)
eGFR: (30–45)	124 (112–135)	120 (107–131)	120 (110–131)
eGFR: (15–30)	119 (106–129)	116 (103–129)	116 (103–124)
eGFR: <15	113 (101–125)	111 (97–125)	116 (103–128)
Ca			
Overall	2.34 (2.26–2.43)	2.31 (2.22–2.41)	2.35 (2.27–2.44)
eGFR: (45–60)	2.35 (2.27–2.41)	2.33 (2.25–2.43)	2.38 (2.31–2.44)
eGFR: (30–45)	2.35 (2.27–2.42)	2.31 (2.23–2.41)	2.36 (2.27–2.43)
eGFR: (15–30)	2.34 (2.25–2.42)	2.31 (2.22–2.40)	2.34 (2.25–2.43)
eGFR: <15	2.35 (2.25–2.49)	2.32 (2.19–2.44)	2.35 (2.23–2.46)
PO_4			
Overall	1.28 (1.10–1.50)	1.36 (1.15–1.60)	1.40 (1.17–1.67)
eGFR: (45–60)	1.15 (1.02–1.32)	1.20 (1.05–1.40)	1.20 (1.10–1.40)
eGFR: (30–45)	1.19 (1.04–1.36)	1.27 (1.10–1.50)	1.28 (1.11–1.46)
eGFR: (15–30)	1.30 (1.11–1.52)	1.36 (1.17–1.58)	1.41 (1.21–1.70)
eGFR: <15	1.50 (1.22–1.82)	1.50 (1.23–1.85)	1.51 (1.28–1.90)
iPTH			
Overall	11.6 (6.4–21.7)	15.9 (7.5–31.1)	19.5 (9.9–38.4)
eGFR: (45–60)	7.9 (4.5–11.6)	10.5 (5.7–28.0)	9.6 (4.9–20.0)
eGFR: (30–45)	9.1 (5.4–14.9)	9.9 (5.8–16.6)	13.0 (8.1–24.1)
eGFR: (15–30)	13.6 (7.3–24.4)	17.7 (8.0–31.2)	21.7 (11.7–38.3)
eGFR: <15	17.1 (8.1–36.2)	24.6 (12.5–45.9)	32.9 (14.5–62.0)
Alb			
Overall	38 (35–41)	37 (33–40)	39 (34–41)
eGFR: (45–60)	39 (36–42)	38 (35–41)	39 (37–43)
eGFR: (30–45)	39 (36–42)	38 (35–41)	40 (37–42)
eGFR: (15–30)	38 (35–41)	37 (33–40)	38 (33–41)
eGFR: <15	36 (32–39)	36 (31–39)	38 (34–42)

eGFR in ml per min per 1.73 m^2.

The issues of bias and confounders may interfere with the conclusions described here. With respect to bias, the two major issues include the potential bias of the modification of diet in renal disease (MDRD) equation and that of referral bias. There has been some suggestion in the literature that the MDRD formula is biased in its estimation of GFR in Asians, which is unlikely to explain our results and is discussed in more detail below. To investigate the possibility of a referral bias, in which Asians are referred to nephrologists at a different stage of their disease compared with Caucasians, we looked at the ethnic mix at each level of eGFR. The database did not include specific information about the time from identification of abnormal eGFR to nephrologist referral by the primary care physician. As the relative mix of ethnicities at each level of eGFR is similar (see Figure 2), a significant referral bias is unlikely. Furthermore, as the prevalence of abnormalities is higher at earlier stages of CKD, this would also argue against referral bias. The slightly lower eGFR (of approximately 2 ml per min per 1.73 m^2) among Asians is statistically significant, but within the ranges described not likely clinically significant. In addition, there are issues of SRR-related environmental factors (such as diet and lifestyle differences) and SRR-related true genetic variability: the impact of these different factors on the reported results cannot be determined. There is currently no formal data collection regarding diet habits for this cohort, due to the primarily administrative nature of the data. This of course is an area that requires further study.

The abbreviated MDRD formula has been shown in Chinese patients to underestimate true GFR at higher levels of eGFR and overestimate it at lower levels of eGFR, raising the possibility that this may introduce bias.[16] However, to compare Asians with Caucasians, we are only interested in the relative performance of the MDRD formula in these two groups, not the absolute performance relative to a gold

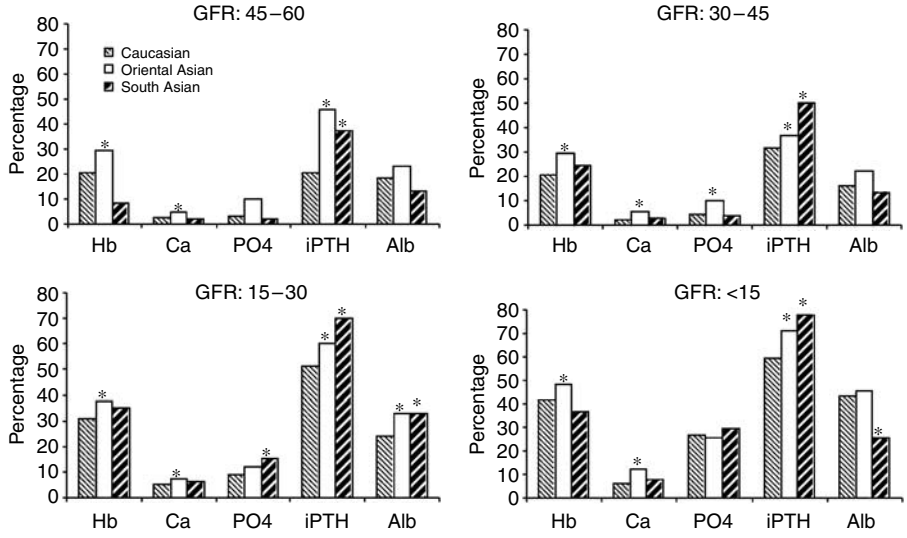

Figure 3 | The prevalence of metabolic abnormalities associated with CKD among Caucasians, South Asians, and Oriental Asians at each eGFR level (ml per min per 1.73 m^2). Stars denote a significant difference from Caucasians (*$P<0.05$). Hb, anemia; Ca, hypocalcemia; PO_4, hyperphosphatemia; iPTH, hyperparathyroidism; Alb, hypoalbuminemia.

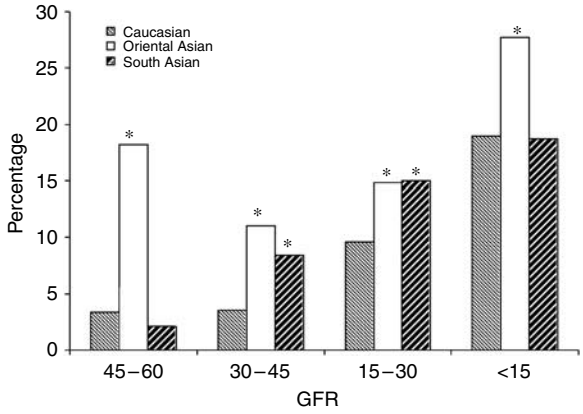

Figure 4 | The prevalence of ⩾3 metabolic abnormalities among Caucasians, South Asians, and Oriental Asians with CKD across all eGFR levels (ml per min per 1.73 m^2). Stars denote a significant difference from Caucasians (*$P<0.05$).

standard for GFR measurement. The abbreviated MDRD formula is known to be less accurate in Asians than it was in the population from which it was derived, comprised largely of Caucasians.[17,18] A modified version of the MDRD formula (which uses a correction factor of 1.227 for Chinese race) has been developed that performs similarly to the abbreviated MDRD formula in the Caucasian population.[17] We reanalyzed our results using this modified MDRD formula in our Oriental Asian patients and found that this shifted some of the Oriental Asian patients up a level of eGFR category (data not shown). This analysis only exaggerated our results, given that more patients were classified as having better kidney function (eGFR) despite worse levels of biochemistry and hematology. Therefore, any inaccuracy introduced by using the abbreviated MDRD formula in our Asian patients does not readily explain our results.

The differences in baseline characteristics seen in Table 1 raise the possibility of confounders. We controlled for known predictors of the outcomes of interest (that is, the abnormalities of laboratory values), including age, sex, presence of diabetes, and primary renal diagnosis among the three SRR groups in multivariate models. Our results were either unchanged or exaggerated, thus these potential confounders do not explain the finding of ethnic differences in the prevalence of abnormalities. Of course, the possibility of unknown confounders exists and cannot be addressed further in this observational study.

Several medications used in the treatment of CKD are titrated to our outcomes of interest, raising the possibility that differences in medication use across SRR may explain the observed differences in laboratory abnormalities. Our database does not include information about medication use at the time of referral to nephrologists, so direct comparisons cannot be made. However, in British Columbia, primary care physicians do not have access to erythropoietin and, in general, do not prescribe phosphate binders or vitamin D analogs. Therefore, it is highly unlikely that the data that we have reported here, status at the time of referral to nephrologists, are affected by the fact that the patients have had significant exposure to medications known to affect the outcomes of interest. Lastly, although there may be concern regarding the relatively small proportion of patients maintained in the analytic cohort, the major driver of the loss of patients for analysis is due to lack of reported SRR. However, this was a predefined parameter of key interest and so those without the parameter could not be included. This is typical of many administrative data-set analyses. Furthermore, we did undertake to ensure that the derived analytic cohort, with SRR, was not systematically different from the complete cohort (which includes those missing SRR) (data not shown). As there were no substantial differences in the distribution of variables by eGFR with the complete versus derived cohort, we were satisfied that the lack of SRR was a random problem related to variable attention to this detail and did not constitute a source of bias.

Implications

The implications of our results are several. The K/DOQI guidelines (on the diagnosis, identification, and evaluation of CKD) defined the stages of CKD using estimated GFR. The stages were derived from analyses of large population-based databases that described greater prevalence and severity of laboratory abnormalities.[19] Our analysis raises the possibility that the traditional GFR cut-offs for the stages of CKD may not be equally appropriate for all races if they are meant to reflect the prevalence of underlying laboratory abnormalities, as a measure of overall kidney function. However, given that a race-specific CKD stage classification would be cumbersome and impractical, we would offer an alternative hypothesis. The degree to which the eGFR stages represent underlying kidney dysfunction (loss of both hormonal and filtration function) may be race specific. Our results suggest that there may be a disconnect between the filtration function of the kidney (as measured by eGFR) and the hormonal and excretory function of the kidney (as measured by laboratory abnormalities), which appears to vary by race. Furthermore, it may be that the prognostic value of these abnormalities with CKD stage, and independent of CKD stage, is also race dependent; future studies will need to examine this more closely. Thus, therapeutic interventions and action plans may need to be altered according to these findings, if they are found to have implications with respect to outcomes. At the current time, the relative importance of eGFR versus laboratory abnormalities in prognostication is not clear.

Asians are noted to have better outcomes on dialysis. In this large cohort, Asians were noted to have less-associated comorbidity such as diabetes and hypertension (see Table 1),[14,15] and yet worse laboratory parameters at every stage of CKD. We were unable to address rates of progression in the current analysis due to data variability and complexity but this will be further explored in subsequent studies using appropriate data sets derived from this cohort. Future studies will need to address the relationship between laboratory

abnormalities and outcomes such as survival in the different ethnic groups and time to renal replacement therapy. Specifically, as has been described in blacks, it may be that Asians have a more rapid progression to end-stage renal disease; or because they have less diabetes and hypertension, they do not have the competing risk of death or cardiovascular disease before dialysis, so they come to dialysis with less comorbidity. Careful analysis with attention to confounders is required to understand the relationship between the current findings and outcomes.

In conclusion, we demonstrate that, at the time of referral to nephrologists in general, the prevalence of each laboratory abnormality associated with CKD is more common in Asians than Caucasians across all levels of eGFR; and that Asians are more likely to have any laboratory abnormality or more likely to have multiple laboratory abnormalities at all levels of eGFR when compared with Caucasians. These findings have not been described before. Given the paradox of better survival of Asians, despite worse laboratory parameters at all stages of CKD, many new questions have been raised by this analysis. Further investigation into race-specific factors, both genetic and environmental, which may potentially affect outcomes, is warranted.

MATERIALS AND METHODS

Study design

This is an observational cross-sectional study examining the prevalence of renal-specific laboratory abnormalities in a cohort of patients at the time of registration in a provincial database.

Description of environment and derivation of the cohort

In British Columbia, all patients with CKD are registered in a database at the time of referral to a nephrologist if they fulfill certain criteria. These include referral to a nephrologist and the presence of CKD (defined as estimated GFR <60 ml per min per 1.73 m^2 or diagnosis of kidney disease, assumed to be chronic based on biopsy, ultrasound results, or clinical history; histological diagnoses are not mandatory for the database). Estimated GFR was calculated using the abbreviated MDRD formula.[18] SRR is recorded and chosen from a list that includes Oriental Asian, Caucasian, South Asian, First Nation, Filipino, or other. At the initiation of the database (in the year 2000), this field was not mandatory, and thus some patients may or may not have had the field complete. For the purposes of the analysis, we derived a cohort of patients who were identifiable, using the SRR field, as Caucasian, South Asian, or Oriental Asian (as these constitute the major ethnicities in British Columbia), and who were enrolled between January 1, 2000, and December 31, 2006, and in whom a complete data set upon registration was available (defined as, in addition to SRR, serum creatinine, phosphate (PO_4), calcium (Ca), intact parathyroid hormone (iPTH), albumin (Alb), and hemoglobin (Hb) levels).

All laboratory results are automatically uploaded to the database and are thus available for each patient once registration occurs (including historical values). Medications for CKD nondialysis patients are paid for provincially (such as erythropoietic stimulating agents, iron therapies, vitamin D analogs, and calcium supplements) and are thus tracked after the patients are registered; no medications at the time of registration would be paid for and are therefore not captured in the database. Other baseline data collected include age, gender, presence of diabetes, type of renal disease, and estimated GFR (derived from standardized creatinine values and using MDRD formula, see below for details). The primary renal diagnosis was based on the clinical judgment of the nephrologists, as in most registries. All patients signed informed consent. All required information had already been collected and was contained in the database. No further additional investigations were performed on the patients for the purposes of this analysis.

Details regarding creatinine measurements and estimation of GFR

Creatinine measurements at all laboratories in British Columbia have been standardized with an isotope dilution mass spectrometry reference for application in a province-wide estimated GFR reporting initiative based on an isotope dilution mass spectrometry traceable format of the MDRD formula.[20] Therefore, although creatinine measurements were performed in different laboratories, they have been standardized, are directly comparable and therefore used in the MDRD formula.

Primary outcomes of interest

The primary outcomes of interest for this analysis are the prevalence of anemia (Hb $<110\,g\,l^{-1}$), hypocalcemia (corrected Ca $<2.1\,mmol\,l^{-1}$), hyperphosphatemia (PO_4 $>1.8\,mmol\,l^{-1}$), hyperparathyroidism (iPTH greater than twice the upper limit of normal, corresponding to $>13\,pmol\,l^{-1}$), hypoalbuminemia (Alb $<36\,g\,l^{-1}$), any laboratory abnormality, and $\geqslant 3$ abnormalities. Definitions for abnormalities were consistent with the currently established K/DOQI guidelines for the management of CKD; however, only one cut-off for iPTH was chosen for ease of analysis. Sensitivity analysis for other levels was performed to ensure consistency of data (not reported).

Baseline estimated GFR was categorized into <15, 15–30, 30–45, and 45–60 ml per min per 1.73 m^2; these cut-off points were chosen to reflect the K/DOQI guidelines for CKD stages, but further separated CKD stage 3 into two levels due to known deficiencies of the MDRD formula (less accurate at eGFR levels above 45 ml per min per 1.73 m^2), and the widely held clinical belief that higher levels of eGFR within stage 3 portend different outcomes.[19]

Statistical methods

Descriptive statistics are presented in percentage for categorical variables, in mean with standard deviation or median with interquartile range for continuous variables depending on distribution. Baseline demographics were compared using χ^2 test for categorical variables and one-way ANOVA for continuous variables.

To investigate if the above dichotomized laboratory variables vary among SRR groups at different levels of eGFR, we fitted several logistic regression models with SRR, eGFR, and an SRR/eGFR interaction term as predictors, and the dichotomized variables as the outcomes. For those primary outcomes where the interaction terms were found not to be statistically significant, we tested for the differences in the primary outcome by SRR, controlling for eGFR. On the other hand, if the interaction term was found to be statistically significant, we constructed a number of contrasts that allowed testing for the effect of SRR on the outcome at each level of eGFR. Further comparisons were made between South Asians or Oriental Asians and Caucasians if outcomes varied by SRR; the estimated OR and its corresponding 95% CI were reported. This

analytical approach was chosen to optimize the number of comparisons performed and reduce the risk of committing type 1 errors. We also performed multivariate analyses adjusting for potential confounders such as diabetes, age, sex, and primary diagnosis of renal disease.

All tests were two-sided, with *P*-values less than 0.05 being considered significant. All statistical analyses were performed in SAS software, version 9.1 (SAS Institute, Cary, NC).

ACKNOWLEDGMENTS

We acknowledge the work of the BC nephrology community in ensuring accurate and timely data collection without which these analyses would not have been possible.

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