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MORTALITY

Urine Protein/Creatinine Ratio as a Mortality Risk Predictor in Non-Diabetics with Normal Renal Function

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Objective.—Determine the relative mortality in apparently healthy adults with various levels of urinary protein measured by urine protein/creatinine (p/c) ratio.

Method.—By use of the Social Security Death Master File, mortality in 2010 was determined for 7.5 million life insurance applicants age 20 to 89 providing urine samples between 1992 and 2006. Relative mortality by Cox regression for bands of p/c ratios was determined using age and sex as covariates and with an age split at 60 after excluding those with hematuria (>3 red cells/hpf), diabetes, evidence of blood sugar elevation, or eGFR <60 mL/min.

Results.—After the exclusions noted above, relative mortality increased to 160% beginning at a p/c ratio of 0.11 mg/mg and rose steadily above that value regardless of sex and age. Most of this risk was not explained by a history of hypertension or elevated systolic blood pressure. Albumin testing identified roughly a third of urine samples with elevated p/c ratios as not containing albumin; those cases appeared to be associated with much lower risk as long as the p/c ratio was ≤1.0 mg/mg.

Conclusion.—Low levels of proteinuria identified as urine protein/creatinine ratios of 0.11 mg/mg or higher (much lower than the usual lower cut-off value of 0.21) are associated with substantial excess mortality risk, even after excluding diabetics and those with reduced kidney function or hematuria.

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INTRODUCTION

The urine protein to creatinine (p/c) ratio is a commonly used and inexpensive laboratory test to determine if excess levels of protein are present in the urine. The question we examine is how effective is that test in predicting the risk of all-cause mortality in a healthy non-diabetic cohort.

The concentration of protein in the urine can be determined by qualitative dipstick or quantitative laboratory testing, but has limited value as a screening tool in apparently healthy adults since it does not correlate well with the amount of protein appearing in the urine over a 24-hour period (the gold standard). The main reason for lack of correlation is that a person's volume of urine (and hence the protein concentration) will vary dramatically depending on their state of hydration. This issue led to the use of timed 24-hour urine collections to measure urinary protein loss.

Unfortunately, in addition to being cumbersome, 24-hour collections have proven inaccurate due to incomplete collection of urine regardless of training and effort. However, it was recognized that since pathologic protein (largely albumin) excretion is relatively constant, a single spot urine could be used as a measure of 24-hour protein excretion if varying urine concentration could be accounted for.[1] Although urine specific gravity had been used to estimate this, a more reliable technique (and one suited for automated processing) is to measure urine creatinine. This waste product of muscle metabolism is produced and then excreted by the kidneys at a constant rate; the urine creatinine concentration is an excellent measure of urine concentration across age and sex.[1–4] This understanding resulted in use of the urine p/c ratio as an accurate, convenient and inexpensive measure of proteinuria.

The normal range for urine protein excretion is usually listed in references as less than 150 mg/day, and there appears to be general agreement that values of 300 mg/day or higher are clearly abnormal.[5,6] This higher value correlates to an approximate p/c ratio of 0.2 mg/mg (200 mg/g); this is the origin of the commonly used p/c ratio ''normal range'' cut-off of 0.2 mg/mg. A lower value of 0.1 mg/mg would correlate to approximately 150 mg/day of protein excretion.

The terms ''proteinuria'' and ''albuminuria'' in association with commonly used tests are misnomers. Dipstick and automated tests for urinary protein are more sensitive to albumin than to other proteins; immunologic tests for albumin are even more so and but not completely specific. At normal levels of protein excretion, albumin makes up approximately one third of urinary protein. At mildly elevated levels of urinary protein excretion, albumin makes up (on average) about half of the protein in the urine, and at higher levels of protein excretion, usually an increasing percentage of the protein over 50%.[5,7]

Proteinuria without other urinary findings (such as red cells or reduced GFR) may be the result of increased albumin loss at the nephron associated with many chronic renal or vascular insults, notably hypertension and diabetes. It may also occur acutely after heavy exercise, with acute febrile illnesses, and less commonly, with increased orthostatic loss occurring while upright. If the urinary protein is not albumin, any associated risk is less clear. Non-albumin urinary protein does not include immunoglobulin light chains (Bence-Jones proteins) because they are not detected by typical urine protein screening.

Proteinuria measured by elevated p/c ratio or more specific albumin testing is clearly associated with mortality risk.[8–12] For those with chronic kidney disease, the p/c ratio, albumin/creatinine ratio, or a 24-hour collection have similar predictive ability for all-cause mortality.[11] However, some of the risk associated with any measure of proteinuria occurs due to the association of diabetes or reduced estimated glomerular filtration rate (eGFR) with proteinuria. If diabetics and those with impaired GFR are identified and examined separately (as is done in the case of individual life insurance applicants), the question becomes: what is the residual risk associated with isolated proteinuria for everyone else? As importantly, is the usual value identified as the upper end of the normal range (0.2 mg protein/mg creatinine) the appropriate cut-off to identify that risk?

METHODS

As part of the individual life insurance application process in the United States, urine and blood samples are routinely collected by the examiner and sent for testing to one of three laboratories that includes Clinical Reference Laboratory (CRL), with which the authors are affiliated. The samples are processed in an automated fashion, and results forwarded to the insurer requesting the test. This provides a large database of test

results from relatively healthy adults because potential applicants who know they are unwell (or their agents) are aware that any insurance offer will likely have higher premiums, if an offer can be made.

Limited history is also collected with the sample, including a question on the presence of diabetes. Urine testing includes protein and creatinine levels, and sometimes an albumin test, which is usually reflex-tested based on an elevated p/c ratio (usually >0.2 mg/mg) or positive disease history. Flow cytometry for red and white cells is performed based on the presence of urine hemoglobin or leukocyte esterase. Blood testing usually includes fructosamine (a glycosylated protein) to screen for chronically elevated blood sugars. For more recent samples (mostly 2004 forward), additional information is often available, including measured body mass index (BMI), blood pressure, and additional history questions.

Urine was examined for the presence of protein, creatinine and glucose with Roche reagents on Roche Modular analyzers per the manufacturer's directions. If requested by the insurer and if proteinuria was detected, the albumin concentration was determined with Roche Tina Quant reagent on a Roche P Modular unit. The presence or absence of hemoglobin and leukocyte esterase was detected with SciTeck Diagnostic reagents on the Roche Modular Units. Urine positive for either hemoglobin or leukocyte esterase was examined by flow cytometry (iQ200 Automatic Urine Microscopy analyzer from Iris Diagnostics) to count the number of red and white cells.

The dataset included applicants with valid p/c ratios age 20 to 89 tested from 1992 to 2006, with the exclusion of those with red blood cells (RBC) >3 per high power field (hpf) on flow cytometry, or a fructosamine result >2.1 mmol/L (suggesting chronically elevated blood sugar), or an admitted history of diabetes, or an eGFR (''Mayo Clinic'' formula from Rule) of <60 ml/min. If an applicant had repeated laboratory results, only the most recent was used. Vital status was determined by reference to the Social Security Death Master File (SS DMF) in May 2010. Match was by Social Security number, name and date of birth. Partial matches were manually reviewed; if the only disparity appeared to be probable name misspelling or transposition of dates, such applicants were included as well. The median duration of follow-up was 8 years.

All analyses were performed using IBM SPSS version 19.

RESULTS

The database having cases with valid p/c ratios and with ≤3 RBC/hpf consisted of 7,512,437 insurance applicants. After excluding those with fructosamine >2.1 mmol/L, an admitted diabetic history, or an eGFR of <60 ml/min, 6,579,630 applicants remained. For this group, 127,469 deaths were recorded by the SS DMF. The exclusions reduced the total number of applicants by 12%, but the number of deaths by 30%, over twice as much. Leaving those applicants with diabetes or reduced GFR in the study population (as most studies have done) will inflate the risk associated with proteinuria alone with those risks more appropriately allocated to diabetes or renal failure. See Table 1 for further population details.

Using the selected population, Cox regression hazard ratios for all-cause mortality based on level of p/c ratio were determined. Our initial investigation used a variety of p/c ratio bands and splits by sex and various age groups, in addition to including age as a covariate (not shown). It was determined that splitting p/c ratios into bands of <0.11 mg/mg, 0.11 to 0.20, 0.21 to 0.50, 0.51 to 1.0, and >1.0 was needed to accurately assign risk. We found that there was little difference in the mortality ratios for men and women (not shown), though a single age split at age <60 and 60+ was needed, since relative risk was sometimes different for those age 20 to 59 compared to those age 60

Table 1. Details of Our Study Population

	With Valid p/c Ratio and ≤3 RBC/hpf		Also Excluding Diabetic hx, Fructosamine Elev. & Low eGFR	
Age-Sex Group	Total	Deaths	Total	Deaths
Female age 20 to 59	2,730,011	24,311	2,483,788	19,703
Male age 20 to 59	4,065,455	69,435	3,545,994	51,966
Female age 60 to 89	270,606	30,130	213,224	19,590
Male age 60 to 89	446,365	58,601	336,624	36,210
Total	7,512,437	182,477	6,579,630	127,469

to 89. For the following analysis, those 5 p/c ratio bands were used; the analysis combined both sexes, with sex as a covariate along with age (in years) in the Cox regressions.

Tables 2 and 3 display the mortality ratios found for p/c ratio bands for age 20 to 59 and age 60 to 89 respectively, with 95% confidence intervals. The reference group was the p/c ratio band of <0.11 mg/mg. Beginning with the p/c ratio band of 0.11 to 0.20 where relative risk is 160% for age 20–89, there is a progressive increase of all-cause mortality risk as the p/c ratio increases. A value of 0.11 mg/mg is much lower than the currently accepted upper end of the normal range for protein/creatinine ratio, which is currently considered to be 0.20 mg/mg.

The percentages of applicants in each p/c ratio band used are shown in Table 4 for age 20 to 59 and 60 to 89. As expected, a higher percentage of those age 60 to 89 (7.2%) had p/c ratio values ≥0.11 mg/mg compared to those age 20 to 59 (4.4%).

Some applicants also had a urine albumin test done, allowing us to examine mortality ratios for those elevated p/c ratios with albuminuria (urine albumin >3 mg/dL) vs those without. Some insurers determine if albumin is the cause of elevated protein levels in all urine samples with p/c ratios >0.20 mg/mg with a urine albumin test. However, this test may also be done for other indications, including medical history. For p/c ratios ≤0.20 mg/mg, all urine albumin tests in our applicant study population would have been performed for indications other than the p/c ratio. Common independent reasons may be an indication of diabetes by history or testing (not identified by our selection criteria), other evidence of renal dysfunction, or a cardiovascular history.

Urine samples in each of the p/c ratio bands from 0.21 to >1.0 mg/mg with a urine albumin test performed were evaluated for the degree of concordance between elevated p/c ratio and an albumin value >3 mg/dL. We found a concordance of 54% for p/c ratio

Table 2. Mortality Ratios of Urine p/c Ratio Bands for Age 20 to 59, with Age and Sex as Covariates

Urine p/c Ratio (mg/mg)	Mortality Ratio (Cox)	95% CI	
		Lower	Upper
<0.11 (reference)	**1.0**		
0.11–0.20	**1.6**	1.6	1.7
0.21–0.50	**2.1**	2.0	2.2
0.51–1.0	**3.0**	2.7	3.4
>1.0	**5.2**	4.8	5.7

Table 3. Mortality Ratios of Urine p/c Ratio Bands for Age 60 to 89, with Age and Sex as Covariates

Urine p/c Ratio (mg/mg)	Mortality Ratio (Cox)	95% CI	
		Lower	Upper
<0.11 (reference)	**1.0**		
0.11–0.20	**1.6**	1.6	1.7
0.21–0.50	**2.0**	1.9	2.1
0.51–1.0	**2.6**	2.3	2.8
>1.0	**3.6**	3.2	4.0

Table 4. Percent of Study Population Falling into Each Urine p/c Ratio Band, by Age Group

Urine p/c Ratio (mg/mg)	Population (%)	
	Age 20 to 59	Age 60 to 89
<0.11	95.6	92.8
0.11–.20	3.1	5.0
0.21–0.50	1.0	1.7
0.51–1.0	0.2	0.3
>1.0	0.1	0.2

values 0.21 to 0.5, and a concordance of 73% for p/c ratio values 0.51 to 1.0, increasing to a concordance of 82% for values >1.0 mg/mg.

The value of reflexive urine albumin testing to further discriminate possible risk associated with an elevated p/c ratio is shown in Table 5. The mortality ratios by Cox regression relative to those applicants with a p/c ratio <0.11 were determined for bands of p/c ratios from 0.21 to 0.5, 0.51 to 1.0 and >1.0 mg/mg, split by albumin results. Within each band of p/c ratios over 0.21 mg/mg, only applicants with albumin testing were included and grouped by urine albumin values ≤3 mg/dL or values >3 mg/dL. Age (in years) and sex were included as covariates, and the analysis split into two age groups (20 to 59 and 60 to 89).

The resulting mortality ratios must be viewed with the recognition that some albumin testing is likely performed because of other adverse history or findings that may elevate the mortality ratios relative to the reference cases with p/c ratios <0.11 mg/mg. To evaluate this, we compared the mortality ratio for each p/c ratio band for all tested vs only those cases with albumin results; the average difference was 0.1 percentage points higher for those with albumin results (data not shown). This suggests that a small portion of urine albumin testing was performed based on other adverse history or findings.

The increased risk associated with p/c ratio elevations that are albumin negative is much less than the risk shown in Tables 2 and 3 based only on p/c ratio, as well as less than the risk shown in Table 5 when the urine albumin is positive. It is likely further reduced when adverse history leading to albumin testing (discussed above) is factored in. The number of applicants (and deaths) with urine albumin testing is much smaller (resulting in wider 95% confidence intervals and less certainty as to the precise mortality ratios for each group), but the pattern of risk for all groups is clear.

We also performed a similar analysis (not shown) using a urine albumin/creatinine ratio cutoff of 30 mg/g in place of the urine albumin concentration of 3 mg/dL. The resulting mortality ratios were very similar to those seen for albumin concentration, and consistent with the findings of other authors showing similar risk identification by either technique.[13]

Table 5. Mortality Ratios by Urine p/c Ratio Band and Albumin Level Relative to All Cases with p/c Ratio <0.11 mg/mg

Urine p/c Ratio (mg/mg) & Albumin (mg/dL)	Total Applicants	Age 20–59			Age 60–89		
		MR	95% CI		MR	95% CI	
		(Cox)	Lower	Upper	(Cox)	Lower	Upper
<0.11 (reference)	6,272,414	**1.0**			**1.0**		
0.21 to 0.5, ≤3	10,596	**1.4**	1.2	1.7	**1.6**	1.4	1.9
0.21 to 0.5, >3	12,552	**3.2**	2.9	3.6	**2.1**	1.9	2.3
0.51 to 1.0, ≤3	1,468	**1.0**	0.6	1.7	**1.7**	1.1	2.5
0.51 to 1.0, >3	3,979	**4.0**	3.4	4.7	**2.8**	2.4	3.3
>1.0, ≤3	702	**2.3**	1.4	3.7	**3.2**	1.9	5.3
>1.0, >3	3,198	**6.1**	5.3	7.1	**3.7**	3.2	4.4

Table 6. Distribution of Admitted Hypertension History by Age Group and Urine p/c Ratio Band for Study Population

Age Group	Urine p/c Ratio (mg/mg)	HTN Question		
		"Yes" Answer	Answered	% "Yes"
20 to 59	<0.11	172,492	2,187,488	7.9%
	0.11 to 0.20	6,803	69,448	9.8%
	0.21 to 0.50	2,683	22,012	12.2%
	0.51 to 1.0	623	3,867	16.1%
	>1.0	480	2,586	18.6%
60 to 89	<0.11	66,068	201,021	32.9%
	0.11 to 0.20	3,829	9,925	38.6%
	0.21 to 0.50	1,348	3,207	42.0%
	0.51 to 1.0	278	577	48.2%
	>1.0	194	408	47.5%

Applicants with hypertension histories or higher BP values were not excluded from our analysis. A hypertension history question has been asked as part of the blood and urine collection since late 2002, and was answered 89% of the time starting in 2003 for our study population. This provided a subpopulation of 2,245,741 applicants who denied a history of hypertension, and 254,798 applicants who admitted a history of hypertension. The correlation between such history and urine p/c ratio results is shown in Table 6. Based on those results, hypertension was associated with more protein excretion, but it explained only a minority of elevations; that history was also common among those without proteinuria.

For those age 60 to 89 in our selected applicant study population with BP measurements (121,428 applicants), a systolic BP of ≥140 mmHg was present on examination in 15% overall, but in 22% of those with p/c ratios over 0.11 mg/mg. Although hypertension history or elevated BP measurement on an insurance examination and elevated p/c ratio have positive associations, this still leaves most urine protein elevations unexplained.

DISCUSSION

In this population of insurance applicants where those admitting to diabetes (or having a serum fructosamine value consistent with a hemoglobin A1c value >6.5%) or those with an eGFR reduced to <60 mL/min were excluded, the urine protein/creatinine ratio is clearly associated with all-cause mortality risk. Increased relative risk (160%) begins at a p/c ratio of 0.11 mg/mg, rather than the 0.21 value, which is typically used as the lower end of the "abnormal" range. Since a p/c ratio of 0.11 mg/mg correlates with a daily protein excretion of 150 mg (which is at or above the maximum level typically found in healthy adults), this is biologically plausible.

In addition, since current urine tests (on average) find half of protein to be albumin at this level of proteinuria, this suggests an albumin excretion of approximately 75 mg/day.[7] If diluted in a representative daily urine output of 1,500 mL, this results in a urine albumin concentration of 5 mg/dL, only a bit higher than the >3 mg/dL (roughly 30 mg of albumin per gram of creatinine) usually considered to be the lowest positive value for albuminuria.

Both the medical literature and our results find the urine p/c ratio to be an effective (and inexpensive) screening tool for the substantial risk associated with proteinuria. Further discrimination of risk is possible by testing for albuminuria in those having elevated p/c ratios simply to identify if albumin is present. For p/c ratios between

0.21 and 1.0 mg/mg, risk for those cases who were albumin negative was only mildly elevated (1 to 1.7 times) relative to those with p/c ratios <0.11 mg/mg. When albumin testing related to other findings is accounted for, this mortality risk is reduced further. After the p/c ratio exceeds 1.0 mg/mg, risk even for those who are albumin negative is more than doubled.

Applicants in our selected study population with urine samples positive for albumin have a much higher relative risk. For p/c ratio values between 0.11 to 0.20 mg/mg, the value of albumin testing could not be directly evaluated since all such testing was based on other indications. The authors expect risk discrimination using albumin in this p/c ratio band to be similar to that seen for higher p/c ratio bands. Because the overall mortality ratio for the 0.11 to 0.20 mg/mg band is 1.6 for all ages, a negative albumin test would be anticipated to reduce risk to <1.3 and may possibly be close to 1.0.

The observation that excess risk is present even if the albumin level is at or below 3 mg/dL (or similarly at or below 30 mg/g of albumin/creatinine) may, in part, be explained by the good but imperfect correlation between spot urine samples and 24-hour albumin excretion. This issue has been reviewed by the National Kidney Disease Education Program–IFCC Working Group on Standardization of Albumin in Urine.[14]

Though hypertension by history or by measured BP also correlates with an increased urine protein/creatinine ratio in our study, such history is common at age 60+ and fails to explain our findings of increased risk associated with elevated p/c ratios.

CONCLUSION

Urine protein/creatinine ratios as low as 0.11 mg/mg are associated with substantial excess mortality, even in a healthy population excluding diabetics and those with reduced eGFR. Given the high level of risk associated with ratios this low and the (still) small and manageable percentage of insurance applicants affected, using a p/c ratio of ≥0.11 mg/mg to prompt further evaluation when screening a healthy population of adults of any age appears justified.

Adding the (much more expensive) urine albumin test on a limited reflex basis to focus evaluation on the roughly two thirds of cases with p/c ratio values of 0.11 to 1.0 mg/mg which confirm as albumin, may reduce the need for further action for the albumin negative cases who appear to have limited excess risk. All applicants with p/c ratios >1.0 mg/mg appear to have substantial excess risk, even when they are negative for urine albumin.

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