BEWARE THAT LOW URINE CREATININE!

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Executive Summary *The presence of low urine creatinine at insurance testing is associated with increased mortality risk across age and sex partly due to intentional dilution to hide the presence of cotinine. The increased relative mortality risk for men begins above the current CRL urine creatinine alert threshold of 10 mg/dL, while increased relative mortality risk for women begins below this threshold, which is consistent with the fact that women (especially older women) have lower average urine creatinine values due to lower muscle mass. Alternative age- and sex-specific urine creatinine cut-offs for underwriting action and the potential nature of that action are discussed.*

Introduction

If the urine is very dilute, the laboratory cannot reliably identify substances such as cotinine and cocaine, or findings such as protein or red blood cells. Measuring the degree of urine concentration can be done by measuring the urine specific gravity optically or by dipstick, but the former is cumbersome and the latter less accurate. Urine concentration can also be assessed by determining urine creatinine concentration. With the introduction of automated laboratory analyzers, this has become the usual method of determining the degree of urine concentration for insurance and most other testing.

Creatinine is produced as a waste product of muscle metabolism and filtered into the urine at a fairly constant rate. This means that as fluid intake and the daily urine volume increases for an individual, the urine creatinine concentration decreases to a proportional degree. That concentration is relatively independent of age or sex and (though still imperfect) serves as the commonly used approximation of the degree of urine concentration. As such, it is the denominator in the widely used urine protein/creatinine ratio. However, because muscle mass (and creatinine production) may vary across age and sex more than glomerular filtration rate does, mean urine creatinine concentrations can vary somewhat.

The World Health Organization has suggested that urine creatinine concentrations <30 mg/dL might be too dilute when monitoring occupational exposure to chemicals. The US Department of Transportation indicates values <20 mg/dL (specific gravity ≈ 1.003) are considered 'dilute' and values <5 mg/dL (specific gravity ≈ 1.001) require a repeat urine for occupational testing. No age or sex adjustment is suggested for these cut-offs.

To hide substances, applicants (who know they are to be tested) can create very dilute urine by drinking large amounts of water (several quarts in a day) in excess of what they need to replace normal losses due to sweating, etc. The alternative is to add water to the urine sample after it is voided (or even into the bladder via a catheter). Without the formal protocols typically used for pre-employment and employee drug testing, preventing and discovering intentional dilution are difficult. Approaches such as measuring urine temperature are of uncertain efficacy in preventing diluted urine samples, given pre-notice of testing and access to warm water.

In addition to the intentional dilution of urine by drinking large amounts of water, drinking water to fill the stomach as an appetite suppressant can be associated with eating disorders. Heavy consumption of beer may achieve a similar urine dilution. Both of these activities are potentially associated with excess mortality.

CRL has long used a urine creatinine concentration of <10 mg/dL (specific gravity ≈ 1.002) as an alert value, suggesting that dilution to that extent may prevent reliable identification of other substances such as drugs, cotinine and protein. In working with clients, CRL staff has noted this suggested cut-off value is sometimes ignored during underwriting, especially in those situations where the applicant (by virtue of age, sex or history), is not considered as having potentially higher risk. The actual increase in mortality risk overall or by age and sex is unknown, as there appears to be no prior medical study on mortality relative to low urine creatinine values (highly dilute urines) in any setting. Given this lack of information in the medical literature, we conducted such a study in insurance applicants.

How the Study Was Done

Applicants with urine samples tested at CRL from 1992 to 2007 were matched to the Social Security Death Master File to obtain mortality status in September 2011, resulting in 8.7 million lives and 203,000 deaths with a median duration of follow-up of 9 years (range 0 to 19 years). The records had identifying information removed at that point and were analyzed for the relationship between urine creatinine concentration and relative mortality with divisions by age and sex. Cox regression analysis from SPSS version 21 was used to account for varying exposure, smoking and age differences within our groups split by sex and age (18 to 59, 60 to 89 years).

Urine creatinine testing was performed on Hitachi chemistry analyzers with Roche Biomedical reagents following the manufacturers' directions for in-vitro diagnosis. Urine samples with a creatinine concentration <10 mg/dL or >300 mg/dL were retested; if the sample had a concentration <10 mg/dL, the specific gravity was also determined using refractive spectroscopy to verify the concentration. Urine cocaine and cotinine testing was done with Microgenics reagents on Hitachi chemistry analyzers following the manufacturers' specifications, except that a 6-point calibration was done for the cotinine test. All cocaine positive samples were confirmed with Hewlett Packard gas chromatography mass spectroscopy (GC/MS).

What the Study Found

Table 1 provides information on the number of applicants tested and deaths recorded by age, sex and urine creatinine level. Sufficient numbers by age, sex and urine creatinine level are available to provide credible mortality results across all parameters.

Because highly dilute urine may often be an attempt to avoid detection of substances, the percentages of those applicants positive for cotinine or cocaine are shown in Table 2 by urine creatinine level. Obviously, if the masking by dilution had been successful, then nothing would have been found. For that reason, cotinine positivity is shown, not just using a typical industry cut-off of 200 ng/mL, but also at a much lower 50 ng/mL, which is more typical of the testing threshold used in epidemiologic studies of smokers vs. non-smokers. Both true-positive and false-positive rates (without mass spectrographic confirmation) are likely higher using the lower cotinine threshold, but the relative increase in positivity as urine creatinine concentration decreases remains valid.

Using the 50 ng/mL cut-off, cotinine positivity increases by 56% for urine creatinine values <10 mg/dL (26% positive) relative to those ≥15 mg/dL (16% positive). Cocaine positivity triples for urine creatinine values <7 mg/dL (0.6%) relative to those ≥15 mg/dL (0.2%). Because urine dilution reduces detection at the cocaine and cotinine cut-off values typically used in underwriting, the percentages of applicants positive for cotinine and cocaine in this study almost certainly understate the increased number of applicants who dilute their urine and present with low urine creatinine levels. This increasing percentage of substance users would account for at least some of the increased mortality noted in our study for applicants with very dilute urines.

Tables 3a and 3b present the all-cause relative mortality risk split by sex and age group for a range of urine creatinine values relative to those having a urine creatinine concentration ≥15 mg/dL (the reference group). Age is included as a covariate in the Cox analysis because each of the two age bands (18 to 59, 60 to 89) are fairly wide. Urine cotinine <200 ng/mL vs. ≥200 ng/mL is also included as a covariate in the Cox analysis to account for the mortality associated with identified tobacco users (using industry cut-offs). Because cocaine use was detected in such a small percentage of samples (less than 1%), it would have little impact on relative risk and was not included as a covariate.

For all males, relative mortality risk increased for urine creatinine values less concentrated than 12 mg/dL; for females age <60, relative risk increased for creatinine concentrations <10 mg/dL; for females age 60+, the relative mortality risk remains low until a concentration of <7 mg/dL was reached.

The cumulative distribution of urine creatinine results is also shown in Tables 3a and 3b from ≥15 mg/dL down to <7 mg/dL by age and sex. A cut-off value of <10 mg/dL identifies approximately 0.7% of female

Table 1. Urine creatinine levels, total applicants and deaths by age group and sex

Urine	Female		Female		Male		Male	
Creatinine	age 18 to 59		age 60 to 89		age 18 to 59		age 60 to 89	
(mg/dL)	Applicants	Deaths	Applicants	Deaths	Applicants	Deaths	Applicants	Deaths
15+ (ref)	3,131,377	25,424	275,346	32,377	4,669,505	78,405	452,828	62,984
14 to 14.9	16,509	137	1,728	197	14,018	249	896	105
13 to 13.9	15,683	136	1,553	182	13,393	250	821	113
12 to 12.9	14,404	147	1,396	164	11,820	219	636	81
11 to 11.9	13,350	151	1,211	134	10,100	195	552	77
10 to 10.9	11,495	119	989	113	8,111	141	425	65
9 to 9.9	9,203	111	763	92	5,584	119	278	40
7 to 8.9	10,819	136	870	97	4,809	120	227	47
<7	2,949	56	284	45	918	39	71	21

ref = reference band

Table 2. Percent of applicants positive for cotinine at cutoffs of 200 and 50 ng/mL, and for cocaine by urine creatinine level

Urine Creatinine	Positive cotinine %		Positive
(mg/dL)	200+	50+	cocaine %
15+ (ref)	12%	16%	.2%
14 to 14.9	13%	21%	.1%
13 to 13.9	13%	21%	.2%
12 to 12.9	14%	22%	.2%
11 to 11.9	14%	23%	.2%
10 to 10.9	15%	24%	.2%
9 to 9.9	15%	25%	.2%
7 to 8.9	15%	25%	.3%
<7	15%	26%	.6%

ref = reference band

applicants but only 0.1 to 0.2% of male applicants, which is consistent with lower creatinine production in women (because of lower muscle mass) relative to level of renal function (filtering of creatinine into the urine). The increase in relative mortality by sex more closely follows distribution of urine creatinine than it does specific levels.

Also included in Tables 3a and 3b are the 95% confidence intervals (CI) for each mortality ratio. The width of the range of values included between the upper and lower 95% CI is largely dependent on the number of outcomes (deaths); the larger the number of deaths observed, the narrower the 95% CI. By looking at how wide or narrow the 95% CIs are, you may evaluate how much of the occasional lack of smooth mortality increase as urine creatinine concentration decreases might simply be the result of random chance when there are few deaths.

Table 4 provides a simplified view of the results noted in Tables 3a and 3b, including both sexes in a single table and substituting the remaining percentage of applicants for the cumulative percentage. This allows easier identification of potential underwriting action points based on relative risk and distribution by age and sex.

What Do the Study Results Contribute to Risk Assessment?

Low urine creatinine is associated with increased relative mortality and that increase is greater than the excess contributed by identified tobacco users attempting to mask their smoking status. Additional elevated relative mortality risk at low urine creatinine levels is likely related to:

- Other substances that were successfully masked by the applicant
- Other laboratory findings hidden by the extent of urine dilution and/or
- The excess mortality potentially related to the reasons for the high level of fluid intake besides intentional masking

Table 3a. Urine creatinine levels, relative mortality and cumulative percentage of applicants by age group for women, with smoking status added as a covariate

Urine	*F 18 to 59*					*F 60 to 89*			
Creatinine		95% CI		Cum.			95% CI		Cum.
(mg/dL)	MR	Lower	Upper	%		MR	Lower	Upper	%
15+ (ref)	1.0			97.1%		1.0			96.9%
14 to 14.9	0.8	0.7	1.0	97.6%		1.0	0.9	1.2	97.5%
13 to 13.9	0.9	0.7	1.1	98.1%		1.1	0.9	1.3	98.1%
12 to 12.9	1.0	0.8	1.2	98.5%		1.1	0.9	1.3	98.6%
11 to 11.9	1.2	1.0	1.4	98.9%		1.0	0.8	1.2	99.0%
10 to 10.9	1.0	0.8	1.3	99.3%		0.9	0.7	1.2	99.3%
9 to 9.9	1.3	1.1	1.6	99.6%		1.1	0.9	1.4	99.6%
7 to 8.9	1.2	1.0	1.5	99.9%		1.0	0.8	1.3	99.9%
<7	1.9	1.3	2.6	100.0%		1.4	0.9	2.0	100.0%

ref = reference band

Table 3b. Urine creatinine levels, relative mortality ratios and cumulative percentage of applicants by age group for men, with smoking status added as a covariate

Urine	*M 18 to 59*					*M 60 to 89*			
Creatinine		95% CI		Cum.			95% CI		Cum.
(mg/dL)	MR	Lower	Upper	%		MR	Lower	Upper	%
15+ (ref)	1.0			98.5%		1.0			99.1%
14 to 14.9	1.2	1.0	1.4	98.8%		1.0	0.8	1.3	99.3%
13 to 13.9	1.1	1.0	1.3	99.1%		1.0	0.8	1.3	99.5%
12 to 12.9	1.1	1.0	1.3	99.4%		1.0	0.8	1.3	99.7%
11 to 11.9	1.2	1.0	1.4	99.6%		1.3	1.0	1.7	99.8%
10 to 10.9	1.2	1.0	1.4	99.8%		1.2	0.9	1.6	99.9%
9 to 9.9	1.3	1.0	1.6	99.9%		1.3	0.9	1.8	99.9%
7 to 8.9	1.6	1.3	2.0	100.0%		1.3	0.9	2.0	100.0%
<7	2.7	1.8	4.1	100.0%		2.5	1.3	4.6	100.0%

ref = reference band

Table 4. Urine creatinine levels, relative mortality ratios and percentage of remaining applicants by age group and sex, with smoking status added as a covariate

Urine Creatinine	*Female 18 to 59*		*Female 60 to 89*		*Male 18 to 59*		*Male 60 to 89*	
mg/dL	MR	Remaining applicants	MR	Remaining applicants	MR	Remaining applicants	MR	Remaining applicants
15+ (ref)	1.0		1.0		1.0		1.0	
14 to 14.9	0.8	2.9%	1.0	3.1%	1.2	1.5%	1.0	0.9%
13 to 13.9	0.9	2.4%	1.1	2.5%	1.1	1.2%	1.0	0.7%
12 to 12.9	1.0	1.9%	1.1	1.9%	1.1	0.9%	1.0	0.5%
11 to 11.9	1.2	1.5%	1.0	1.4%	1.2	0.6%	1.3	0.3%
10 to 10.9	1.0	1.1%	0.9	1.0%	1.2	0.4%	1.2	0.2%
9 to 9.9	1.3	0.7%	1.1	0.7%	1.3	0.2%	1.3	0.1%
7 to 8.9	1.2	0.4%	1.0	0.4%	1.6	0.1%	1.3	0.1%
<7	1.9	0.1%	1.4	0.1%	2.7	0.0%	2.5	0.0%

ref = reference band

Relative mortality risk begins to increase at higher urine creatinine levels for males as compared to females, especially compared to females age 60+. Risk for males actually begins to increase at urine creatinine concentrations <12 mg/dL, but taking underwriting action at that point would triple the number of males impacted as compared to using <10 mg/dL as the threshold for underwriting action.

Relative mortality risk increases for females age <60 below urine creatinine values <10 mg/dL, but looking at the trend across urine creatinine bands and at the 95% confidence intervals suggests the relative risk might actually be smaller than the 1.3 measured in this study. For females age 60+, no increase in risk is seen until urine creatinine values <7 mg/dL.

If cotinine or another substance is detected for an applicant despite low urine creatinine, excess mortality may already be accounted for by designating the applicant as a tobacco or other substance user, which is typically associated with substantially higher premiums. If no substance is found and there is no other obvious cause for the low urine creatinine result, underwriting action to prevent excess mortality may be needed (and be acceptable based on the number of applicants impacted) for urine creatinine values <11 or <10 mg/dL in men and either <10 or <9 mg/dL in women age <60, while an even lower urine creatinine cut-off may be appropriate for women age 60+.

As compared to the excess mortality captured and number of applicants affected by using a universal urine creatinine cut-off of <10 mg/dL, using a 1 mg/dL higher urine creatinine threshold for males and a 1 mg/dL lower urine creatinine threshold for females could equalize the percentage of applicants affected by sex while capturing more excess mortality. Choosing other urine creatinine values as cut-offs or different cut-offs for each age-sex combination might improve accuracy further, but would create more complex decision matrices.

Underwriting action could be in the form of extra premium to account for the average extra risk or a repeat urine specimen. The first action is simpler but, because some of those dilute urines are within the physiologic range and will have no extra mortality risk and some will have substantial extra risk, the burden of a repeat urine specimen may be justified, leading to better risk selection and profitability. If the repeat urine specimen is chosen, a requirement that the urine creatinine concentration be greater than (an easily achieved) 20 mg/dL in the repeat specimen will likely improve the detection of substances.

One important caution in generalizing from this CRL study is that there may be slight variation between laboratories using different analyzers and reagents in reporting urine creatinine level for the same specimen. This can be largely accounted for by finding out what urine creatinine values at the other laboratory correspond to the cumulative percentiles noted in Tables 3a and 3b and substituting those urine creatinine values. This step applies to insurance-focused laboratories as well as clinical laboratories.

Conclusion

Low urine creatinine at the time of insurance testing is associated with increased mortality risk across age and sex partly due to intentional dilution to hide the presence of cotinine. Likely because women (especially older women) have lower average urine creatinine values, increased relative mortality risk for men begins above the current CRL alert threshold of 10 mg/dL while increased risk for women begins below this threshold. Risk is sufficiently high that some underwriting action is likely required for low urine creatinine, and alternative age- and sex-specific cut-offs for underwriting action should be considered.

References

1 de Buys Roessingh AS, Drukker A, Guignard J-P. Dipstick measurements of urine specific gravity are unreliable. *Arch Dis Child*. 2001;85:155-7.

2 Muscat JE, Liu A, Richie Jr. JP. A comparison of creatinine vs. specific gravity to correct for urinary dilution of cotinine. *Biomarkers*. 2011;16:206-11.

3 Barr DB, Wilder LC, Caudill SP, et al. Urinary creatinine concentrations in the U.S. population: Implications for urinary biologic monitoring measurddements. *Environ Health Perspect*. 2005;113:192-200.

4 US Department of Transportation, Federal Transit Administration Office of Safety and Security. Drug and alcohol testing procedures and program requirements update. *Drug & Alcohol Newsletter*. Issue 37, Summer 2008. www.fta.dot.gov/safetysecurity/12533_12666.html

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