# Urine Protein and Urine Albumin

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The following is additional commentary on a study originally published in the Journal of Insurance Medicine in 2012, *Urine Protein/Creatinine Ratio as a Mortality Risk Predictor in Non-Diabetics with Normal Renal Function*.

## The Mortality and Optimal Reflex Criteria for Urine Protein Measurements

Urine protein is a marker of damage to the renal filtering unit known as the glomerulus. Previously published research from CRL has demonstrated that urine protein is a reliable marker of increased mortality risk (link). Generally speaking urine protein is a mortality concern only when the protein is albumin or a portion of an immune globulin. Urine protein may be elevated due to the presence of non-albumin proteins from post-tubular proteinuria, semen or vaginal secretions.

It is therefore valuable for insurers to know if urine protein reflects albuminuria or not. Because urine albumin testing is more expensive than protein testing, it is also important to identify the protein threshold at which albumin testing becomes worthwhile.

In this study, recent CRL data will be used to answer two questions:

1. Is urine albumin, in fact, a better mortality predictor than urine protein?
2. What level of urine protein most efficiently identifies those with potentially hazardous elevations of urine albumin?

### Notes on the analysis

This study includes nearly 1 million subjects who had urine tested for both protein and albumin since 1992. There were a total of 23161 deaths over an average of 8.3 years of follow up. The average age is 50.4 years and 63% of the subjects are male. All urine protein levels were entered as a ratio to the level of urine creatinine to account for concentration effects. All admitted diabetics were excluded from analysis, as were women who were likely pregnant based on a logistic model trained on other CRL data. It should be noted that in many cases, albumin measurements were only done because of elevated protein measurements, which can skew somewhat the distribution of albumin levels to the higher side, though it would not be expected to have a large impact on mortality.

### Which measure is a better mortality predictor?

To answer this question the urine protein:creatinine ratio and albumin:creatinine ratio were categorized by percentile. Because of the abundance of data, these percentile ranks

were calculated within single years of age and sex. Tables 1 and 2, below, present the thresholds for various age ranges. For instance, the 75th percentile of protein:creatinine ratio for the youngest group of women is 0.23 - which is to say that 75% of young women in the sample had P/C ratios below this level. Table 3 presents hazard ratios for various levels of P/C and A/C ratios for men and women. The higher hazard ratios in the A/C models demonstrate conclusively that it is a superior mortality indicator. This should come as no suprise since we have already mentioned that the causes of non-albumin proteinuria are largely benign.

*Table 1: Urine Protein:Creatinine Ratio (mg/mg) Percentile Thresholds*

| Sex | Age Group | 25th | 50th | 75th | 90th | 95th | 99th |
|---|---|---|---|---|---|---|---|
| F | 17-35 | 0.05 | 0.12 | 0.24 | 0.42 | 0.65 | 1.82 |
| F | 36-45 | 0.05 | 0.11 | 0.23 | 0.42 | 0.70 | 2.27 |
| F | 46-55 | 0.05 | 0.08 | 0.17 | 0.32 | 0.54 | 1.91 |
| F | 56-70 | 0.05 | 0.08 | 0.14 | 0.27 | 0.42 | 1.45 |
| F | 71-85 | 0.06 | 0.09 | 0.15 | 0.30 | 0.49 | 1.68 |
| M | 17-35 | 0.03 | 0.07 | 0.21 | 0.40 | 0.65 | 2.05 |
| M | 36-45 | 0.03 | 0.06 | 0.14 | 0.33 | 0.57 | 1.83 |
| M | 46-55 | 0.04 | 0.06 | 0.12 | 0.29 | 0.50 | 1.74 |
| M | 56-70 | 0.04 | 0.06 | 0.12 | 0.29 | 0.50 | 1.75 |
| M | 71-85 | 0.05 | 0.08 | 0.15 | 0.34 | 0.61 | 1.85 |

*Table 2: Urine Albumin:Creatinine Ratio (mg/g) Percentile Thresholds*

| Sex | Age Group | 25th | 50th | 75th | 90th | 95th | 99th |
|---|---|---|---|---|---|---|---|
| F | 17-35 | 4.8 | 13.5 | 58 | 169 | 303 | 923 |
| F | 36-45 | 4.2 | 10.3 | 43 | 148 | 289 | 1044 |
| F | 46-55 | 4.0 | 8.5 | 27 | 107 | 229 | 1011 |
| F | 56-70 | 4.3 | 8.7 | 21 | 73 | 172 | 885 |
| F | 71-85 | 5.5 | 11.1 | 28 | 91 | 210 | 964 |
| M | 17-35 | 2.6 | 5.4 | 18 | 115 | 263 | 1070 |
| M | 36-45 | 2.7 | 5.9 | 21 | 116 | 264 | 1060 |
| M | 46-55 | 2.8 | 6.1 | 19 | 97 | 229 | 1007 |
| M | 56-70 | 3.3 | 7.1 | 23 | 106 | 237 | 1070 |
| M | 71-85 | 4.3 | 10.0 | 35 | 146 | 314 | 1177 |

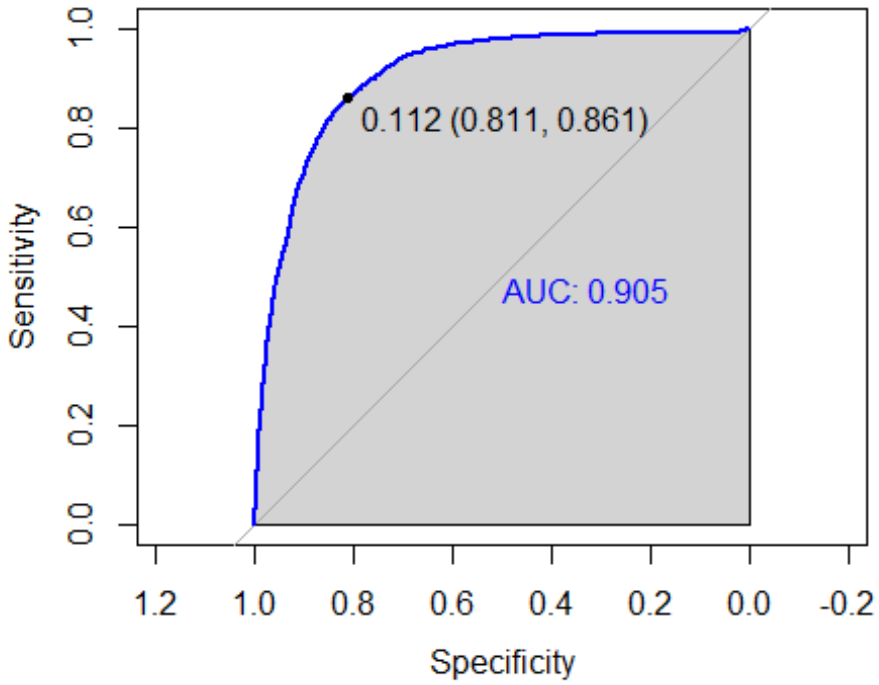
*Table 3: Hazard Ratios (controlled for age and sex)*

| | P:Cr Ratio | Alb:Cr Ratio |
|---|---|---|
| 0-25th (ref) | 1.0 | 1.0 |
| 25-75th | 1.1 | 1.4 |
| 75-90th | 1.9 | 2.4 |
| 90-95th | 2.2 | 2.9 |
| 95-99th | 3.2 | 4.1 |
| 99th+ | 5.7 | 7.2 |

## Best threshold for albumin testing

From the first part of the analysis it can be seen that the mortality effects of the A/C ratio start to appear on the 75-90th percentile range and that this corresponds to a level of around 30 mg albumin/g creatinine. Receiver operating characteristic (ROC) curve analysis was used to identify the best threshold of P/C ratio to find A/C ratios over 30. Figure 1 shows the ROC curve which has an area of 91%, shows that at a threshold of 0.11, the P/C ratio has a sensitivity of 86% and specificity of 81% for identifying a high A/C ratio.

## ROC plot



It has been somewhat more common in the industry to test urine sample for albumin only when the P/C ratio is 0.2 or higher, while this analysis would support a threshold of 0.12. To estimate the impact of using the higher threshold, the scatter plot in Figure 2 was generated. The dark blue points represent those with P/C ratios between these thresholds who have A/C ratios over 30 - implying higher mortality risk. Though this region of the graph is small, it contains nearly 5% of applicants. Thus, using this higher referral threshold misses more than twice the number of high-risk individuals compared to the lower threshold.

Obviously, if the treshold is moved lower, the rate of albumin testing will increase. Based on all available data in non-pregnant individuals (diabetics NOT excluded), the rate of testing would be about 11.5% at the lower threshold vs. 3.1% at the higher threshold in women. In men, the rate is about 6.9% at the lower threshold vs. 2.4% at the higher threshold.