

USING URINE PROTEIN CREATININE RATIO ALONE OR REFLEXING TO URINE ALBUMIN IN THE APPLICANT WITH HbA1c ELEVATION



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Introduction

In a previous study, we compared using urine protein creatinine ratio (p/c) or urine albumin (often called microalbumin which actually refers to positive results from ≥ 3 to 30 mg/dL rather than a different test) to assess the presence of albuminuria or proteinuria associated with increased mortality risk when HbA1c is elevated.¹ We found that urine albumin < 3 mg/dL and urine p/c < 0.11 (mg of protein per mg of creatinine) each yielded equally low mortality, but that urine p/c had markedly lower cost and reduced the (false) positive rate associated with urine albumin screening by more than one-third. This new study continues that evaluation by looking at the use of urine p/c alone or followed by urine albumin if the p/c is ≥ 0.11 mg/mg to identify if that combination could provide better risk discrimination and at what additional test cost.

How the Study Was Done

The same de-identified applicants age 40 to 79 with HbA1c 5.0% or higher tested at CRL from 1992 to 2007, included in the prior study, were analyzed further.¹ All included applicants had urine p/c results (limited to those < 1 mg/mg) and were further limited to those who had a urine albumin result if HbA1c was $\geq 6\%$. The decision to perform urine albumin screening for HbA1c elevations is largely driven by individual insurance company rules based on the HbA1c level. For urine p/c elevations ≥ 0.21 mg/mg, the urine p/c level itself might have triggered the addition of urine albumin testing. These criteria resulted in 380,902 lives and 17,143 deaths studied with a median follow-up of 7 years (range 0 to 19). Analysis was divided by age 40 to 59 and 60 to 79 and HbA1c level with results compared for urine p/c alone and for p/c elevated ≥ 0.11 mg/mg followed by urine albumin.

Executive Summary *When HbA1c is 6.0% or higher, adding urine albumin testing on a reflexive basis for urine protein creatinine ratio (p/c) elevations ≥ 0.11 mg/mg reduces the number of positives by 30 to 40% (older to younger ages, respectively) at limited additional cost, while the mortality in the negative pool increases minimally. Urine p/c alone or adding a reflexive urine albumin if urine p/c is elevated are each superior to universal urine albumin screening when HbA1c is elevated and a urine sample collected at a single time is utilized.*

Analysis of relative mortality utilized Cox regression in IBM SPSS 22 with age, sex and smoking status included as covariates for all relative mortality calculations. The group with HbA1c of 5 to 5.9% and urine p/c < 0.11 mg/mg was the (normal) reference group for all relative mortality analysis, whether based on p/c or urine albumin, to allow direct comparison of risk reduction between the two tests. All testing was performed at CRL in the manner described in our prior paper.¹

What the Study Found

Table 1 (next page) provides the percentage of applicants with urine p/c $<$ and ≥ 0.11 mg/mg and for those who also had a urine albumin ≥ 3 mg/dL in addition to p/c ≥ 0.11 mg/mg for each band of HbA1c split into age 40 to 59 and age 60 to 79. No values are shown for urine albumin in the HbA1c 5 to 5.9% band, as such testing is not routinely done for “normal” HbA1c values. We found the percentage of positives for both measures of proteinuria increased as HbA1c increased, but the percentage jointly positive for urine albumin as well as urine p/c was overall 40% lower

Table 1. HbA1c level and presence of urine p/c ≥ 0.11 mg/mg or both p/c ≥ 0.11 and urine albumin >3 mg/dL

HbA1c %	% with p/c ≥ 0.11		% with both p/c ≥ 0.11 and urine albumin >3	
	Age 40-59	Age 60-79	Age 40-59	Age 60-79
5 to 5.9	4.9%	7.9%	-----	-----
6 to 6.9	8.9%	12.9%	4.7%	7.4%
7 to 7.9	13.9%	18.8%	8.6%	12.2%
8 to 9.9	20.4%	25.4%	13.1%	15.7%
10+	29.7%	36.0%	18.5%	22.5%
6 to 10+	15.9%	18.8%	9.5%	13.1%

than for p/c alone at younger ages and 30% lower at older ages.

Figures 1 (below) and 2 (next page) show the relative risk by HbA1c value split by level of urine p/c and by p/c plus urine albumin for age 40 to 59 and 60 to 79, respectively. Allowing re-entry into the proteinuria negative group if the urine p/c was elevated but the reflex urine albumin was <3 mg/dL gave a similar risk (minimally higher dashed line) to using p/c alone. This was true for both age bands.

For those jointly positive for albuminuria and proteinuria, the risk was intermediate relative to the two levels identified by proteinuria alone (0.11 to 0.20

and 0.21 to 0.99 mg/mg). For HbA1c elevations of 6.0 to 6.9%, that meant a risk of approximately 250 to 350% of the risk for those with both normal HbA1c (5 to 5.9%) and no proteinuria.

What Do the Study Results Contribute to Risk Assessment?



Adding urine albumin as a reflex test when urine p/c is elevated ≥ 0.11 mg/mg in those with HbA1c 6.0% or higher, and allowing re-entry into the proteinuria negative pool if urine albumin is negative, captures almost all of the risk while reducing the number of applicants potentially identified with proteinuria by 30 to 40% depending on age, allowing those applicants to be priced for HbA1c elevation alone. If 10 to

Figure 1. Relative mortality by HbA1c for urine p/c or for p/c and reflexive urine albumin for age 40 to 59 (Reference: HbA1c 5 to 5.9% and urine p/c <0.11 mg/mg)

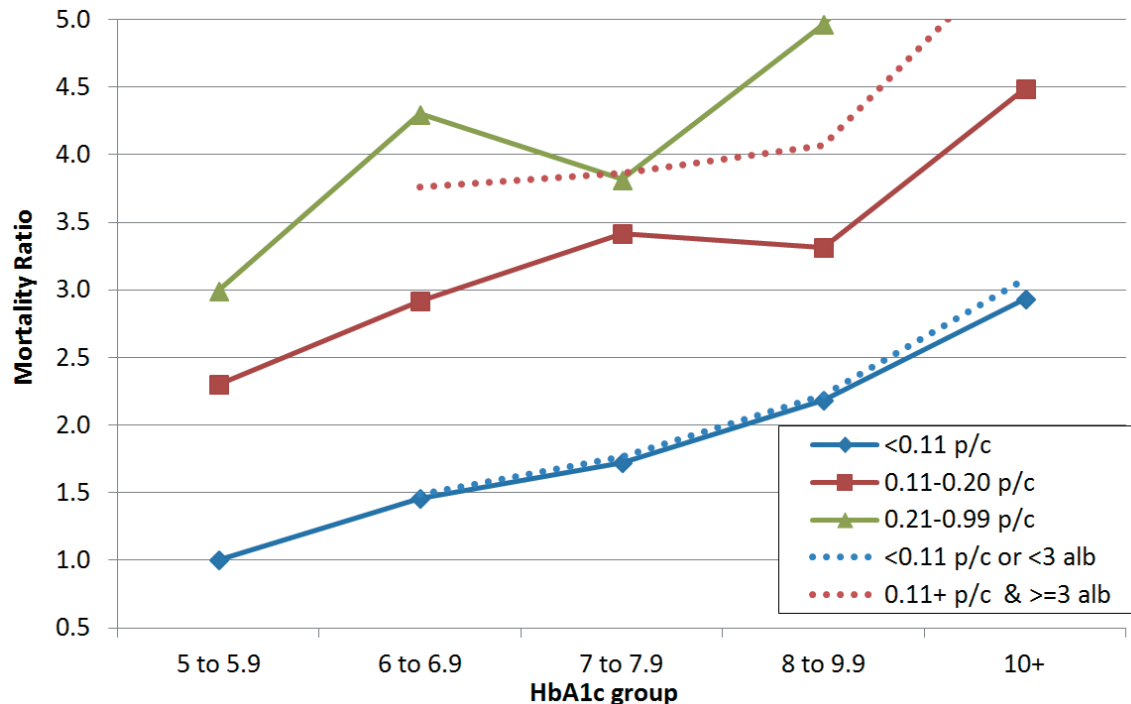
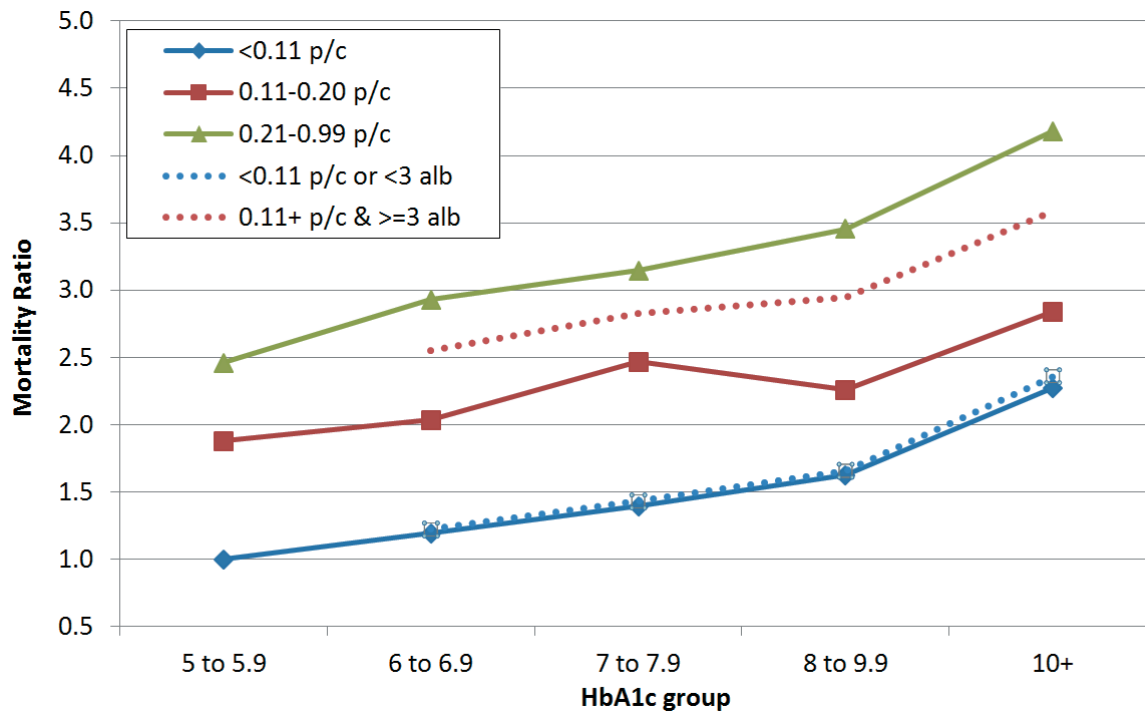


Figure 2. Relative mortality by HbA1c for urine p/c or for p/c and reflexive urine albumin for age 60 to 79 (Reference: HbA1c 5 to 5.9% and urine p/c <0.11 mg/mg)



20% of applicants age 40+ are identified as having HbA1c values 6% or higher and 16% of those urines are positive for proteinuria by urine p/c, then this gain includes 0.5 to 1% of all applicants age 40+.

The direct cost of adding the urine albumin in this manner, assuming a test cost of up to \$10 with 10 to 20% of applicants age 40+ having elevations of HbA1c and 16% of those positive for proteinuria, would be about 15 to 30 cents averaged over all samples in this age group.

Key Conclusion

We previously showed that urine p/c is superior to urine albumin screening in identifying those with

increased risk associated with proteinuria or albuminuria when HbA1c is elevated and only one urine specimen is obtained.¹ However, adding urine albumin testing as a reflex only when urine p/c is ≥0.11 mg/mg reduces the positive rate of that approach by 30 to 40% with only slightly increased risk in the pool with a negative result. This would allow a much more favorable insurance offer to be made in up to 1% of all applicants age 40+ as compared to use of urine p/c alone.

References

1. Fulks M, Dolan VF, Stout RL. Evaluating the risk of renal disease using urine proteinuria or urine albuminuria in the applicant with HbA1c elevation. *ON THE RISK*, December 2014.