WHICH eGFR CALCULATION OFFERS THE BEST MORTALITY PREDICTION FOR INSURANCE?

Michael Fulks, MD
fulksmd@volcano.net

Vera F. Dolan, MSPH, FALU
dolanvp@consultancy.com

Robert L. Stout, PhD
stoutr@crlcorp.com

Clinical Reference Laboratory
Lenexa, KS

Executive Summary *We compared the commonly used rule (Mayo Clinic) and CKD-EPI algorithms for the calculation of eGFR. There was substantial disparity in the distribution of results, but similar efficacy in predicting mortality risk. Both algorithms perform substantially better than the creatinine alone, but each requires a separate underwriting table linking eGFR results to the corresponding relative risk.*

Introduction

The use of serum creatinine level to assess the glomerular filtration rate (GFR) of the kidneys has limited accuracy because serum creatinine is dependent not just on excretion by the kidneys, but by the level of creatinine production. Because it is a waste product of muscle (creatine) metabolism, the influence of muscle mass on serum creatinine level needs to be adjusted for. The commonly used estimated GFR (eGFR) calculations do this by incorporating age and sex into the calculation, improving prediction of actual GFR and the associated mortality risk.

Earlier eGFR algorithms were based on and optimized to individuals with impaired renal function as that was the group of interest. They tend to underestimate renal function in healthy adults. In 2004, the Rule (Mayo clinic or quadratic) eGFR equation was developed using individuals with normal renal function as well as individuals with impaired function to create an algorithm more accurate for general population use.[1] This eGFR calculation has been in widespread use in the insurance industry and the basis for several eGFR calculators.

More recently, the Chronic Kidney Disease Epidemiology Collaboration (associated with many of the prior eGFR algorithms) released the CKD-EPI eGFR algorithm, also designed to screen renal function in groups where most had "normal" rather than impaired function.[2] This equation is in widespread use by clinical laboratories and increasingly by insurers and reinsurers.

Our goal was to determine the predictive power of eGFR by both algorithms for all-cause mortality in insurance applicants, while taking advantage of serum glucose results to adjust the serum creatinine for presence of pseudo-creatinines associated with extended time before centrifugation common with insurance sample handling.[3]

How the Study Was Done

The samples tested at CRL were obtained from 2001 to 2007, with mortality follow-up of the applicants associated with the samples in late 2011 by the Social Security Death Master File. Because the goal was to determine the independent impact of eGFR on all-cause mortality, those applicants with urine protein/creatinine ratios of ≥0.21 g/g or HbA1c ≥7.0% were excluded. For those with eGFR <80 mL/min (possibly lower than expected), these exclusions account for 7% of applicants but 21% of deaths. Those excess deaths increase the mortality ratio for low eGFR but might reasonably be wholly or partly attributed to proteinuria and/or diabetes instead. After these exclusions, the study group included 4.9 million applicants with 54,489 deaths.

Measurements of serum creatinine were performed on Roche Hitachi Cobas analyzers with FDA-approved reagents following the manufacturer's recommended methodology. That measured creatinine value was then adjusted downward for the likely presence of pseudo-creatinines based on the measured serum

glucose if ≤40 mg/dL.[3] This adjusted creatinine value then served as the basis for calculating the eGFR and all further analysis.

Bands of eGFR values appropriate to the Rule and CKD-EPI algorithms were determined based on distribution of values and differences in relative mortality as eGFR decreased.

Relative mortality by Cox regression analysis and receiver operator characteristics (ROC) curves were calculated using IBM SPSS 22.

What the Study Found

The accuracy for mortality prediction of each eGFR algorithm was assessed by generating an area under the curve (AUC) by a ROC calculation. The higher the AUC, the better the combination of sensitivity and specificity across the entire range of values included to produce more accurate mortality prediction. Because very low creatinine and corresponding high eGFR may be associated with low muscle mass or hyper-dynamic circulatory state and higher mortality, including such values in a ROC calculation obscured the impact of reduced renal function on the mortality outcome. Therefore, only the 9% of applicants with eGFR by Rule algorithm of ≤90 mL/min were included in each of the ROC analyses. Even then, increasing mortality associated with low creatinine limited the AUC for some age-sex groups but did not change the relative accuracy of each measurement approach.

Applicants were split by sex and age 20-49, 50-69 and 70-89 to minimize the impact of age and sex (rather than actual renal function) on the ROC analysis. Results are shown in Table 1 for eGFR by Rule, by CKD-EPI and for glucose-adjusted creatinine as a reference. Both eGFR algorithms were superior to creatinine but there was no consistent advantage in using one or the other, with each having small advantages at different age-sex combinations. Note that the inverse of creatinine is used (creatinine moves opposite to eGFR), so that results for all are shown in an identical manner.

Because both eGFR algorithms had similar accuracy and both are in common use, we determined median values by age and sex for both shown in Figure 1. The eGFR calculated by each algorithm varies by 10 mL/min or more from the other, and the relationship of eGFR between sexes was also different.

The difference in calculated eGFR based on each method required that different reference (normal) bands of eGFR be used for each when calculating relative risk and when looking at distributions by eGFR. The reference band used for Rule eGFR is ≥80 and for CKD-EPI is ≥70 mL/min. For simplicity, bands of 10 mL/min were used down to <50 mL/min and <40 mL/min, respectively. This provided reasonably comparable (but not identical) distributions and mortality ratios as shown in Table 2 for Rule and Table 3 for CKD-EPI.

Mortality and distribution of eGFR values vary by age, sex and eGFR formula, but in all cases the relative risk is low except for a small percentage of applicants (<5% at younger and <10% at oldest ages) with the lowest eGFR values.

What Do the Study Results Contribute to Risk Assessment?

When proteinuria and diabetes are excluded, the predictive power of eGFR is modest except for the lowest values. Some of this may relate to the documented inaccuracy in estimating actual GFR by any algorithm (or even by direct measurement).[4,5] Clearly, eGFR by either formula is more predictive of relative mortality than creatinine, and final decisions regarding risk related to kidney function should use those calculated values.

Using the Rule algorithm (Table 2) for males, values <60 mL/min are present in <1% of younger, 1.3% of middle and 9.5% of older ages, and have sufficient relative risk (≥2.5, 1.6 and 1.3, respectively) that additional review (even in the absence of proteinuria and diabetes) may be in order. For the younger ages, that eGFR review point may be at <70 and for the oldest at <50 mL/min depending on underwriting standards. Values <80 at younger ages and <70 mL/min at middle and older ages show gradually increasing risk.

Using the Rule algorithm for females, values <70 mL/min are present in <1% of younger, 2% of middle and 14% of older ages, and have sufficient relative risk (≥1.9, 1.7 and 1.3, respectively) that additional review (even in the absence of proteinuria and diabetes) may be in order. For the younger ages, that review point may be at <80 and for the oldest at <60 mL/min depending on underwriting standards. Values <80 mL/min at all ages show gradually increasing risk.

Using the CKD-EPI algorithm (Table 3, page 61) instead, the eGFR including a similar proportion of the population and level of risk will be approximately 10 mL/min lower than for Rule with less variation by sex. Because reported eGFR by the two algorithms is so different, separate distribution and mortality tables must be used.

Table 1. AUC for predicting mortality by kidney function test split by age band and sex (higher AUC reflects better combination of sensitivity and specificity)

	Females			*Males*		
	20-49	**50-69**	**70-89**	**20-49**	**50-69**	**70-89**
eGFR by Rule	.621	.522	.600	.547	.565	.571
eGFR by CKD-EPI	.626	.499	.553	.559	.578	.574
Creatinine (1/creat.)	.567	.468	.534	.521	.519	.546

Figure 1. Median values of eGFR Rule and eGFR CKD-EPI by decade of age and sex

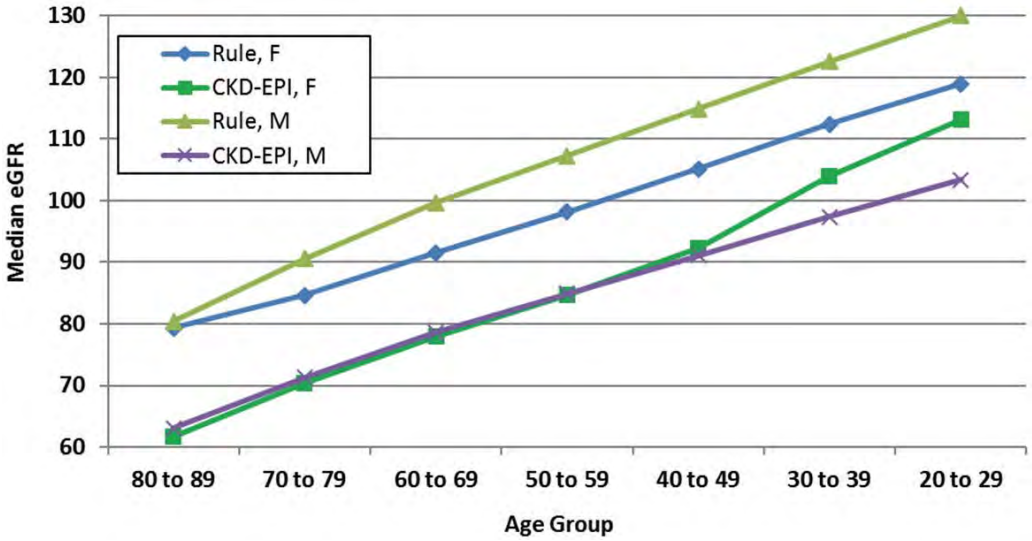

Table 2. Distribution and mortality ratios by glucose-adjusted eGFR (Rule) for age-sex combinations indicated

		Males		*Females*	
Age group	**eGFR (Rule)**	**% in band**	**MR (Cox)**	**% in band**	**MR (Cox)**
20 to 49	<50	0.1%	2.5	<0.1%	5.1
	50 to 59	0.1%	2.7	<0.1%	3.9
	60 to 69	0.4%	1.4	0.1%	1.9
	70 to 79	1.4%	1.2	0.3%	1.6
	80+ (ref)	98.0%	1.0	99.4%	1.0
50 to 69	<50	0.5%	2.7	0.3%	2.9
	50 to 59	0.8%	1.6	0.5%	2.1
	60 to 69	2.4%	1.3	1.1%	1.7
	70 to 79	5.4%	1.0	3.3%	1.3
	80+ (ref)	90.9%	1.0	94.7%	1.0
70 to 89	<50	4.3%	1.9	3.1%	2.2
	50 to 59	5.2%	1.3	3.6%	1.4
	60 to 69	9.0%	1.2	7.5%	1.3
	70 to 79	13.4%	1.0	17.5%	1.2
	80+ (ref)	68.0%	1.0	68.3%	1.0

ref=reference

Table 3. Distribution and mortality ratios by glucose-adjusted eGFR (CKD-EPI) for age-sex combinations indicated

		Males		*Females*	
Age group	**eGFR (CKD-EPI)**	**% in band**	**MR (Cox)**	**% in band**	**MR (Cox)**
20 to 49	<40	<0.1%	4.6	<0.1%	5.4
	40 to 49	0.1%	2.4	0.1%	2.6
	50 to 59	0.6%	1.5	0.6%	1.7
	60 to 69	3.1%	1.1	2.8%	1.2
	70+ (ref)	96.2%	1.0	96.5%	1.0
50 to 69	<40	0.2%	3.3	0.4%	2.7
	40 to 49	0.9%	1.8	1.3%	1.9
	50 to 59	3.9%	1.2	4.9%	1.4
	60 to 69	13.0%	1.0	12.9%	1.1
	70+ (ref)	81.9%	1.0	80.5%	1.0
70 to 89	<40	2.7%	2.1	4.0%	1.9
	40 to 49	7.0%	1.4	9.1%	1.4
	50 to 59	15.8%	1.1	17.1%	1.2
	60 to 69	24.6%	1.0	22.9%	1.0
	70+ (ref)	49.9%	1.0	46.9%	1.0

ref=reference

A potential alternative to creatinine-based measures is cystatin C. However, it is not free of variability between individuals and the test cost for insurers is in the range of $10+ rather than pennies for creatinine or eGFR based on creatinine, making cystatin C more attractive as a reflex rather than a universal screening test. With optimal specimen handling, any advantage in predictive accuracy compared to using creatinine to estimate GFR is small.[5] The adjustment for low glucose or substitution of enzymatic creatinine testing for blood samples with low glucose can substitute in part for "optimal handling."[3]

Conclusion

After excluding applicants with proteinuria and diabetes, renal function as measured by eGFR (based on creatinine adjusted for low glucose) has modest mortality prediction except for the lowest values. The eGFR by the Rule and CKD-EPI algorithms have similar overall predictive ability for mortality and both are superior to using creatinine alone. However, eGFR calculated by Rule is higher by 10 mL/min or more (depending on age and sex) than that for CKD-EPI, so separate underwriting tables must be used for each algorithm.

For the Rule eGFR algorithm, values <60 mL/min for males and <70 mL/min for females likely will require further underwriting review at younger ages and values <60 mL/min at older ages, but cut-off values will vary depending on underwriting standards. For CKD-EPI, corresponding values are <60 mL/min at younger age and <50 mL/min at older ages.

References

1. Rule AD, Larson TS, Bergstralh EJ, et al. Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. *Ann Int Med.* 2004;141:929-937.
2. Levey AS, Stevens LS, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Int Med.* 2009;150:604-612.
3. Fulks M, Dolan VF, Stout RL. Adjusting measured creatinine for low serum glucose to improve mortality prediction. *ON THE RISK.* 2014. In press.
4. Earley A, Miskulin D, Lamb EJ, et al. Estimating equations for glomerular filtration rate in the era of creatinine standardization. A systematic review. *Ann Int Med.* 2012;156:785-795.
5. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *NEJM.* 2012;367:20-29.