Glomerular filtration rate is a predictor of mortality after endovascular abdominal aortic aneurysm repair

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Objective: Clinically evident renal disease is a risk factor for mortality after aneurysm repair. Serum creatinine is widely used as a measure of renal function in the preoperative evaluation of patients. Unfortunately, serum creatinine concentration is influenced by muscle mass, hydration status, and glomerular filtration rate (GFR). Calculated GFR, which takes predictors of muscle mass such as age, gender, and weight into account, is a more sensitive determinant of renal function than serum creatinine. We hypothesized that GFR would more accurately predict mortality after EVAR than serum creatinine.

Methods: We retrospectively evaluated our database of 398 patients who underwent EVAR with the AneuRx device between October 1999 and October 2004. There were 340 men and 58 women with a mean age of 73. GFR was calculated using the Cockcroft-Gault equation. The patients were divided into four quartiles by preoperative GFR: I (7 to 45), II (45 to 60), III (61 to 79), and IV (≥80). Survival was estimated with the Kaplan-Meier method, and heterogeneity of mortality across strata was evaluated using the log-rank test. The GFR quartiles were compared with clinically accepted criteria for abnormal renal function (serum creatinine level ≥1.7).

Results: Actuarial survival at 48 months was 61.5%, 70.5%, 86.0%, and 85.7% for GFR quartiles I to IV, respectively ($P < .003$). Thirty-day mortality was 2.2% in quartile I, 3.2% in quartile II, and 0 in quartiles III and IV ($P = .03$ for q1 + q2 vs q3 + q4, $P < .02$ for q2 vs q3 + q4). Survival curves for quartiles II to IV were statistically indistinguishable, with quartile II running tangential to the two higher quartiles after the perioperative period. Quartile I fared significantly worse than the other three quartiles for the entire follow-up period ($P < .005$). According to American Kidney Foundation criteria (GFR <90), 83.3% of patients had abnormal renal function compared with 16.1% with abnormal serum creatinine (>1.7) ($P < .0002$).

Conclusion: The risk of perioperative and long-term mortality in patients undergoing EVAR is more accurately stratified by using calculated GFR than serum creatinine alone. A GFR <45 is associated with decreased survival after EVAR. Perioperative mortality at a GFR of 45 to 60 is comparable with that of the lower quartile (GFR <45), but late survival is comparable with that of patients with GFR >60. The finding of increased risk of early mortality in patients in the 45 to 60 GFR range, with survivors enjoying good long-term outcome, suggests that these patients may most benefit from the use of alternative contrast agents and periprocedural renal protection techniques. (J Vasc Surg 2006;43:14-8.)

Preoperative renal dysfunction is a risk factor for mortality after aneurysm repair.[1-4] Accurate identification of preoperative risk factors allows clinicians to develop alternative treatment strategies, provide better informed consent, and assess outcome and quality of care. Traditionally, serum creatinine has been used as a preoperative measure of renal function. Although creatinine is a specific marker for renal function, it may be insensitive to mild and moderate degrees of renal impairment, because it depends on predictors of muscle mass such as age, gender, and body weight. As a result, patients with subclinical renal disease may go undiagnosed because of a normal serum creatinine value.

According to the National Kidney Foundation guidelines, estimates of glomerular filtration rate (GFR) are the best overall indices of renal function.[5] An index that accounts for predictors of muscle mass in addition to serum creatinine is a more sensitive determinant of renal function. GFR is most commonly estimated using the Cockcroft-Gault[6] equation, which calculates creatinine clearance from serum creatinine, age, gender, and body weight. We hypothesized that GFR would be a more accurate predictor of mortality after endovascular abdominal aortic aneurysm repair (EVAR) than serum creatinine.

METHODS

Between October 1999 and October 2004, we performed 398 EVAR procedures using the AneuRx device (Medtronic, Santa Rosa, Calif) in 340 men and 58 women (mean age, 73 years). All patients undergoing endovascular aortoiliac aneurysm repair at our institution are prospec-

tively entered in a database for long-term follow-up and comparison of their outcomes. These patients and their associated data were reviewed under a Health Insurance Portability and Accountability Act-compliant protocol approved by the Washington University Human Studies Committee. For the purpose of this publication, the review of the database was supplemented with a retrospective review of medical records.

Glomerular filtration rate was calculated using the Cockcroft-Gault equation: Creatinine clearance (mL/min) = (140 – age/years) × (body weight/kg)/72 × serum creatinine (mg/dL) × (0.85 if female).

Twenty patients were excluded because of incomplete data. The preoperative serum creatinine was used for this calculation. Preoperative GFR was used to divide the patients into four quartiles: I (7 to 45), II (46 to 60), III (61 to 79), IV (≥80).

Descriptive statistics for the cohort were computed by using standard measures of frequency and central tendency. Survival outcome was evaluated with logistic regression and contingency table approaches at 30 days and along a 60-month distribution of failure times by using Kaplan-Meier and Cox proportional hazards regression.

For univariate analysis, categoric variables were analyzed by contingency table, and continuous variables were divided into quartiles for contingency table and stratified survival analysis. Continuous variables were also left in their continuous distributions for univariate logistic regression and Cox regression analyses.

For the 30-day analysis, serum creatinine was dichotomized at 1.7, which is a standard clinical criterion for an abnormal value at our institution for men aged ≥69 years old. No 30-day deaths were present in the upper two quartiles of GFR, so we dichotomized GFR at the median. None of the continuous risk factors departed grossly from normality. Multivariable analyses were conducted by using logistic regression and Cox regression. All computations were performed with SAS software version 8.2 (SAS Inc, Cary, NC).

RESULTS

Actuarial survival at 48 months for GFR quartiles I to IV was 61.5%, 70.5%, 86.0%, and 85.7%, respectively; 30-day mortality was 2.2% in quartile I, 3.2% in quartile II, and 0% in quartiles III and IV ($P = .03$ for q I + II vs q III + IV). Survival curves for quartiles II to IV were statistically indistinguishable, with quartile II running tangential to the two higher quartiles after the perioperative period (Fig 1). Patients with the lowest GFR (quartile I) did significantly worse than the other three quartiles for the entire follow-up period ($P < .0005$). According to the American Kidney Foundation criteria (GFR <90), 83.3% of patients had abnormal renal function compared with 16.1% with abnormal creatinine (1.7 mg/dL) ($P < .0002$). For short-term mortality, significant univariate predictors were age and GFR (Table I). For long-term mortality, GFR was predictive (Fig 1), but serum creatinine failed to meet statistical significance
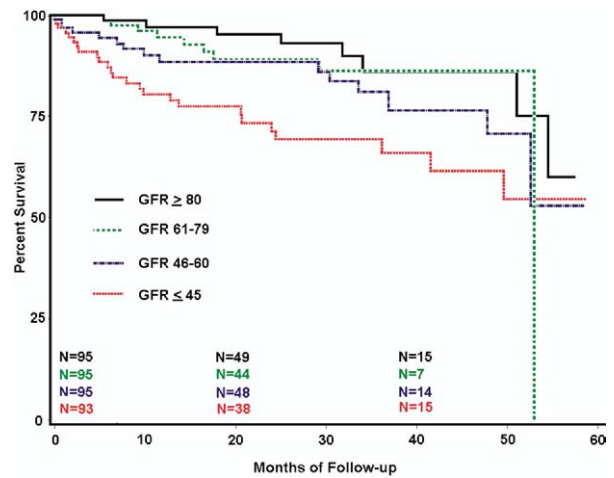

Fig 1. Survival by glomerular filtration rate *(GFR)*. At key time points (0, 20, 40 months), the number of patients in each quartile is listed above.

(Fig 2). In multivariable Cox proportional hazards regression analysis, GFR was significant ($P < .004$), but creatinine failed to reach significance ($P = .11$)

DISCUSSION

Renal insufficiency is a risk factor for mortality after abdominal aortic aneurysm repair.[7] Serum creatinine has traditionally been used as a screening tool for renal dysfunction. The serum creatinine value can be influenced by a variety of factors independent of GFR, including tubular secretion and reabsorption, endogenous production, extrarenal elimination, and medications.[8] As a result, serum creatinine values may be insensitive to mild or moderate degrees of renal dysfunction.

One study of 2,781 patients in the community found "a substantial prevalence of significantly abnormal renal function among patients identified by laboratories as having normal range serum creatinine."[9] The Third National Health and Nutrition Examination Survey (NHANES III) found that the prevalence of chronic kidney disease in the United States population was 11% (19.2 million).[10] Advanced age, diabetes mellitus, and hypertension were found to be key predictors of chronic kidney disease. The study concluded that, "chronic kidney disease is common and warrants improved detection and classification using standardized criteria to improve outcomes." In a recent study, we found that the incidence of subclinical renal disease in a patient population undergoing thoracoabdominal aortic aneurysm repair was >70%.[11] In other words, >70% of patients with normal serum creatinine values had an abnormal GFR.

Owing to the severe limitations in using serum creatinine as the only screening tool for renal dysfunction, a more sensitive measure of GFR becomes necessary. The inherent difficulties associated with measuring creatinine clearance (GFR) with a 24-hour urine collection have resulted in the development of a number of formulas for estimating GFR.
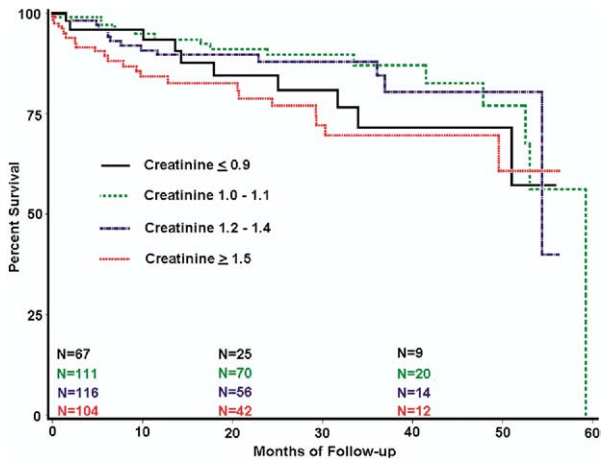
Table I. Thirty-day mortality

Variable	No. patients (%)	No. deaths (%)	Odds ratio*	95% CI†	P‡
Overall	398 (100)	5 (1.3)			
Age					
48–68	107 (26.9)	0 (0.0)	1.18	1.01–1.35	.02
69–73	97 (24.4)	0 (0.0)			(.006)
74–78	106 (26.6)	1 (0.9)			
79–91	88 (22.1)	4 (4.5)			
Female	58 (14.6)	1 (1.7)	1.47	0.16–13.42	.73
Male	340 (85.4)	4 (1.2)	1		
GFR ≤60§	184 (48.7)	5 (2.7)	11.9	0.65–217.1	.03
GFR >60§	194 (51.3)	0 (0.0)	1		
Creatinine					
≥1.7	64 (16.1)	2 (3.1)	3.56	0.58–21.74	.15
<1.7	334 (83.9)	3 (0.9)	1		

*For dichotomous variables, the odds ratio represents a test against a reference category whose referent odds ratio = 1. For continuous data, the odds ratio refers to the increase in odds associated with a one-unit increase in the variable value. Although continuous data are presented in quartiles, the odds ratios are against the continuous variable.

†Reflects the units against which its companion odds ratio is computed. Confidence intervals *(CI)* are test-based.

‡Probability of type I statistical error (common *P* value). V alues without parentheses are Pearson χ^2 probabilities. Probability values in parentheses are univariate logistic regression likelihood ratio *P* values.
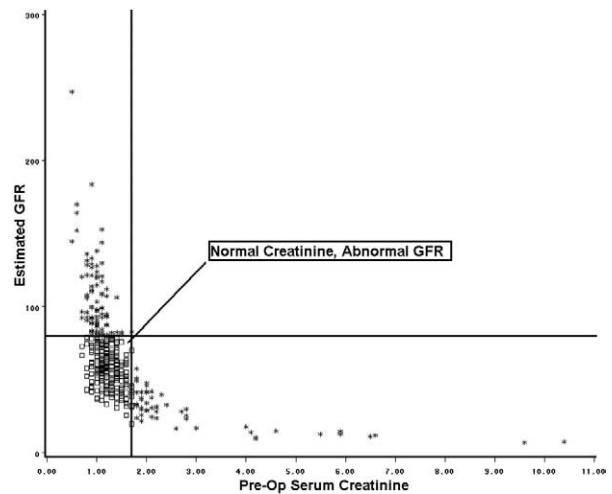
§Glomerular filtration rate *(GFR)* could not be computed for 20 cases.

Fig 2. Survival by serum creatinine *(Cr)*.

Fig 3. Discrimination of glomerular filtration rate *(GFR)* vs that of serum creatinine in detecting subclinical kidney disease. Only 16.1% of patients had an abnormal creatinine value, but 83.3% of patients had an abnormal GFR.

In a study comparing 10 equations used to estimate creatinine clearance (GFR), Spinler et al[12] found the Cockcroft-Gault formula, which uses serum creatinine, age, sex, and body weight, to be one of the most accurate. In the NHANES III study, GFR was estimated using the Modification of Diet in Renal Disease Study equation (MDRD) and compared with the Cockcroft-Gault equation for creatinine clearance.[6] The Cockcroft-Gault equation estimates closely matched the MDRD, but showed a "steeper decline with age," and were "lower in non-Hispanic blacks." For the purposes of this study, we selected the Cockcroft-Gault equation for estimating GFR because of its simplicity, accuracy, and availability of the required information in our database.

Our study has demonstrated the sensitivity of GFR in detecting subclinical renal disease compared with serum creatinine alone. Only 16.1% of patients had an abnormal creatinine value, but 83.3% of patients had an abnormal GFR (Fig 3).

Our results indicate that GFR is a more sensitive predictor of perioperative and long-term mortality than serum creatinine. Five patients reached the end point of mortality at 30 days (Table I). Among them, serum creatinine was not predictive (three patients had an abnormal creatinine and two had normal creatinine); however, GFR was predictive: all 5 patients had an abnormal GFR. The results for long-term mortality us-

Table II. Multivariable survival analysis by Cox proportional hazards regression

Variable	Parameter estimate	Hazard ratio	95% CI	P
GFR	−0.01975	0.980	0.967–0.994	.004
Creatinine	0.15418	1.167	0.967–1.408	.108

CI, Confidence interval; *GFR*, glomerular filtration rate.

ing the Kaplan-Meier method showed a similar trend for the predictive power of GFR.

The multivariable survival analysis summarized in Table II clearly demonstrates that GFR is able to account for all of the prognostic information available through creatinine and to retain significant predictive power. The data demonstrate that for every point increase in GFR, the mortality hazard ratio was reduced by 2%.

CONCLUSION

This study suggests that the calculation of preoperative GFR for patients undergoing EVAR has prognostic value. This information will allow physicians to better tailor the patient's long-term medical care. Consideration should also be given to the use of perioperative renal protection techniques, alternative contrast agents, and imaging modalities. Finally, early recognition of postoperative renal failure and a multimodality approach to its treatment may improve results in high-risk patients.

AUTHOR CONTRIBUTIONS

Conception and design: AA, HJS, CCM, JCP, GAS
Data collection: LAM, LAS
Analysis and interpretation: AA, LAS, CCM, BGR
Writing the article: AA, LAS, CCM, BGR
Critical revision of the article: AA, LAS, CCM, BGR, HJS, GAS
Final approval of the article: GAS
Statistical analysis: CCM

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DISCUSSION

Dr G. Patrick Clagett (Dallas, Tex). I have a simple question: How do these people die? And is there a direct pathophysiologic link between the abnormal GFR and their death, or is it simply a marker? Because if it is just a marker, correcting renal function preoperatively or taking measures to prevent deterioration may not have any influence on the outcome.

Dr Azizzadeh. Of the 5 patients who died in the perioperative period, 4 died from cardiovascular complications. This is consistent with abnormal GFR being a marker for generalized atherosclerotic disease.

In the calculation for GFR vs mortality over the long term, patients in quartile II did significantly worse in the perioperative period. I think, in this instance, the use of alternative imaging technology and contrast agents may be helpful in decreasing the postoperative renal morbidity secondary to contrast nephropathy and possibly improving mortality.

Dr John Blebea (Philadelphia, Penn). What baseline serum creatinine values did you use? Since most of these patients would have undergone contrast studies, either subtraction angiography or CT angios in the preoperative time period in addition to the hydration associated with these studies, these could very significantly affect your measured serum creatinine levels and also estimated creatinine clearance. Did you utilize as the baseline creatinine the value before the CT or angiogram or that following these studies? Could you go back and compare the results both ways and see if it would have affected your results?

Dr Azizzadeh. Most of these patients underwent outpatient procedures and this was done in the outpatient laboratory. We used the preoperative serum creatinine. Usually there was no angiography or immediate CT scan done prior to that measurement.

Dr Kimberley Hansen (Winston-Salem, NC). In your proportional hazards regression model, did you adjust for age? Since age appears in the Cockcroft-Gault equation, the effect on long-term survival may be an age effect and not a renal function effect.

Dr Azizzadeh. Age was evaluated in the Cox model but was not statistically significant when added to the other terms.

Dr Timothy Roush (Charlotte, NC). I have a question regarding your protocol when you are doing your EVAR. Our group published a paper in the *New England Journal of Medicine* using a fairly simple bicarbonate protocol for renal protection last year. In addition, we will usually use some form of nonionic contrast.

My question concerns these mandatory follow-up studies and their relationship to renal failure. A lot of these patients that we are following are going to go through radiology for CT scans. At our institution, 150 mL of ionic contrast will be given to patients with a creatinine of up to 1.4.

I was curious what your thoughts are in relationship to this entity of subclinical renal insufficiency, ongoing mortality, and how that relates to some of the statistics that we're seeing. Is there, in fact, an ongoing decrement in renal function in patients that we are now clinically following who have had successful EVAR and does that explain some of the numbers that we're seeing with decreased survival later on?

Dr Azizzadeh. I think renal failure continues to remain a risk factor for mortality. Consideration should be given to the use of alternative contrast agents and imaging modalities.

Dr Michele Carmo (Rochester, Minn). You showed in your multivariable analysis that creatinine is not statistically significant, and I was wondering if it was significant in the univariate analysis?

Did you check for colinearity existing between the GFR and creatinine in the multivariable analysis? We know that GFR depends on creatinine and they may travel together.

Dr Azizzadeh. The creatinine failed to reach significance in all the statistical analysis that was performed both in the 30-day and long-term mortality as well as the multivariable analysis. None of our regression diagnostics showed important colinearity.