Preoperative Estimates of Glomerular Filtration Rate as Predictors of Outcome after Surgery

A Systematic Review and Meta-analysis

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What We Already Know about This Topic

- Estimated glomerular filtration rate is a better estimate of kidney function than increased creatinine concentration

What This Article Tells Us That Is New

- This meta-analysis of 49 studies finds that estimated glomerular filtration rate less than 60 ml·min·1.73 m^{-2} is associated with a three-fold increase in 30-day mortality
- There was a strong nonlinear increase in mortality at lower preoperative estimated glomerular filtration rates

ABSTRACT

Background: Kidney dysfunction is a strong determinant of prognosis in many settings.

Methods: A systematic review and meta-analysis was undertaken to explore the relationship between estimated glomerular filtration rate (eGFR) and adverse outcomes after surgery. Cohort studies reporting the relationship between eGFR and major outcomes, including all-cause mortality, major adverse cardiovascular events, and acute kidney injury after cardiac or noncardiac surgery, were included.

Results: Forty-six studies were included, of which 44 focused exclusively on cardiac and vascular surgery. Within 30 days of surgery, eGFR less than 60 ml·min·1.73 m^{-2} was

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

◆ This article is accompanied by an Editorial View. Please see: Augoustides JG, Neuman MD, Fleisher LA: Estimated glomerular filtration rate: More bang for the buck. ANESTHESIOLOGY 2013; 118:775–6.

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associated with a threefold increased risk of death (multivariable adjusted relative risk [RR] 2.98; 95% confidence interval [CI] 1.95–4.96) and acute kidney injury (adjusted RR 3.13; 95% CI 2.22–4.41). An eGFR less than 60 ml·min·1.73 m^{-2} was associated with an increased risk of all-cause mortality (adjusted RR 1.61; 95% CI 1.38–1.87) and major adverse cardiovascular events (adjusted RR 1.49; 95% CI 1.32–1.67) during long-term follow-up. There was a nonlinear association between eGFR and the risk of early mortality such that, compared with patients having an eGFR more than 90 ml·min·1.73 m^{-2} the pooled RR for death at 30 days in those with an eGFR between 30 and 60 ml·min·1.73 m^{-2} was 1.62 (95% CI 1.43–1.80), rising to 2.85 (95% CI 2.49–3.27) in patients with an eGFR less than 30 ml·min·1.73 m^{-2} and 3.75 (95% CI 3.44–4.08) in those with an eGFR less than 15 ml·min·1.73 m^{-2}.

Conclusion: There is a powerful relationship between eGFR, and both short- and long-term prognosis after, predominantly cardiac and vascular, surgery.

MAJOR surgery results in significant physiological stress and may be associated with adverse early and long-term outcomes. With an aging population surgery is now performed on more than 200 million patients annually, many with comorbidities and advanced disease. The ability to stratify risk ensures that patients are well informed, clinicians can decide on the most appropriate management, and that suitable perioperative care is planned.

Renal dysfunction is an established marker of an adverse outcome, in particular cardiovascular complications, in many settings.[1–3] Its role in patients undergoing surgery is not, however, as clearly defined. Although individual studies have identified kidney dysfunction as predictor of worse perioperative outcome these have varied in terms of the measure used, the threshold(s) chosen, the surgical population, the outcomes selected, and the duration of follow-up.

Traditionally, renal function has been estimated using serum creatinine levels, often dichotomized around a largely arbitrary level. These have been incorporated into some perioperative risk scoring systems[4–6] but not in all,[7,8] reflecting residual uncertainty about the independence and strength of the relationship. Indeed, although increased creatinine levels (>2.0 mg/dl [177 μM]) are included in the most commonly used risk prediction score for noncardiac surgery, the Revised Cardiac Risk Index,[5] they were not found to be significant predictors of outcome in the validation cohort used in this study.[5] Likewise, although the American Heart Association/American College of Cardiology 2007 guidelines on noncardiac surgery[9] identify "renal insufficiency" as an intermediate clinical risk factor they acknowledge the lack of good quality evidence in this setting.

It is now generally accepted that creatinine is an inexact measure of kidney function and is limited in defining mild renal impairment.[10,11] A variety of more precise measures have been described and used for risk stratification. In particular, the estimated glomerular filtration rate (eGFR) can be derived by combining creatinine with other demographic parameters and is a more accurate indicator of renal function,[12–14] identifies milder degrees of renal dysfunction,[15–17] and predicts cardiovascular and renal outcomes in diverse populations.[1,18] For these reasons, the National Kidney Foundation recommends[12] that eGFR, calculated using the Cockcroft-Gault[19] or Modification of Diet in Renal Disease study equations,[13] be used to determine renal function in adults, particularly those with, or at risk of, cardiovascular disease.[20]

Against this background, the aim of the current systematic review and meta-analysis of the literature is to clarify the nature, strength, and consistency of the relationship between eGFR and adverse outcomes (all-cause mortality, cardiovascular events, and acute kidney injury) after any type of surgery.

Materials and Methods

Study Selection

We included prospective or retrospective cohort studies that reported data on preoperative eGFR (or creatinine clearance) as predictors of postoperative adverse events. When eGFR was calculated by different formulae in the same article, and data were presented for each method separately, we used the most recent, validated, method of calculation. We excluded articles that were not cohort studies, articles that measured only postoperative renal function as a predictor, articles that did not describe the outcomes of interest, and articles on transplant surgery.

Outcomes

The outcomes of interest were all-cause mortality, composite cardiovascular events, and AKI. Composite cardiovascular events were defined as acute myocardial infarction, heart failure, cardiac arrest, cardiovascular death, and stroke, or as defined by the study authors. AKI was collected according to the definitions used in the studies reporting this outcome, though these varied considerably. Both short-term (in hospital or up to 30 days postoperatively) and long-term (any follow-up beyond 30 days) outcomes were assessed.

Search Strategy

A prospective study protocol was devised and followed (see Supplemental Digital Content 1, http://links.lww.com/ALN/A910, which outlines the search protocol).The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed.[21] Two reviewers (J.F.M. and I.R.) independently searched the literature from Medline, EMBASE, CINAHL, and Cochrane central register of controlled trials up to May 17, 2010. No language restrictions were applied. A quality assessment tool was used to ensure selected articles were consistent with the study design and to maintain uniformity between reviewers. Disagreement on article inclusion was resolved by discussion with a third party (G.S.H. and C.K.C.).

Data Extraction and Quality Assessment

Relevant data, expressed as relative risk (RR), hazard ratio, or odds ratio, were extracted from each article and entered into a standardized database. For studies that used differing categories of eGFR, we extracted data into the equivalent stages of chronic kidney disease as defined by the Kidney Disease Outcomes Quality Initiative.[12] Data were expressed as either short or long term depending on the duration of follow-up. To facilitate the analysis and interpretation of data, estimates of GFR derived from different formulae (almost exclusively the Cockcroft-Gault or modified diet in renal disease study equations) were considered to be equivalent.

Methodological quality for each study was assessed based on guidelines for assessing quality in prognostic studies.[22] Two reviewers (J.F.M. and C.K.C.) independently used these guidelines to assess bias from six potential sources. The degree to which the study had taken adequate measures to eliminate the potential for bias in each domain was graded as "yes" (when there was clear evidence that adequate measures had been taken), "no" (when the measures taken were inadequate to eliminate bias), "not reported" (when the article did not report the measures taken in this domain), and "unclear" (where the adequacy of the reported measures was difficult to assess). The control for potential confounding factors was defined as being of adequate quality ("yes") if some degree of multivariable assessment had been performed and the variables included had been clearly reported.

Statistical Analysis

Meta-analysis was performed where sufficient studies contributed data measuring an association between preoperative eGFR and the risk of a relevant outcome. Results were pooled using random effects meta-analyses to calculate summary estimates of RRs with confidence intervals (CIs) using the function Metan in STATA software version 11 (College Station, TX). Multivariable adjusted RRs were determined using the maximally adjusted model presented in the article. Where data were presented categorically by range of eGFR, the nature of the association was determined by using meta-regression models (Metareg in STATA). When comparing the utility of serum creatinine and eGFR in predicting 30-day mortality only unadjusted binary data were available.

The trend of the association between increasing levels of GFR and risk of mortality was examined using methodology outlined in a previous community-based systematic review and meta-analysis.[1] Eight studies provided RRs of 30-day mortality by subgroups of GFR. The level of GFR in each subgroup was categorized by substituting the midpoint of the range for interval data and adding or subtracting 15 ml·min·1.73 m^{-2} from bounded data. The association between index levels of GFR and risk of mortality was estimated using a logistic model with a random intercept for study to take account of autocorrelation of estimates generated from the same study. The estimated risk and 95% CIs were plotted against the corresponding index levels of GFR using a bubble plot graph, with the size of the circles proportional to the size of the study (SAS/STAT version 9.2, Cary, NC).

The percentage of variability across studies attributable to heterogeneity, rather than chance, was estimated using the I^2 statistic.[23] Subgroup analysis was conducted to explore potential causes of heterogeneity and account for inherent bias due to selection, classification, and confounders among the different studies. Subgroups assessed included: surgery type (cardiac or noncardiac), age, sex, hypertension, heart failure, diabetes, method of GFR estimation (Cockcroft-Gault or modified diet in renal disease study equation), prospective or retrospective study, length of follow-up, emergency surgery, and advanced kidney disease (defined as dialysis dependence and/or an eGFR <15 ml·min·1.73 m^{-2}). Publication bias was tested by the use of funnel plots (Metafunnel in STATA) using both Egger and Begg tests for heterogeneity.[24]

Results

Characteristics of Included Studies

The search incorporated 4,828 articles of which 150 were selected for abstract review. A further 60 potential articles were identified from bibliography review. A total of 46 articles met inclusion criteria for the review.[16–18,25–67] A flowchart outlining the search results is shown in figure 1.

Of the included studies, 28 involved cardiac surgery[16–18,29,30,32,34,36–40,42–44,47,51,53,56–59,61–64,66,67] and 18 noncardiac surgery,[25–28,31,33,35,41,45,46,48–50,52,54,55,60,65] of which 16 exclusively related to vascular surgery.[26,27,31,33,35,41,45,46,48–50,52,54,55,60,65] The average age of study participants was 65 yr and 59% were male. Twenty-five studies excluded patients with severe renal disease.[17,25,30,32,35–41,43,44,48,49,51,53,55,59–64,66,67] Most commonly, this was defined as dialysis dependence though some studies excluded patients with an eGFR below 30 ml·min·1.73 m^{-2}. Six studies specifically excluded emergency surgical cases from their analysis.[18,29,30,50,51,65] Fifteen studies were prospective[15,17,18,25,28,29,35,38,42,43,51,57,59,62,65] and 31 retrospective.[16,26,27,30–34,36,37,39–41,44–50,52–56,58,60,61,63,64,66] Of the 18 studies[17,18,28,29,35,37,39,42–45,50,52,56,60,62,64,65] that performed follow-up after hospitalization, the average length of follow-up was 5.9 yr. The characteristics of the studies are outlined in table 1.

With regard to preoperative measurement of renal function, 26 articles calculated eGFR with the Cockcroft-Gault equation[25,26,28,31,33,36,37,40,41,43–47,51,54,56–63,65,66] and 18 used the Modified diet in renal disease study equation.[16–18,27,29,30,32,34,35,38,39,48–50,52,53,55,64] One article used serum cystatin C[42] and derived eGFR with a specific cystatin c-based formula.[68] Where data were presented as eGFR, the studies varied in definition of what was considered an abnormal eGFR, by either binary representation or stage of eGFR decline.

The methodological quality of each study is shown in appendix 1, table 2. Ten studies did not adequately report

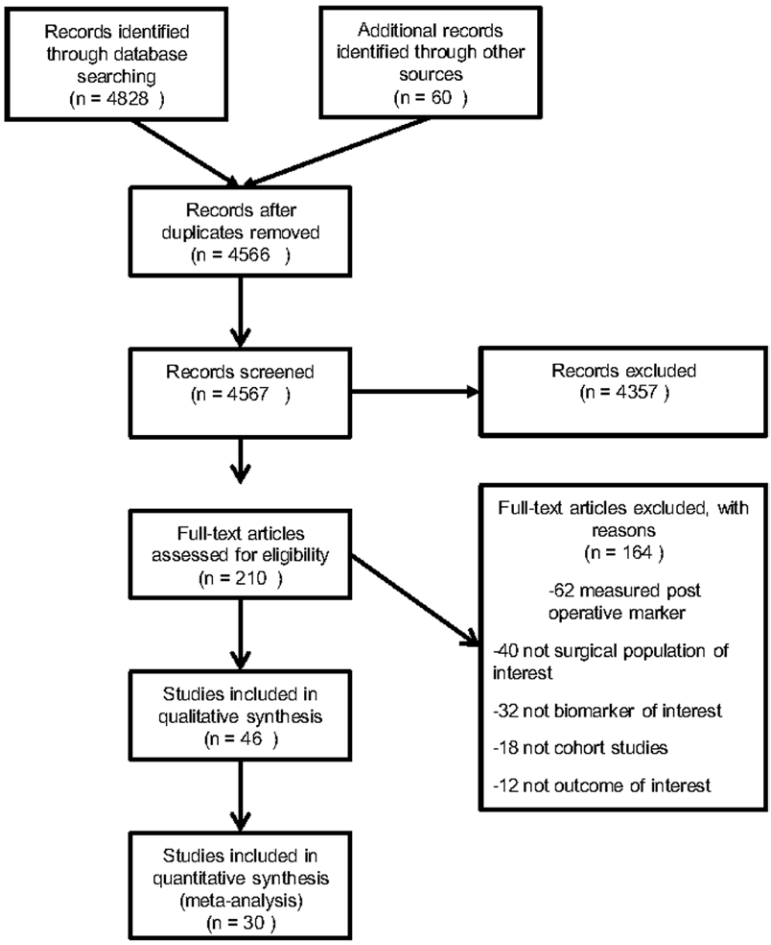

Fig. 1. Flow diagram of study selection.

attrition.[25,27,31,35,41,45,46,54,58,59] Otherwise most studies satisfied the qualitative assessments in the other domains of potential bias. Publication bias was detected in analysis of all cause mortality, demonstrated in the final sentence of paragraph 3 on this page, and also acute kidney injury, which is discussed in the second paragraph on page 14.

All-cause Mortality

Data regarding the relationship between eGFR and all-cause mortality were available for eGFR as a categorical variable (14 studies representing 19,993 patients),[17,18,26,28,29,38,39,43,47,52,56,63–65] and for multiple categories of eGFR (14 studies representing 586,516 patients),[16–18,34,36,37,39,44,48–50,53,55] as a continuous variable (16 studies representing 30,734 patients),[17,18,28,29,31,33,34,37,39,41–43,46,50,59,60] or as both a categorical and continuous variable (9 studies representing 20,182 patients).[17,18,28,29,34,37,39,43,50]

An eGFR less than 60 ml·min·1.73 m^{-2} was associated with an increased risk of all-cause mortality in the short term (unadjusted RR 3.68, 95% CI 2.71–4.99; multivariable adjusted RR 2.98, 95% CI 1.95–4.96, I^2 53.8%; fig. 2), and long-term (unadjusted RR 2.15, 95% CI 1.87–2.46; multivariable adjusted RR 1.61, 95% CI 1.38–1.87, I^2 36.5%; fig. 2). Subgroup analysis (figs. 3 and 4) showed significant heterogeneity according to length of follow-up, with a reduced though still significant effect (RR 1.47, 95% CI 1.31–1.64; P = 0.03) from studies that followed outcomes for more than 5 yr.[39,56,65] There was also a nonsignificant trend (P = 0.09) toward a stronger relationship in retrospective studies compared with that in prospective studies. Comparison between binary data calculated from the Cockcroft-Gault and the modified diet in renal disease study equations showed that the method used to estimate GFR had no significant effect on the RR that was observed.

Where data were present for categories of eGFR, the pooled results demonstrate an increased risk of death with a lower eGFR. Using meta-regression models, a significant inverse exponential association was observed between the category of eGFR and the risk of death during short-term follow-up (fig. 5). In relative terms, the estimated relative odds for death within 30 days of surgery associated with an eGFR of 60, 30, and 15 were 2.04, 4.17, and 6.00, respectively (with an eGFR of 90 ml·min·1.73 m^{-2} used as the reference).

Many studies reported the risk of short- and long-term mortality in terms of the excess hazard associated with a defined decline in eGFR, most commonly a reduction of

10 ml·min·1.73 m^{-2}. These data assume a linear relationship between declining eGFR and outcome. This was evident in some cohorts,[18,29,42] but not in all,[17] and in several studies[29,33,46,59] was not reported. Accepting this limitation, an analysis of continuous data showed that, on average, for every 10 ml·min·1.73 m^{-2} decline of eGFR, the RR of death within 30 days was 1.27 (95% CI 1.23–1.31, I^2 0%; fig. 6).

Major Adverse Cardiovascular Events

No studies reported data on cardiovascular events within the first 30 days of surgery. Meta-analysis was conducted using data from three studies representing 8,388 patients reporting cardiovascular events during long-term follow-up.[29,37,39] The pooled results demonstrate an unadjusted RR of 1.81 (95% CI 1.60–2.02) for an eGFR less than 60 ml·min·1.73 m^{-2}. After multivariable adjustment the RR was 1.49 (95% CI 1.32–1.67, I^2 0%; fig. 7).

Acute Kidney Injury

The risk of AKI was determined in eight studies (representing 17,679 patients) as a binary variable,[25,30,40,47,51–53,61] and in five studies (representing 554,403 patients) by category of eGFR.[16,32,49,53,66] Unadjusted data were not available for analysis. Definitions of AKI varied markedly among the studies that contributed data and included an increase in serum creatinine by 25% by the third postoperative day and/or commencement of dialysis[30]; postoperativeserum creatinine more than 150 μM,[47] or dialysis requirement alone.[61] The risk associated with an eGFR less than 60 ml·min·1.73 m^{-2} was reported by six studies, and the multivariable adjusted RR of AKI was 3.13 (95% CI 2.22–4.41, I^2 44%; fig. 7). Subgroup analyses (fig. 8) showed the prognostic importance of a lower preoperative eGFR was lower in studies that excluded emergent surgery (adjusted RR 1.68, 95% CI 1.09–2.59; P value for heterogeneity = 0.003). There was also a trend for studies with more than 1,000 participants to report a weaker association than studies with a smaller sample size. The risk associated with a reduced eGFR was also attenuated after adjusting for heart failure, with every 10% increase in heart failure rate reducing the RR for AKI by 32% (95% CI 7–50%; P value for heterogeneity = 0.015). Postoperative renal outcomes according to eGFR category were available from four studies but meta-analysis was not performed due to limited data and significant heterogeneity among study results.

Comparison of the Ability of Creatinine and eGFR to Predict 30-Day Mortality

Nine studies,[17,18,26,28,29,47,57,60,63] representing 11,571 patients, provided unadjusted binary data of either creatinine, eGFR, or both to predict 30-day mortality in the same cohort. Both measures of renal function were strong predictors of this outcome (RR for eGFR < 60 ml·min·1.73 m^{-2} 3.68, 95% CI 2.71–4.99, I^2 = 18.2%; RR for creatinine above threshold defined by study 2.80, 95% CI 1.57–5.00, I^2 = 69.3%; fig. 9). However, comparison of the two markers showed no difference (χ^2 = 0.40, P = 0.40).

The pooled area under the receiver operating characteristic curves (c-statistic) was derived from five studies (representing 20,368 patients).[36,39,41,59,64] The c-statistic for creatinine was 0.65 (95% CI 0.59–0.71) and for eGFR 0.70 (95% CI 0.64–0.78); there was, however, considerable heterogeneity in the results for both measures. Comparison between the two markers showed no significant difference (χ^2 = 1.13, P = 0.29).

Discussion

Renal dysfunction is a well-established marker of cardiovascular risk in many settings. In patients undergoing surgery, chronic kidney disease is recognized as an important determinant of a worse outcome and is included in several,[4–6] though not all,[7,8] risk scores. However, until recently, studies have almost exclusively used creatinine, usually used as a dichotomous variable so that it identifies patients with moderate to severe renal dysfunction. Likewise, the single previous systematic review on this area focuses on the excess perioperative risk associated chronic kidney disease, primarily identified using preoperative creatinine measurements.[69]

The current study supports and adds to this existing literature. In particular, it addresses the prognostic importance of the preoperative eGFR. This reflects the general acceptance that, although the eGFR has limitations,[70] it is a more accurate measure of renal function than creatinine and enables milder degrees of renal dysfunction to be detected.[12,71] For these reasons, eGFR is now recommended as the optimal measurement of renal function and has in recent years been increasingly used in the perioperative setting. Our review consolidates this research. In particular, we have confirmed that eGFR predicts both short- (<30 days) and long-term mortality after, predominantly cardiac and vascular, surgery. The prognostic importance of the eGFR is apparent regardless of the method of calculation. We also confirm that there is a nonlinear relationship between preoperative eGFR category and early postoperative mortality but that even mild kidney dysfunction imparts a higher risk. The study also demonstrates that the relationship between renal function and postoperative prognosis persists despite correction for potential confounding variables and is consistent for several crucial outcomes and in several important subgroups. We found no evidence, however, that, when considered as a binary variable, eGFR was superior to creatinine in predicting 30-day mortality. Finally, but importantly, the review has identified significant gaps in the literature, in particular the lack of data exploring the relationship between more accurate and discriminatory measures of renal function and outcome in noncardiac and nonvascular surgery.

The strength of observed relationship between eGFR and adverse outcomes, in particular death, after surgery is very

Table 1. Characteristics of Included Studies

Primary Author, yr	Country	Sample Size	Mean Age (yr)	Male (%)
Karkouti, 2008[40]	Canada	3,460	66	73
Holzmann, 2007[37]	Sweden	6,575	61	81
Palomba, 2007[51]	Brazil	603	60	62
van de Wal, 2005[56]	The Netherlands	358	53	89
van Gameren, 2008[57]	The Netherlands	1,205	62	69
Wang, 2003[59]	Canada	6,364	Range	74
Wijeysundera, 2006[61]	Canada	10,751	62	74
Yu, 2007[62]	Taiwan	2,102	65	75
Zakeri, 2005[63]	United Kingdom	4,403	63	79
Lok, 2004[44]	Canada	26,506	Range	76
Holzmann, 2005[37]	Sweden	6,711	61	81
Loef, 2005[43]	The Netherlands	843	63	73
Noyez, 2006[47]	The Netherlands	627	64	78
Walter, 2003[58]	Germany	8,138	65	76
Wijeysundera[66]	Canada	20,131	63	72
Thakar, 2005[32]	United States	31,677	65	69
Cooper, 2006[16]	United States	483,914	64	72
Ramon Perez-Valdivieso, 2009[53]	Spain	864	66	60
Chonchol, 2007[29]	France	931	67	82
Del Duca, 2007[30]	Canada	649	65	69
Foot, 2009[34]	Australia	7,440	64	71
Gibson, 2008[18]	United Kingdom	514	69	60
Hillis, 2006[17]	United Kingdom	2,067	66	77
Ibanez, 2007[38]	Spain	681	68	55
Lin, 2009[64]	China	5,559	60	84
Kangasniemi, 2007[39]	Finland	882	63	75
Huang, 2011[67]	Taiwan	1,052	66	76
Ledoux, 2007[42]	Belgium	376	71	68
Browner,1992[28]	United States	474	68	100
Aveline, 2009[25]	France	755	71	30
Powell, 1997[54]	United States	210	69	76
Estrera, 2008[33]	United States	920	65	61
Welten, 2007[60]	Netherlands.	2,126	66	76
Azizzadeh, 2006[26]	United States	398	73	85
Kertai, 2003[41]	The Netherlands	852	67	79
Miller, 2010[46]	United States	1,088	64	65
Marrocco-Trischitta, 2009[45]	Italy	179	70	84
Welten, 2007[65]	The Netherlands	952	66	79
Huynh, 2005[31]	United States	1,106	67	64
O'Hare, 2003[49]	United States	18,217	—	99
O'Hare, 2004[48]	United States	16,994	—	99
Bakken, 2009[27]	United States	635	66	64
Haddad, 2005[35]	United States	72	75	82
Owens, 2007[50]	United States	456	68	61
Pearce, 2007[52]	United States	150	71	72
Sidawy, 2008[55]	United States	20,899	68	98

*eGFR C-G: estimated glomerular filtration rate derived from Cockcroft-Gault equation. **eGFR (MDRD): estimated glomerular filtration rate derived from Modified Diet in Renal Disease Study equation. ***eGFR (CC): estimated glomerular filtration rate derived from serum cystatin c levels and calculated using cystatin c based formula.[68]

Diabetic Patients (%)	Patients with Hypertension (%)	Type of Surgery	Measurement of Renal Function	Study Definition of Abnormal Renal Function
34	74	Cardiac	eGFR (C-G)*	<60 ml·min·1.73 m^{-2}
12	30	Cardiac	eGFR (C-G)*	<90 ml·min·1.73 m^{-2}
28	83	Cardiac	eGFR (C-G)*	<60 ml·min·1.73 m^{-2}
97	—	Cardiac	eGFR (C-G)*	<70 ml·min·1.73 m^{-2}
—	—	Cardiac	eGFR (C-G)*	<90 ml·min·1.73 m^{-2}
22	3	Cardiac	eGFR (C-G)*	<80 ml·min·1.73 m^{-2}
22	55	Cardiac	eGFR (C-G)*	<60 ml·min·1.73 m^{-2}
48	—	Cardiac	eGFR (C-G)*	<60 ml·min·1.73 m^{-2}
20	59	Cardiac	eGFR (C-G)*	<60 ml·min·1.73 m^{-2}
28	—	Cardiac	eGFR (C-G)*	<100 ml·min·1.73 m^{-2}
13	30	Cardiac	eGFR (C-G)*	<90 ml·min·1.73 m^{-2}
11	23	Cardiac	eGFR (C-G)*	Not defined
19	65	Cardiac	eGFR (C-G)*	<50 ml·min·1.73 m^{-2}
—	—	Cardiac	eGFR (C-G)*	Not defined
24	57	Cardiac	eGFR (C-G)*	<60 ml·min·1.73 m^{-2}
25	—	Cardiac	eGFR (MDRD)**	<90 ml·min·1.73 m^{-2}
30	75	Cardiac	eGFR (MDRD)**	<90 ml·min·1.73 m^{-2}
32	66	Cardiac	eGFR (MDRD)**	<60 ml·min·1.73 m^{-2}
26	49	Cardiac	eGFR (MDRD)**	<60 ml·min·1.73 m^{-2}
25	72	Cardiac	eGFR (MDRD)**	<60 ml·min·1.73 m^{-2}
24	—	Cardiac	eGFR (MDRD)**	<90 ml·min·1.73 m^{-2}
11	40	Cardiac	eGFR (MDRD)**	<60 ml·min·1.73 m^{-2}
15	60	Cardiac	eGFR (MDRD)**	<60 ml·min·1.73 m^{-2}
27	58	Cardiac	eGFR (MDRD)**	<60 ml·min·1.73 m^{-2}
25	60	Cardiac	eGFR (MDRD)**	<90 ml·min·1.73 m^{-2}
20	41	Cardiac	eGFR (MDRD)**	<90 ml·min·1.73 m^{-2}
41	67	Cardiac	eGFR (MDRD)**	<60 ml·min·1.73 m^{-2}
22	71	Cardiac	eGFR (CC)***	<90 ml·min·1.73 m^{-2}
20	61	Major noncardiac	eGFR (C-G)*	<50 ml·min·1.73 m^{-2}
9	52	Orthopaedic	eGFR (C-G)*	<60 ml·min·1.73 m^{-2}
13	60	Vascular	eGFR (C-G)*	<45 ml·min·1.73 m^{-2}
6	69	Vascular	eGFR (C-G)*	<99 ml·min·1.73 m^{-2}
16	49	Vascular	eGFR (C-G)*	<60 ml·min·1.73 m^{-2}
—	—	Vascular	eGFR (C-G)*	<60 ml·min·1.73 m^{-2}
12	41	Vascular	eGFR (C-G)*	<63 ml·min·1.73 m^{-2}
—	83	Vascular	eGFR (C-G)*	<60 ml·min·1.73 m^{-2}
—	—	Vascular	eGFR (C-G)*	<90 ml·min·1.73 m^{-2}
6	41	Vascular	eGFR (C-G)*	<60 ml·min·1.73 m^{-2}
—	—	Vascular	eGFR (C-G)*	<90 ml·min·1.73 m^{-2}
35	—	Vascular	eGFR (MDRD)**	<60 ml·min·1.73 m^{-2}
57	—	Vascular	eGFR (MDRD)**	<60 ml·min·1.73 m^{-2}
51	83	Vascular	eGFR (MDRD)**	<60 ml·min·1.73 m^{-2}
17	74	Vascular	eGFR (MDRD)**	<60 ml·min·1.73 m^{-2}
59	73	Vascular	eGFR (MDRD)**	<60 ml·min·1.73 m^{-2}
16	89	Vascular	eGFR (MDRD)**	<60 ml·min·1.73 m^{-2}
27	—	Vascular	eGFR (MDRD)**	<60 ml·min·1.73 m^{-2}

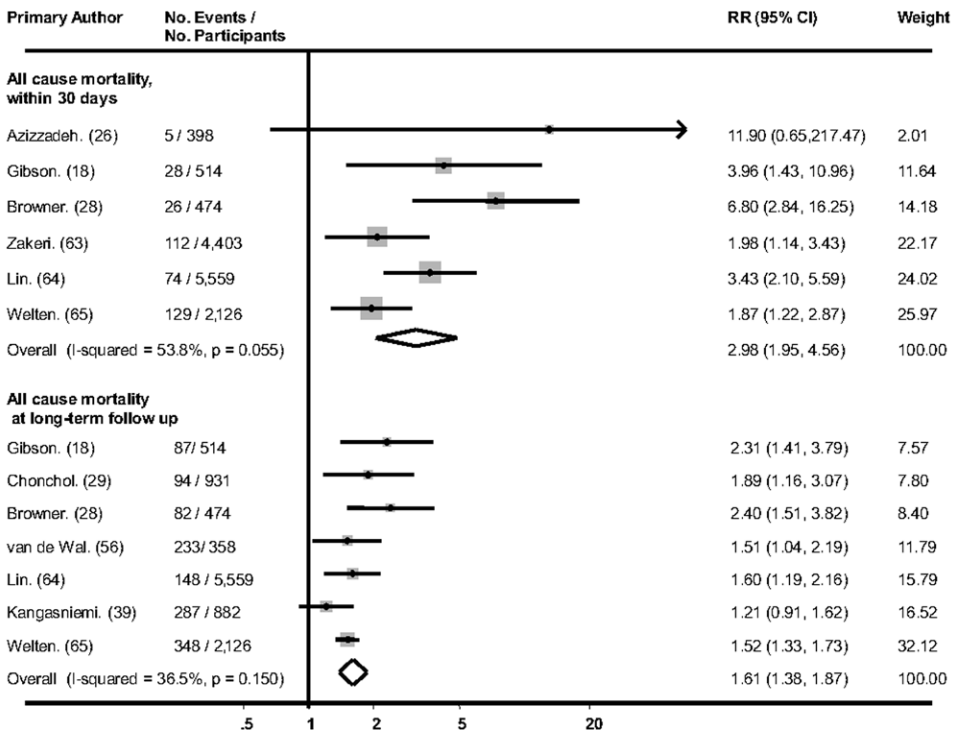

Fig. 2. Risk of death for patients with estimated glomerular filtration rate <60 ml·min·1.73 m^{-2} compared with ≥60 ml·min·1.73 m^{-2} at both short-term and long-term follow-up.

similar to those reported in large community-based studies[15] and meta-analyses in nonsurgical populations.[1,2] These have generally found an exponential relationship between renal dysfunction and all-cause mortality during long-term follow-up.[1,2,15] Despite a tendency for patients with end-stage kidney disease or dialysis dependence to be less likely to undergo surgery or undergo it at a younger age,[16] we found evidence of a similar relationship between categories of eGFR and early mortality. Thus, although some studies[18,29,42] have reported a linear relationship between eGFR and outcome after surgery, it seems likely that the prognostic implications of a decline of 10 ml·min·1.73 m^{-2} in eGFR are greater in patients with more severe renal dysfunction.

A consistent relationship between eGFR and composite cardiac events was observed, but was limited by the small number of studies reporting this endpoint and restricted to people undergoing cardiac surgery. Similarly, preoperative chronic kidney disease was also found to be predictive of

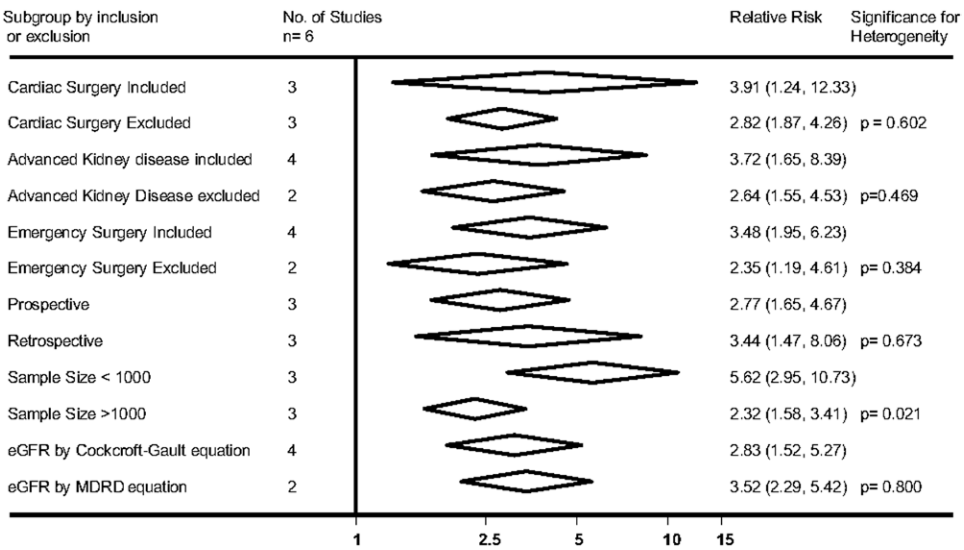

Fig. 3. Relative risk of all-cause mortality within 30 days of surgery in patients with baseline estimated glomerular filtration rate (eGFR) <60 ml·min·1.73 m^{-2} according to selected subgroups. MDRD = Modified Diet in Renal Disease Study.

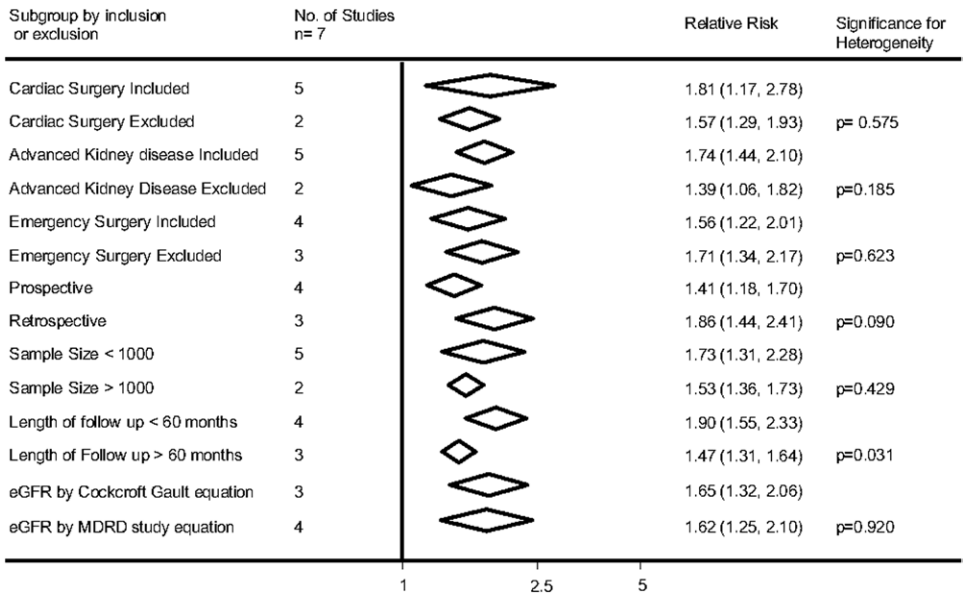

Fig. 4. Relative risk of long-term all-cause mortality in patients with baseline estimated glomerular filtration rate (eGFR) <60 ml·min·1.73 m^{-2} according to selected subgroups. MDRD = Modified Diet in Renal Disease Study.

postoperative AKI. There was, however, significant heterogeneity across the pooled studies. In particular, studies that used preoperative eGFR to predict AKI after emergency surgery tended to report a stronger relationship, which may be explained by the presence of extrarenal factors such as sepsis and dehydration. The presence of heart failure and the sample size also influenced the magnitude of the observed effect. The heterogeneity identified may also reflect differences in the definition of AKI.

Potential Mechanisms

The mechanisms whereby renal dysfunction portends a worse prognosis after surgery are likely to be similar to those seen in the nonsurgical setting. These are complex and multiple, with

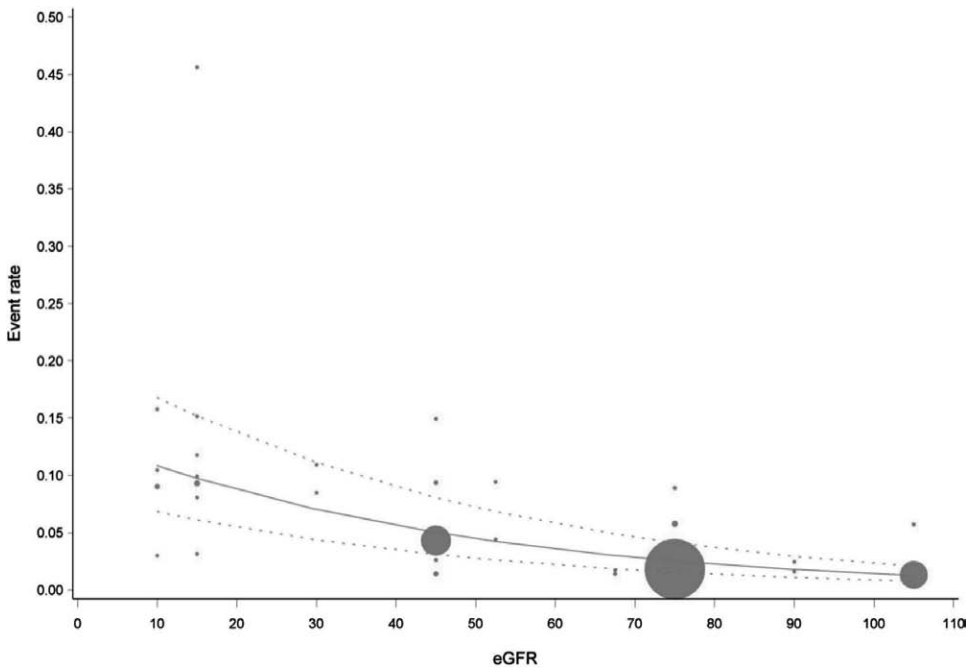

Fig. 5. All-cause mortality within 30 days of surgery. Events categorized according to preoperative estimated glomerular filtration rate (eGRF). A total of eight cohort studies are represented. Risks are expressed as proportions (*e.g.*, 0.10 = 10% increased risk) and the area of the circle is proportional to the sample size. The *center line* models estimated risk from adjusted data of preoperative estimated glomerular filtration rate categorized into Chronic Kidney Disease by stage, with *dotted lines* representing 95% confidence intervals. Regression equation logit(*p*) = −1.8701 to 0.0238 *eGFR.

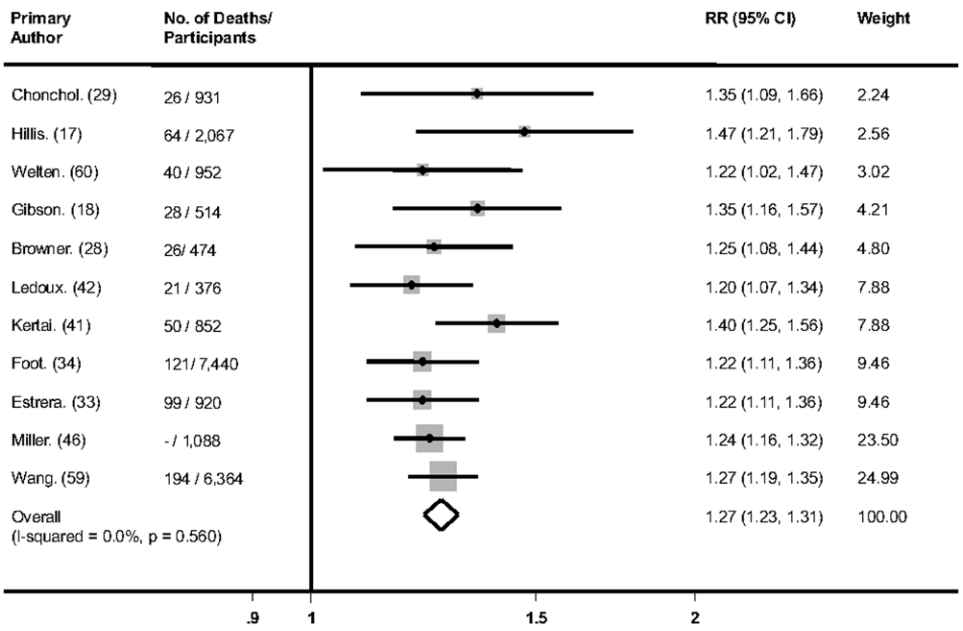

Fig. 6. Risk of death at short-term follow-up with stepwise reduction in creatinine clearance by 10 ml·min·1.73 m^{-2}.

kidney disease serving both as a marker and a mediator of an adverse outcome.[72] Renal function declines with age and as a consequence of several other conditions that are associated with a worse perioperative outcome such as diabetes mellitus, dyslipidemia, and hypertension.[73] Renal dysfunction both amplifies the adverse effects of these traditional risk factors and is associated with a greater prevalence of other abnormalities that may be detrimental to surgical outcome, such as anemia, abnormal calcium/phosphate homeostasis, and inflammation. A lower eGFR is also both a consequence and cause of reduced left ventricular systolic dysfunction and heart failure. In addition, kidney function is a sensitive indicator of vascular health and hemodynamic stability, both of which are important determinants of perioperative

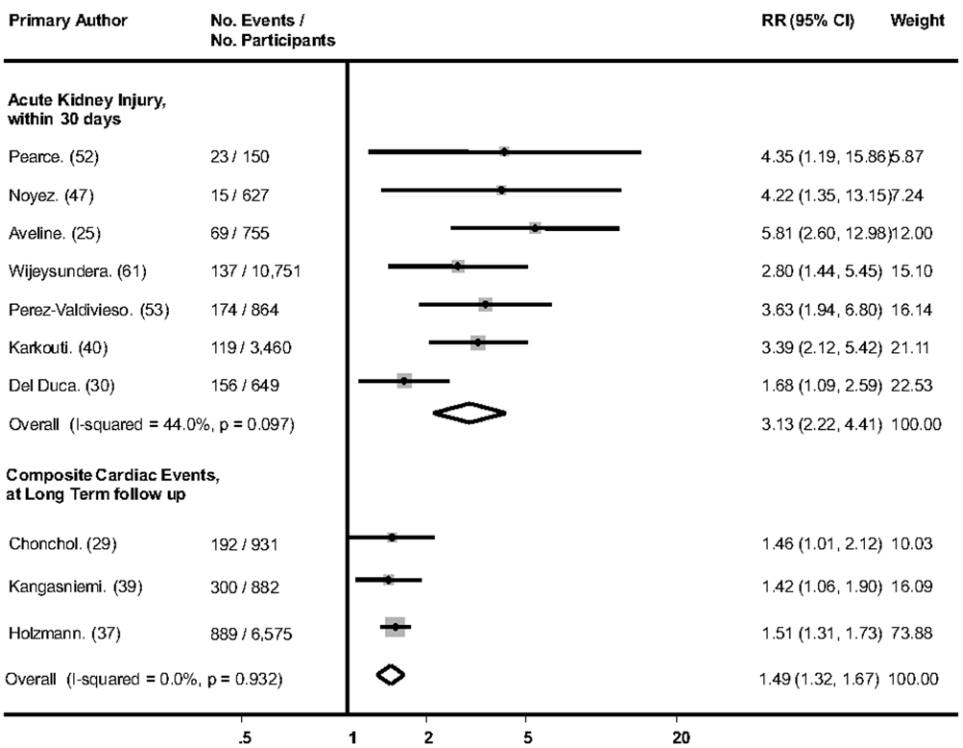

Fig. 7. Risk of acute renal injury or adverse cardiovascular event for patients with estimated glomerular filtration rate <60 ml·min·1.73 m^{-2}.

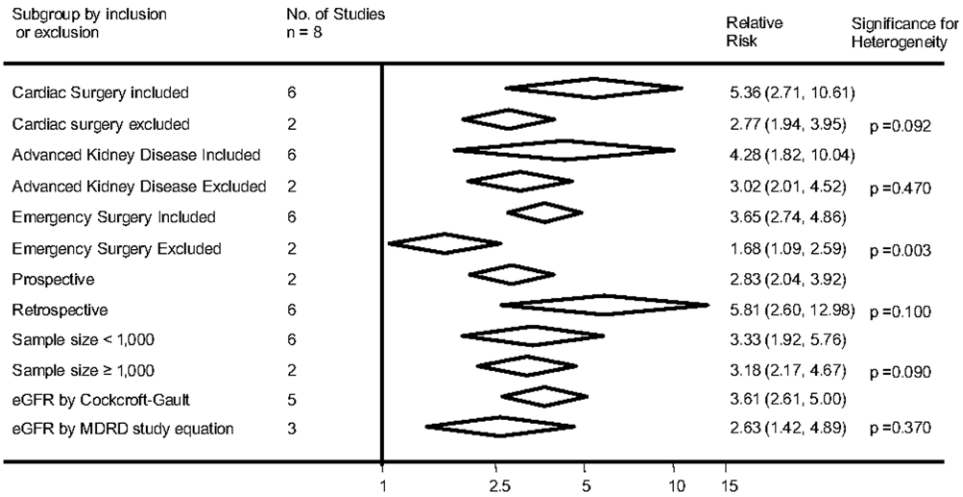

Fig. 8. Relative risk of postoperative acute kidney injury in patients with baseline estimated glomerular filtration rate (eGFR) <60 ml·min·1.73 m^{-2} according to selected subgroups. MDRD = Modified Diet in Renal Disease Study.

complications. There is also strong evidence that patients with renal disease frequently do not receive treatments that protect against vascular events[74] and, even if they do, those with severe chronic kidney disease may derive less benefit.[75,76]

Renal Function and Existing Risk Prediction Scores

In cardiac surgery there are limited data suggesting that the incorporation of more discriminatory and continuous measures of renal function can improve the precision of risk prediction scores.[57,58] The European System for Cardiac Operative Risk Evaluation investigators have recently incorporated creatinine clearance by category to better estimate the risk of operative mortality in patients undergoing cardiac surgery.††† None of the currently recommended risk scores used in noncardiac surgery use the eGFR. Indeed some do not include any measure of renal function whereas others, such as the revised Cardiac Risk Index and the more recently described American College of Surgeons' National Surgical Quality Improvement Program model,[56] use creatinine but dichotomize the attributable risk.

For simplicity, it may remain preferable to use categories of eGFR to determine the postoperative risk. Our data suggest, however, that the thresholds used in traditional risk indices may need to be reviewed. For example, the revised Cardiac Risk Index attributes the excess risk associated with renal dysfunction when the creatinine is above 2 mg/dl (177 μM). For a 70-yr-old Caucasian male this equates to an eGFR of 33 ml·min·1.73 m^{-2} and for a black female of the same age an eGFR of 29 ml·min·1.73 m^{-2} In contrast, the current analyses suggest that, in keeping with other settings, the risk of early mortality after surgery begins to rise more steeply once the eGFR falls below 60 ml·min·1.73 m^{-2} (fig. 4). Thus, milder degrees of preoperative renal dysfunction, identified using the eGFR, may be associated with an important increase in postoperative risk, and reliance on a single cutoff level may limit the prognostic information available.

The Relative Prognostic Utility of Creatinine and eGFR

Several individual studies have assessed the relative ability of preoperative creatinine and eGFR levels to predict adverse postoperative outcomes.[16,41,59,63] These have generally found the latter to be a better discriminator, though even in large data sets, the observed differences have sometimes been marginal.[16] Likewise, in our meta-analysis of studies which provided unadjusted binary data we found that both measures are strong predictors. Although the risk ratio associated with an eGFR less than 60 ml·min·1.73 m^{-2} was higher than that observed for creatinine (dichotomized at various levels determined by the individual studies) no statistically significant difference was observed; though, as might be expected given the differences in the cutoff levels used, creatinine demonstrates greater statistical heterogeneity. Thus, although eGFR is regarded as a better indicator of renal function and is recommended for this purpose,[71] the evidence that it will enhance postoperative risk prediction, when compared with creatinine, is limited.

Limitations of the Current Study

A key limitation of this review was the poor representation of noncardiac surgery in the literature. In addition, the remaining data relate almost exclusively to vascular surgery. Therefore, current evidence focuses heavily on selected populations with a high prevalence of overt atherosclerotic disease and a high cardiovascular risk profile, undergoing high-risk surgery. Further research is essential to better understand the importance of kidney function as a marker of risk in more diverse surgical populations[77] and what role, if any, it plays in pathogenesis of postoperative events.

††† European System for Cardiac Operative Risk Evaluation. Available at: http://www.euroscore.org/calc.html. Accessed November 11, 2011.

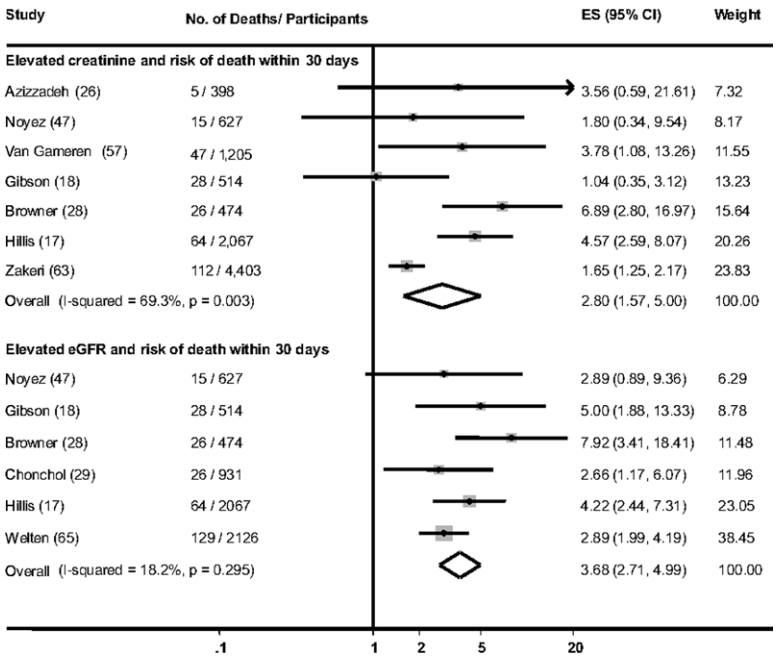

Fig. 9. Comparison of creatinine and estimated glomerular filtration rate (eGFR) in prediction of death within 30 days of surgery.

There were also limitations in terms of the outcome data that were available, with the majority of studies reporting only all-cause mortality. Few data were, therefore, available to explore the relationship between eGFR and composite and specific cardiac and renal outcomes. Likewise, we did not address the relationship between eGFR and other important, though inconsistently reported, outcomes such as postoperative atrial fibrillation, length of stay in intensive care, and duration of hospitalization. Another limitation is the retrospective nature of many studies, though the objective nature of the measurements and outcomes should reduce any tendency toward bias. In addition, significant heterogeneity was detected in the analyses measuring long-term all-cause mortality and AKI as outcomes. Potential causes have been sought and, although the predictive value remains significant even with adjustment, it remains possible that other confounders may not have been identified.

Clinical Implications

The current data support the use of eGFR as an indicator of the risk of postoperative complications, particularly after cardiac or vascular surgery. The strength of the relationship, its consistency among multiple subgroups, and the graded relationship support the importance of a declining eGFR as a risk factor for adverse postoperative outcome.

The results also suggest that reliance on dichotomous measures of renal function, as widely used currently, will considerably reduce the amount of prognostic information obtained. With better risk assessment there is the prospect of improved surgical outcomes. Potential interventions might be to limit the use of perioperative nephrotoxins and/or increase the intensity of postoperative observation in patients identified as being at high risk. In addition, because patients with kidney dysfunction are at increased risk for adverse cardiovascular outcomes after major surgery they may benefit from aggressive treatment of atherosclerotic risk factors and potentially the targeted use of therapeutic interventions such as statin therapy.[78] Similarly, interventions such as *N*-acetyl cysteine[79] might potentially be used to prevent renal injury.

In conclusion, we have found that kidney function, defined using eGFR, predicts cardiovascular events and AKI after, predominantly cardiac and vascular, surgery and, in particular, exhibits a powerful inverse nonlinear relationship with all-cause mortality in this setting.

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Appendix 1. Postsurgical Renal Failure Systematic Review: Quality Assessment Tool

1. Observational Studies1.How did the study define renal injury/damage or failure, and in what time frame?
   a.Yes
   b.No
2. Did the study define a particular adverse outcome, and in what time frame? *E.g.,* AMI at 30 days.
   a.Yes
   b.No
3. Did the study define a specific endpoint, *e.g.*, mortality, dialysis dependence?
   a.Yes
   b.No
4. Which fluid was used to sample biomarkers?
   a.Urine
   b.Serum
   c.Both
5. Was there a series of biomarkers taken before surgery?
   a.Yes
   b.No
6. Was this in comparison to a standard measurement (*i.e.*, creatinine)?
   a.Yes
   b.No
7. Did the study include people with existing renal disease?
   a.Yes
   b.No
8. Was this accounted for/adjusted for?
   a.Yes
   b.No
9. Were other preexisting comorbidities, *e.g.*, cardiovascular disease accounted for?
   a.Yes
   b.No
10. Did the study draw comparison with a current predictive clinical model?
    a.Yes
    b.No

Appendix 1, Table 2. Methodological Quality of Articles in Systematic Review

Primary Author	Representative Sample	Attrition Accounted For	Prognostic Factor Clearly Stated	Outcome Adequately Measured	Confounders Accounted for
Karkouti, 2008[40]	Yes	Yes	Yes	Yes	Yes
Holzmann, 2007[37]	Yes	Yes	Yes	Yes	Yes
Palomba, 2007[51]	Unsure	Yes	Yes	Unclear	Yes
van de Wal, 2005[56]	Yes	Yes	Yes	Yes	Yes
van Gameren, 2008[57]	Yes	Yes	Yes	Yes	Yes
Wang, 2003[59]	Yes	No	Yes	Yes	Yes
Wijeysundera, 2006[61]	Yes	Yes	Yes	Yes	Yes
Yu, 2007[62]	Yes	Yes	Yes	Yes	Yes
Zakeri, 2005[63]	Yes	Yes	Yes	Yes	Yes
Lok, 2004[44]	Yes	Yes	Yes	Yes	Yes
Holzmann, 2005[37]	Yes	Yes	Yes	Yes	Yes
Loef, 2005[43]	Yes	Yes	Yes	Yes	Yes
Noyez, 2006[47]	Yes	Yes	Yes	Yes	Unclear
Walter, 2003[58]	No	No	Yes	Yes	Yes
Wijeysundera[66]	Yes	Yes	Yes	Yes	Yes
Thakar, 2005[32]	Yes	Yes	Yes	Yes	Yes
Cooper, 2006[16]	Yes	Yes	Yes	Yes	Yes
Ramon Perez-Valdivieso, 2009[53]	Yes	Yes	Yes	Yes	Yes
Chonchol, 2007[29]	Yes	Yes	Yes	Yes	Yes
Del Duca, 2007[30]	Yes	Yes	Yes	Yes	Yes
Foot, 2009[34]	Yes	Yes	Yes	Yes	Yes
Gibson, 2008[18]	Yes	Yes	Yes	Yes	Yes
Hillis, 2006[17]	Yes	Yes	Yes	Yes	Yes
Ibanez, 2007[38]	Yes	Yes	Yes	Yes	Yes
Lin, 2009[64]	Yes	Yes	Yes	Yes	Yes
Kangasniemi, 2007[39]	Yes	Yes	Yes	Yes	Yes
Huang, 2011[67]	Yes	Yes	Yes	Yes	Yes
Ledoux, 2007[42]	Yes	Yes	Yes	Yes	Yes
Browner,1992[28]	Yes	Yes	Yes	Yes	Yes
Aveline, 2009[25]	Yes	Unclear	Yes	Yes	Yes
Powell, 1997[54]	Yes	No	Yes	Yes	Yes
Estrera, 2008[33]	Yes	Yes	Yes	Yes	Yes
Welten, 2007[60]	Yes	Yes	Yes	Yes	Yes
Azizzadeh, 2006[26]	Yes	Yes	Yes	Yes	No
Kertai, 2003[41]	Yes	No	Yes	Yes	Yes
Miller, 2010[46]	Yes	Not Reported	Yes	Yes	Yes
Marrocco-Trischitta, 2009[45]	Yes	Not Reported	Yes	Yes	Yes
Welten, 2007[65]	Yes	Yes	Yes	Yes	Yes
Huynh, 2005[31]	Yes	No	Yes	Yes	Yes
O'Hare, 2003[49]	Yes	Yes	Yes	Yes	Yes
Welten, 2007[65]	Yes	Yes	Yes	Yes	Yes
Huynh, 2005[31]	Unsure	Not reported	Yes	Yes	Yes
O'Hare, 2003[49]	Yes	Not reported	Yes	Yes	Yes
Welten, 2007[65]	Yes	Yes	Yes	Yes	Yes
Huynh, 2005[31]	Yes	Yes	Yes	Yes	Yes
O'Hare, 2003[49]	Yes	Yes	Yes	Yes	Yes
Sidawy[55]	Yes	Yes	Yes	Yes	Yes