Published in final edited form as:

Ann Thorac Surg. 2012 January ; 93(1): 337–347. doi:10.1016/j.athoracsur.2011.09.010.

Predicting Acute Kidney Injury Following Cardiac Surgery: A Systematic Review

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Abstract

Background—Acute kidney injury (AKI) after cardiac surgery confers a significant increased risk of mortality. Several risk models have been developed to predict postoperative kidney failure after cardiac surgery. The objective of this systematic review is to evaluate the available risk models for AKI after cardiac surgery.

Methods—Literature searches were performed in the Web of Science/Knowledge, Scopus, and MEDLINE databases for articles reporting the primary development of a risk model and articles reporting validation of existing risk models for AKI after cardiac surgery. Data on model variables, internal and/or external validation, measures of discrimination, and measures of calibration were extracted.

Results—Seven articles with a primary development of a prediction score for AKI after cardiac surgery and 8 articles with external validation of established models were included in the systematic review. The models for AKI requiring dialysis are the most robust and externally validated. Among the prediction rules for AKI requiring dialysis after cardiac surgery, the Cleveland Clinic model has been the most widely tested thus far and has shown high discrimination in most of the tested populations. A validated score to predict non-dialysis requiring AKI is lacking.

Conclusions—Further studies are required to develop risk models to predict milder, non-dialysis requiring AKI after cardiac surgery. Standardizing risk factor and AKI definitions will facilitate both the development and validation of risk models predicting AKI.

Keywords

Statistics; risk analysis/modeling; kidney Ischemia/reperfusion injury; cardiac surgery; CABG

Introduction

Acute kidney injury (AKI) after cardiac surgery portends significant morbidity and mortality. Depending on the definition, post-operative AKI occurs in 3–30% of patients [1–

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5]. One to 5% of patients develop AKI necessitating renal replacement therapy [6]. The prognosis among this subgroup of patients is poor, with an increased mortality risk exceeding 60% compared to the overall mortality rate of 2–8% after cardiac surgery [2, 7–9]. Patients who develop non-dialysis requiring AKI also have up to a 4-fold increased risk of short-term and long-term mortality compared to patients with normal renal function after cardiac surgery [10]. Even small increases of serum creatinine (SCr) after cardiac surgery have been observed to be associated with a significant increase in 30-day mortality, from a 3-fold increase risk for a small increase of up to 0.5 mg/dl from baseline to an 18-fold increase risk of death with a SCr rise greater than 0.5 mg/dl [11]. A model that accurately estimates a patient's risk for AKI after cardiac surgery can optimize clinical decision-making and preoperative treatment strategies to minimize the risk for AKI. Prediction scores can also be utilized as valuable research tools by identifying high-risk patients for AKI clinical trials. Currently there is neither consensus nor a guideline to recommend the use of prediction models for AKI after cardiac surgery. We performed this systematic review to evaluate the existing models developed to predict AKI after cardiac surgery.

Material and Methods

Four electronic databases (Web of Science/Knowledge, Scopus, and MEDLINE) were searched from 1950 to May 2011 for articles on prediction models for AKI after cardiac surgery. MeSH headings and keywords used included *acute kidney injury* (renal failure, renal insufficiency), *cardiac surgery* (heart surgery, cardiovascular surgical procedure, coronary bypass surgery, coronary artery surgery), *prediction* (model, risk, predict, score), and *validation*. References and citing articles of identified publications were searched for additional studies. No language restrictions were used.

Study Selection

Studies were included if a model was developed to predict AKI after cardiac surgery and reported in the form of a scoring system or algorithm. Studies reporting external validation of a primary risk model were also included. Models predicting AKI requiring dialysis and those predicting AKI independent of the need for dialysis were also included. Studies included had to report either an area under the receiver-operating characteristic curve (AUC) or c-statistic for predicting the outcome of interest as well as internal validation of the model. Studies were excluded if only logistic regression was performed without reporting a scoring system that could be used clinically. Unpublished conference abstracts were also excluded.

Data Extraction and Quality Assessment

For each included study, variables included in the model, internal and/or external validation, measures of discrimination (AUC, log likelihood, or c-statistic), and measures of calibration (Hosmer-Lemeshow [H-L]) were documented. AUC, or sometimes called c-statistic, is used as a measure of discrimination, or a model's ability to distinguish patients who will develop AKI from those who will not. AUC ranges from 0.5 (no discrimination, no better than chance) to 1.0 (perfect discrimination). Calibration as measured by the H-L statistic refers to the concordance between observed and predicted risks. A H-L statistic with a small, significant p-value suggests poor calibration. For the purposes of this review, all AUCs and H-L statistics in the studies evaluated are reported as published. While these measures are critical in model development, caution must be used when interpreting AUC and H-L statistics in external validation of prediction models, as both measures are sensitive to sample size and incidence of predicted outcome, requiring large sample sizes for adequate performance assessment and model comparison [12–15].

Extracted information on training and testing sets included sample size, demographic and clinical characteristics, study site(s), type of cardiac surgery, time period, definition of AKI, and exclusion criteria. Quality in this review refers to the study design and internal validity of the derivation models, while generalizability is separately analyzed. As there is no consensus to a standardized scoring system for quality assessment of prediction rules [16, 17], the quality of the models was analyzed to address the internal validity of the model. The following questions were considered for each model:

- 1) Does the article state both inclusion and exclusion criteria?
- 2) Was the study population well described?
- 3) Was there a discussion included about the rationale to include the predictors?
- 4) Were the predictive variables clearly defined?
- 5) Was the outcome clearly defined?
- 6) Were criteria used to determine indication for dialysis?
- 7) How was missing data managed?
- 8) Was an adequate strategy performed to build the multivariable model?
- 9) Were more than 10 events per variable included?
- 10) Were confidence intervals for measures of discrimination reported?
- 11) Was the model internally validated? If so, what method (bootstrapping, independent or split sample validation cohort) of internal validation was used?

The generalizability of the model was assessed by the level of external validation: 0-internal validation (accuracy of score tested only in the sample used to develop the score), 1-prospective validation (accuracy of score tested in data collected after the development of score at same institution), 2-independent validation (accuracy of score tested in data collected by independent investigators at a different site), 3-multisite validation (accuracy of score tested at multiple geographic sites), 4-multiple independent validations (accuracy of score tested by diverse investigators at diverse geographic sites), as defined by Justice et al [18]. Data was extracted by two independent reviewers.

Results

We found 227 references in our search (Figure 1), from which we included 7 articles with a primary development of a prediction score or algorithm for AKI after cardiac surgery [5, 6, 19–23] and 8 articles with external validation of established models [24–31]. Six studies [32–37], which reported logistic regression models without a formulation of a prediction score, and one unpublished conference abstract [38], were excluded. Four studies reported a primary development of a risk score for the development of AKI requiring dialysis after cardiac surgery, while three studies developed a score to predict a broader definition of AKI (Table 1). The incidence of AKI requiring dialysis ranged from 1.1 to 1.7%. Indication for dialysis was not uniformly defined in all studies and frequently dependent on the discretion of the treating nephrologists. The definition of AKI was not uniform among risk scores that included a broader definition of AKI, as described below. Variables included in the models varied among the risk scores (Table 2). While age, history of diabetes mellitus, and preoperative renal insufficiency were included in most of the risk scores, no one risk factor was common to all risk models. The quality and generalizability of the risk scores as measured by internal and external validation are summarized in Tables 3 and 4, respectively.

Models Predicting AKI Requiring Dialysis

Continuous Improvement in Cardiac Surgery Study (CICSS)

In 1997, Chertow et al first published a risk stratification algorithm using data from the CICSS, which prospectively followed patients who underwent coronary artery bypass graft surgery (CABG) or valvular surgery at 43 Veterans Affairs medical centers [6]. AKI was defined as deterioration of renal function sufficient to require dialysis within 30 days after surgery. Indications for dialysis were not defined. Patients were excluded if baseline SCr was ≥ 3.0 mg/dl and/or had active endocarditis at the time of surgery. The data from the derivation cohort of 42,773 patients was prospectively collected. The cohort was predominantly male, only 0.9% female, and included few African American patients. The overall risk of developing AKI requiring dialysis was 1.1%. The AUC was 0.76 for the multivariable analysis which included 10 variables. A clinical risk algorithm was derived by recursive partitioning which included 7 variables and divided the sample into 11 separate groups based on interactions between key discriminating variables. The risk algorithm was internally validated using an independent sample of 3,795 CICSS patients, though an AUC was not reported. The model was subsequently tested in the Quality Measurement and Management Initiative cohort [24], which only included patients undergoing isolated CABG, a small European cohort [25], and a cohort at the Cleveland Clinic [26]. As part of the validation of another scoring system, it was also tested in two Canadian cohorts [23]. In all external validations, the AUC of the CICSS model was modest, possibly due to the predominantly Caucasian and male CICSS cohort.

Cleveland Clinic Score

In 2005, Thakar et al developed a clinical scoring model from a cohort patients who had underwent open heart surgery at the Cleveland Clinic [19]. The primary outcome was defined as AKI requiring dialysis during the postoperative period after open-heart surgery. Indications for dialysis included uremia, volume overload, or biochemical abnormalities and were based on clinical judgment. Variables examined were defined and chosen based on prior analysis of a portion of the database [7]. Patients with more severe preoperative renal dysfunction were excluded only if they required preoperative dialysis. Patients were also excluded if they were heart transplant recipients; required preoperative extracorporeal membrane oxygenation, preoperative tracheostomy or mechanical ventilation; underwent procedures for automated implantable cardioverter-defibrillator, left ventricular assist devices, or sternal work; or had missing data. A total of 31,677 patients were included in the analysis. One half of the total number of patients were randomly selected as the derivation cohort, while the remaining served as the validation cohort. The frequency of AKI requiring dialysis in the test set was 1.7%. The authors further formed four risk categories of increasing severity, with frequency of AKI requiring dialysis ranging from 0.4 to 22%. The AUC for the model was 0.81 for the derivation set and 0.82 for the validation set. When compared to its predecessor, the Cleveland Clinic model included a more diverse population, with more women, African Americans, and patients with more severe preoperative renal dysfunction. One limitation of the model is the lack of prospective testing during the initial analysis.

The Cleveland Clinic score has been subsequently validated in multiple cohorts. The score tested well in a Spanish cohort [28], an Italian cohort [27], two Canadian cohorts [23], and a Mayo Clinic (Rochester, MN) cohort, with good discrimination, AUCs ranging from 0.8 to 0.86 (Table 4). When tested in a German cohort by Heise et al [31], the Cleveland Clinic score was found to be less accurate in predicting AKI requiring dialysis with an AUC of 0.662. Both the small sample size and a significantly higher overall incidence of AKI requiring dialysis compared to the Cleveland Clinic dataset may have contributed to low

discrimination power in the German cohort. Candela-Toha et al reported poor calibration of both the Cleveland Clinic Score and the Toronto Simplified Renal Index (SRI) in higher risk groups, underestimating the risk for AKI requiring dialysis except for patients in the very-low risk group at a single center in Madrid, Spain. This was likely due to the higher frequency of AKI requiring dialysis in the Spanish cohort (3.7% compared to 1.7% in the Cleveland Clinic cohort), small sample size, and differences in the population. The Spanish cohort was older and had a higher proportion of female patients and emergent cases. It also showed discriminative power to predict a composite end point of severe AKI (defined as SCr rise > 2.0 mg/dl or a 2-fold increase from preoperative values) in the Mayo Clinic cohort [30].

Society of Thoracic Surgeons (STS) Bedside Risk Tool

In 2006, Mehta et al developed a bedside risk tool to predict postoperative dialysis using the STS National Cardiac Surgery Database, a large multi-center dataset including over 600 hospitals from 50 US states and 5 Canadian provinces [20]. Patients undergoing CABG alone, mitral or aortic surgery alone, or the combination of CABG and aortic or mitral valve surgery were included. Patients on dialysis prior to cardiac surgery and those with missing values of SCr, age, gender or race were excluded. Indications for dialysis were not defined. The incidence of postoperative dialysis was 1.4% in the derivation sample with a total of 449,524 patients and 1.6% in the validation sample of 86,009 patients. Despite having the advantage of a multi-center, multi-national database and a large cohort, this risk model was not prospectively validated during the initial analysis and has been cited for having too many variables [23, 30, 39]. Furthermore, the model can only be applied to the subset of cardiac surgery patients undergoing isolated CABG, isolated mitral or aortic surgery, or CABG and aortic or mitral valve surgery. The authors internally validated a simplified model with 10 variables (c statistic = 0.83). External validation was performed on the full model in two Canadian cohorts [23], while the simplified model was validated in a Mayo Clinic cohort [30]. In 2009, the STS published three new risk models for isolated CABG, isolated valve, and valve surgery combined with CABG procedures [35–37]. While these models were identified in the literature search, they were excluded as only logistic regression data were reported without a clinical scoring system. Up to 41 variables are included to predict postoperative mortality, renal failure, stroke, prolonged ventilation, sternal wound infection, risk of reoperation, and length of stay. Patients requiring preoperative dialysis were excluded when developing the risk model for prediction of postoperative renal failure, defined as a new requirement for dialysis postoperatively or an increase of the SCr to more than 2.0 mg/dL and double the most recent preoperative SCr level. The new STS risk models have not been externally validated. The STS online calculator is available at <http://209.220.160.181/STSWebRiskCalc261/>.

Simplified Renal Index (SRI)

Wijeysundera et al developed the SRI score from a Toronto cohort [23]. Patients who required pre-operative dialysis, had a SCr ≥ 3.4 mg/dL, and/or required procedures such as heart transplant and ventricular assist device insertion were excluded. Initiation of dialysis was at the discretion of the clinical nephrologists. The derivation cohort included 10,571 patients who underwent cardiac surgery under cardiopulmonary bypass (CPB) at Toronto General Hospital. The rate of AKI requiring dialysis was 1.3% in the derivation cohort. The score consisted of 8 variables and was validated in two distinct cohorts: 2,566 cases at Toronto General Hospital during a different time period and 6,814 cases at the Ottawa Heart Institute, both with an AUC 0.78. Using the validation cohorts, the SRI was also compared against other models available. In this analysis, the Cleveland Clinic score had the highest discrimination in the Toronto and Ottawa validation cohorts, AUC 0.81 and 0.80, respectively, compared to the other predictive indices, including the SRI. The SRI has been

externally validated in small cohorts in Poland [29] and Spain [28], in which the model required recalibration but discriminated well as previously discussed. When tested in a Mayo Clinic cohort [30], the SRI score showed lower discrimination power to predict AKI requiring dialysis and severe non-dialysis requiring AKI as compared to the Cleveland Clinic and STS Mehta scores.

Models Predicting Non-Dialysis Requiring AKI

Multicenter Study of Perioperative Ischemia (MCSPI) Score

The MCSPI Research Group developed a risk score to predict a renal composite event after cardiac surgery in a cohort of 4,801 patients from 70 centers in 17 countries [21]. The renal composite outcome included either renal dysfunction, defined as postoperative SCr of at least 2.0 mg/dl accompanied by an increase of at least 0.7 mg/dl from preoperative baseline, or renal failure, defined by renal dysfunction requiring dialysis or evidence of renal failure at autopsy. Patients who were scheduled to have coronary revascularization requiring the use of CPB were enrolled prospectively. Concomitant valvular surgery was not specified. The study sample was divided into two cohorts, a derivation cohort of 2,381 patients and a validation set including 2,420 patients. The incidence of the composite renal outcome was 4.8%. The risk score included 8 variables, including both preoperative variables as well as intra-operative variables. The performance of the model on the derivation set had an AUC of 0.84, and the discrimination was acceptable with an AUC of 0.8 when applied to the validation cohort. The score predicts for a composite renal outcome and can identify a broader subset of AKI patients at increased risk for complications and mortality. The model includes intra-operative variables, thus a risk prediction cannot be made prior to surgery to assist in preoperative counseling or medical optimization. The sample size used to create this model is relatively small though it has an advantage of being a multi-center and multi-national cohort. The MCSPI risk score has yet to be externally validated.

Acute Kidney Injury After Cardiac Surgery (AKICS) Score

The AKICS Score was developed from a prospective study of 603 patients who underwent elective CABG and/or valve replacement surgery at the Heart Institute of the University of São Paulo, Brazil [22]. AKI was defined as an increase of SCr above 2.0 mg/dl within 7 days after cardiac surgery in patients with a baseline SCr less than 1.5 mg/dl. For patients with a baseline SCr between 1.5 and 3.0 mg/dl, AKI was defined as a SCr increase of 50% over the baseline value, defined as the last SCr measurement prior to hospitalization or the first SCr measurement during hospitalization. Criteria for the initiation of dialysis were not defined. Exclusion criteria consisted of: age less than 18 years or greater than 90, emergent surgeries, congenital heart disease repair, aortic aneurysm, preoperative SCr greater than 3.0 mg/dl, and renal transplant patients. The overall incidence of AKI was 11%, of whom 18% required dialysis. The AKICS score included 8 variables comprising of pre-, intra-, and post-operative variables. The discrimination of the AKICS score in the derivation sample had an AUC of 0.843. When applied to an independent, prospectively followed validation cohort of 215 patients who underwent cardiac surgery at the same institute, the AKICS score showed good discrimination with an AUC of 0.847. The AKICS score was derived and validated with small sample sizes, with fewer than a 10:1 ratio of outcome events to independent variables increasing the risk of the model overfitting the data [40]. The inclusion of intra- and post-operative variables precludes the preoperative use of the AKICS score. The AKICS has yet to be externally validated.

Northern New England Cardiovascular Disease Study Group (NNECDSG) Score

The NNECDSG score is a risk prediction model for non-dialysis requiring renal insufficiency [5]. The NNECDSG prospectively collected data on patients undergoing

isolated CABG surgery at 8 medical centers in Vermont, New Hampshire, and Maine. Patients with moderate or severe renal insufficiency, defined as an estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) equation of < 60 or < 30 (mL/min/1.73²), respectively, at baseline were excluded from the analysis. The renal outcome of severe renal insufficiency after CABG was defined as a post-operative eGFR < 30 , calculated by the highest postoperative SCr. A total of 8,363 patients were included in the derivation cohort. The overall incidence of severe renal insufficiency was 3%. AKI requiring dialysis resulted in only 0.37% of the patients. The NNECDSG risk model included 11 preoperative risk factors and discriminated modestly well in the derivation cohort with an AUC of 0.72. The main limitations of this model are the lack of internal validation with an independent validation cohort and the definition of severe renal insufficiency, as the use of the MDRD equation to estimate GFR is limited in an acute setting when SCr is not in steady state. The use of the MDRD eGFR estimation will most likely underestimate the incidence of AKI with a true GFR < 30 . The NNECDSG score has not yet been externally validated.

Comment

Currently the models for AKI requiring dialysis are the most robust and externally validated. However, dialysis events are rare (1–2%) and frequently occur several days after surgery limiting the benefit of application of these scoring systems. Models with a more sensitive definition of AKI suffer from differing definitions of AKI, small cohorts, intra-operative variables, and the lack of external validation. More studies are needed to develop and validate scores to predict milder, non-dialysis requiring AKI which is very common and contributes to several in-hospital outcomes. Among the current prediction rules for AKI requiring dialysis after cardiac surgery, the Cleveland Clinic model has been the most widely tested thus far and has shown to have high discrimination in most of the tested populations.

Clinical Implications

There continues to be a lack of therapeutic options to prevent and treat AKI. Clinical trials testing potential therapies are often limited in power given the low incidence of AKI. Given the significant mortality associated with AKI after cardiac surgery, preventive and therapeutic interventions are greatly needed. Validated prediction scores to predict both dialysis requiring and non-dialysis requiring AKI will facilitate rapid identification of high-risk patients for enrollment into AKI clinical trials thereby enhancing the power of trials to detect efficacy. It is important that a score is developed from variables that are readily available and quick to calculate in order to efficiently enroll the patients in clinical trials. An accurate, validated prediction model for AKI following cardiac surgery will also aid in clinical decision-making, patient counseling and informed decision-making, resource utilization, and preoperative medical optimization [41]. Differing definitions for model variables and AKI may affect generalizability and calibration of the risk scores, thus requiring validation in large cohorts and in a wide variety of populations in order for clinicians to appropriately determine which scoring system to apply to their specific patient population. Standardization of risk factor and AKI definitions will facilitate in the assessment of generalizability. Ultimately, further research is needed to determine whether the application of such risk scores in the clinical setting leads to improved outcomes.

Acknowledgments

Special thanks to Umo Inayam for her assistance in data acquisition and to Mark Gentry for his assistance in the development of the literature search strategy. Dr. Parikh was supported by the NIH grant R01 HL-085757. Dr. Huen was supported by NIH grant T32-DK007276-32.

Abbreviations and Acronyms

AKI	Acute kidney injury
AKICS	Acute Kidney After Cardiac Surgery
AUC	Area under the curve
CABG	Coronary artery bypass graft
CBP	Cardiopulmonary bypass
CICSS	Continuous Improvement in Cardiac Surgery Study
eGFR	Estimated glomerular filtration rate
H-L	Hosmer-Lemeshow
MCSPi	Multicenter Study of Perioperative Ischemia
MDRD	Modification of Diet in Renal Disease
NNECDSG	Northern New England Cardiovascular Disease Study Group
Scr	Serum creatinine
SRI	Simplified Renal Index
STS	Society of Thoracic Surgeons

References

1. Loef BG, Epema AH, Smilde TD, et al. Immediate postoperative renal function deterioration in cardiac surgical patients predicts in-hospital mortality and long-term survival. *J Am Soc Nephrol*. 2005; 16:195–200. [PubMed: 15563558]
2. Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT. Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. *Ann Intern Med*. 1998; 128:194–203. [PubMed: 9454527]
3. Frost L, Pedersen RS, Lund O, Hansen OK, Hansen HE. Prognosis and risk factors in acute, dialysis-requiring renal failure after open-heart surgery. *Scand J Thorac Cardiovasc Surg*. 1991; 25:161–6. [PubMed: 1780730]
4. Robert AM, Kramer RS, Dacey LJ, et al. Cardiac surgery-associated acute kidney injury: a comparison of two consensus criteria. *Ann Thorac Surg*. 2010; 90:1939–43. [PubMed: 21095340]
5. Brown JR, Cochran RP, Leavitt BJ, et al. Multivariable prediction of renal insufficiency developing after cardiac surgery. *Circulation*. 2007; 116:1139–43. [PubMed: 17846294]
6. Chertow GM, Lazarus JM, Christiansen CL, et al. Preoperative renal risk stratification. *Circulation*. 1997; 95:878–884. [PubMed: 9054745]
7. Thakar CV, Liangos O, Yared J-P, et al. ARF after open-heart surgery: Influence of gender and race. *Am J Kidney Dis*. 2003; 41:742–51. [PubMed: 12666060]
8. Landoni G, Zangrillo A, Franco A, et al. Long-term outcome of patients who require renal replacement therapy after cardiac surgery. *Eur J Anaesthesiol*. 2006; 23:17–22. [PubMed: 16390560]
9. Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J. Independent association between acute renal failure and mortality following cardiac surgery. *Am J Med*. 1998; 104:343–8. [PubMed: 9576407]
10. Lok CE, Austin PC, Wang H, Tu JV. Impact of renal insufficiency on short- and long-term outcomes after cardiac surgery. *Am Heart J*. 2004; 148:430–8. [PubMed: 15389229]
11. Lassnigg A, Schmidlin D, Mouhieddine M, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. *J Am Soc Nephrol*. 2004; 15:1597–605. [PubMed: 15153571]

12. Steyerberg EW, Bleeker SE, Moll HA, Grobbee DE, Moons KGM. Internal and external validation of predictive models: a simulation study of bias and precision in small samples. *J Clin Epidemiol*. 2003; 56:441–447. [PubMed: 12812818]
13. Vergouwe Y, Steyerberg EW, Eijkemans MJC, Habbema JDF. Substantial effective sample sizes were required for external validation studies of predictive logistic regression models. *J Clin Epidemiol*. 2005; 58:475–483. [PubMed: 15845334]
14. Peek N, Arts DGT, Bosman RJ, van der Voort PHJ, de Keizer NF. External validation of prognostic models for critically ill patients required substantial sample sizes. *J Clin Epidemiol*. 2007; 60:491–501. [PubMed: 17419960]
15. Kramer AA, Zimmerman JE. Assessing the calibration of mortality benchmarks in critical care: The Hosmer-Lemeshow test revisited*. *Crit Care Med*. 2007; 35:2052–2056. [PubMed: 17568333]
16. Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules. Applications and methodological standards. *The New England journal of medicine*. 1985; 313:793–799. [PubMed: 3897864]
17. Laupacis A, Sekar N, Stiell IG. Clinical prediction rules. A review and suggested modifications of methodological standards. *JAMA : the journal of the American Medical Association*. 1997; 277:488–494. [PubMed: 9020274]
18. Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. *Ann Intern Med*. 1999; 130:515–24. [PubMed: 10075620]
19. Thakar CV, Arrigain S, Worley S, Yared J-P, Paganini EP. A clinical score to predict acute renal failure after cardiac surgery. *J Am Soc Nephrol*. 2005; 16:162–8. [PubMed: 15563569]
20. Mehta RH, Grab JD, O'Brien SM, et al. Bedside tool for predicting the risk of postoperative dialysis in patients undergoing cardiac surgery. *Circulation*. 2006; 114:2208–16. quiz 2208. [PubMed: 17088458]
21. Aronson S, Fontes ML, Miao Y, et al. Risk index for perioperative renal dysfunction/failure: critical dependence on pulse pressure hypertension. *Circulation*. 2007; 115:733–42. [PubMed: 17283267]
22. Palomba H, de Castro I, Neto ALC, Lage S, Yu L. Acute kidney injury prediction following elective cardiac surgery: AKICS Score. *Kidney Int*. 2007; 72:624–631. [PubMed: 17622275]
23. Wijeyesundera DN, Karkouti K, Dupuis J-Y, et al. Derivation and validation of a simplified predictive index for renal replacement therapy after cardiac surgery. *JAMA*. 2007; 297:1801–9. [PubMed: 17456822]
24. Fortescue EB, Bates DW, Chertow GM. Predicting acute renal failure after coronary bypass surgery: Cross-validation of two risk-stratification algorithms. *Kidney Int*. 2000; 57:2594–2602. [PubMed: 10844629]
25. Eriksen BO, Hoff KRS, Solberg S. Prediction of acute renal failure after cardiac surgery: retrospective cross-validation of a clinical algorithm. *Nephrol Dial Transplant*. 2003; 18:77–81. [PubMed: 12480963]
26. Thakar CV, Liangos O, Yared J-P, Nelson DA, Hariachar S, Paganini EP. Predicting Acute Renal Failure after Cardiac Surgery: Validation and Re-definition of a Risk-Stratification Algorithm. *Hemodial Int*. 2003; 7:143–7. [PubMed: 19379354]
27. Di Bella I, Da Col U, Ciampichini R, et al. Validation of a new scoring system to predict the risk of postoperative acute renal failure in cardiac surgery. *G Ital Cardiol (Rome)*. 2007; 8:306–10. [PubMed: 17650689]
28. Candela-Toha A, Elias-Martin E, Abaira V, et al. Predicting acute renal failure after cardiac surgery: External validation of two new clinical scores. *Clin J Am Soc Nephrol*. 2008; 3:1260–1265. [PubMed: 18463173]
29. Knapik P, Rozentryt P, Nadziakiewicz P, Polonski L, Zembala M. Retrospective cross-validation of simplified predictive index for renal replacement therapy after cardiac surgery. *Interact Cardiovasc Thorac Surg*. 2008; 7:1101–6. [PubMed: 18669528]
30. Englberger L, Suri RM, Li Z, et al. Validation of Clinical Scores Predicting Severe Acute Kidney Injury After Cardiac Surgery. *Am J Kidney Dis*. 2010; 56:623–631. [PubMed: 20630639]

31. Heise D, Sundermann D, Braeuer A, Quintel M. Validation of a clinical score to determine the risk of acute renal failure after cardiac surgery. *Eur J Cardiothorac Surg.* 2010; 37:710–6. [PubMed: 19716313]
32. Shroyer ALW, Coombs LP, Peterson ED, et al. The Society of Thoracic Surgeons: 30-day operative mortality and morbidity risk models. *Ann Thorac Surg.* 2003; 75:1856–64. discussion 1864–5. [PubMed: 12822628]
33. Rahmanian PB, Filsoufi F, Castillo JG, et al. Predicting Postoperative Renal Failure Requiring Dialysis, and an Analysis of Long-Term Outcome in Patients Undergoing Valve Surgery. *J Heart Valve Dis.* 2008; 17:657–665. [PubMed: 19137798]
34. Antunes PE, de Oliveira JF, Antunes MJ. Risk-prediction for postoperative major morbidity in coronary surgery. *Eur J Cardiothorac Surg.* 2009; 35:760–767. [PubMed: 19243970]
35. O'Brien SM, Shahian DM, Filardo G, et al. The Society of Thoracic Surgeons 2008 Cardiac Surgery Risk Models: Part 2-Isolated Valve Surgery. *Ann Thorac Surg.* 2009; 88:S23–S42. [PubMed: 19559823]
36. Shahian DM, O'Brien SM, Filardo G, et al. The Society of Thoracic Surgeons 2008 Cardiac Surgery Risk Models: Part 1-Coronary Artery Bypass Grafting Surgery. *Ann Thorac Surg.* 2009; 88:S2–S22. [PubMed: 19559822]
37. Shahian DM, O'Brien SM, Filardo G, et al. The Society of Thoracic Surgeons 2008 Cardiac Surgery Risk Models: Part 3-Valve Plus Coronary Artery Bypass Grafting Surgery. *Ann Thorac Surg.* 2009; 88:S43–S62. [PubMed: 19559824]
38. Vives M, Monedero P, Valdivieso JRP, et al. EXTERNAL VALIDATION AND COMPARISON OF THREE SCORES TO PREDICT THE NEED FOR RENAL REPLACEMENT THERAPY AFTER CARDIAC SURGERY: A MULTICENTER COHORT. *Intensive Care Med.* 2010; 36:0824.
39. Harel Z, Chan CT. Predicting and preventing acute kidney injury after cardiac surgery. *Curr Opin Nephrol Hypertens.* 2008; 17:624–628. [PubMed: 18941357]
40. Concato J, Feinstein AR, Holford TR. The risk of determining risk with multivariable models. *Annals of internal medicine.* 1993; 118:201–210. [PubMed: 8417638]
41. Thakar CV. Predicting Acute Kidney Injury After Cardiac Surgery: How to Use the “Crystal Ball”. *Am J Kidney Dis.* 2010; 56:605–608. [PubMed: 20851315]

Figure 1.
Literature Search Strategy

Table 1

Selected AKI Risk Scores

Risk Score	CICSS [6]	Cleveland Clinic [19]	STS (Mehta) [20]	SRI [23]	MCSP1 [21]	AKICS [22]	NNECDSG [5]
Patient Population	Cardiac +/- valvular surgeries	CABG +/- valvular surgeries	CABG, Aortic/mitral valve only, or CABG + aortic/mitral valve	Cardiac surgery under CPB	CABG under CPB	Elective CABG +/- valvular surgery	Isolated CABG
Outcome Predicted	AKI-RRT	AKI-RRT	AKI-RRT	AKI-RRT	AKI	AKI	AKI
Derivation Time Period	1987–1994	1993–2002	2002–2004	1999–2004	1996–2000	2003–2005	2001–2005
Derivation Sample Size	42,733	15,838	449,524	10,751	2,381	603	8,363
Validation Time Period	1994	1993–2002	2005	2004–2005	1996–2000	2005–2006	NR
Validation Sample Size	3,795	15,839	86,009	2,566	2,420	215	NR
Number of Centers Included	43 Veterans Affairs centers in the US	Single Center	> 600 hospitals in US and Canada	Single Center	70 centers in 17 countries	Single center	8 centers in the US
Number of Variables	7	13	10 ^a	8	8	8	11
Type of Variables	Preop	Preop	Preop	Preop	Preop Intraop	Preop Intraop Postop	Preop
Incidence of Outcome (derivation cohort)	1.1%	1.7%	1.4%	1.3%	4.8%	11%	3%
Considerations	Large cohort, 99.1% male, mostly Caucasian cohort.	Single center.	Multi-center, multi-national database	Single center.	Small sample size. Multi-center, multi-national cohort.	Small sample size.	Multi-center
	Prospective internal and external validations.	prospective internal validation	Lack of prospective internal validation	Prospective internal and external validation	Prospective internal validation.	Prospective internal validation.	Lack of an independent internal validation cohort.
		Multiple external validations.		performed during initial	Lack of external validation.	Lack of external validation.	Lack of external validation.

Risk Score	CICSS [6]	Cleveland Clinic [19]	STS (Mehta) [20]	SRI [23]	MCSP1 [21]	AKICS [22]	NNECDSG [5]
	Excluded patients with preoperative SCr > 3.0 mg/dl			analysis of score. Excluded patients with preoperative SCr > 3.4 mg/dl	Broader definition of AKI.	Broader definition of AKI.	
					Unable to use preoperatively.	Unable to use preoperatively.	Use of MDRD to estimate GFR to define AKI.

Table 2

Variables Included in the Models

Variable	CICSS	Cleveland	STS (Mehta)	SRI	MCSPi	AKICS	NNECDSG
Demographics							
Age			×		×	×	×
Gender		×					×
Race			×				
Clinical							
Preoperative renal insufficiency	×	×	×	×	×	×	
Prior heart surgery	×	×	×	×			×
Advanced NYHA	×		×			×	
Congestive Heart Failure		×			×		×
Decreased Ejection Fraction		×		×			
Cardiomegaly	×						
Pulse Pressure					×		
Hypertension							×
PVD/CVD	×						×
COPD/Chronic lung disease		×	×				
Diabetes mellitus		×	×	×			×
Preoperative capillary glucose > 140						×	
MI within last 3 weeks			×				
Prior MI					×		

Variable	CICSS	Cleveland	STS (Mehta)	SRI	MCSPI	AKICS	NNECDSG
Endocarditis							
Reoperation							
Preoperative IABP	×	×	×	×			×
Emergent surgery		×		×			
Cardiogenic shock			×				
Preoperative WBC > 12,000							×
Surgery Type							
Valvular surgery	×	×	×				
CABG+valve		×	×			×	
Other cardiac procedures		×		×			
Intraoperative							
Increased CPB time					×	×	
Intraoperative > 2 inotrope requirement					×		
Intraoperative IABP					×		
Postoperative							
CVP > 14 cm H ₂ O						×	
Low Cardiac Output						×	
CABG: Coronary artery bypass graft							
COPD: Chronic obstructive pulmonary disease							
CPB: Cardiopulmonary bypass							
CVD: Cardiovascular disease							
CVP: Central Venous Pressure							
IABP: Intra-aortic balloon pump							

MI: Myocardial infarction

NYHA: New York Heart Association Functional Classification

PVD: Peripheral vascular disease

WBC: White blood cell count

Table 3

Quality Assessment of AKI Risk Scores

	CICSS	Cleveland Clinic	STS (Mehta)	SRI	MCSPI	AKICS	NNECDSCG
Inclusion criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Exclusion criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study population characteristics described	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Discussion about predictors	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Definition of measurement of predictors	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome Definition	AKI-RRT within 30 days after cardiac surgery	Postoperative AKI-RRT	Postoperative AKI-RRT	Postoperative AKI-RRT	Composite postoperative AKI or AKI-RRT ^f	Postoperative AKI ^g	Postoperative AKI ^h
Indications for dialysis defined	NR	Based on clinical judgment	NR	Decision made by consulting nephrologists	NR	NR	NR
Missing Data	Excluded ^a	Excluded	Excluded ^d	Imputed ^e	Excluded	Not specified	Imputed
Multivariable Analysis Approach	Combination	Forward	Backward	Not specified	Combination	Not specified	Backward
> 10 events per variable	Yes	Yes	Yes	Yes	Yes	No	Yes
Confidence intervals for measures of discrimination	NR	Yes	NR	Yes	NR	Yes	Yes
Internal Validation							
-Bootstrapping	Yes ^b	Yes	NR	Yes	NR	NR	Yes
-Validation Cohort	Independent ^c	Split Sample	Independent	Independent	Split Sample	Independent	NR

AKI: non-dialysis requiring acute kidney injury

AKI-RRT: acute kidney injury requiring renal replacement therapy

eGFR: estimated glomerular filtration rate

SCr: serum creatinine

NR: Not reported

- ^a Models developed with or without missing data were reported to not be appreciably different.
- ^b Bootstrap analysis on logistic regression model.
- ^c Prospective validation performed on clinical risk algorithm created by recursive partitioning.
- ^d Records with missing SCr, age, gender, and race were excluded from all consideration.
- ^e All other risk factors were imputed.
- ^f Renal dysfunction (postoperative SCr of at least 2.0 mg/dl and an increase of > 0.7mg/dl from preoperative baseline) or renal failure (requiring dialysis or evidence of renal failure at autopsy).
- ^g Increase of SCr above 2.0 mg/dl in patients with baseline SCr < 1.5 mg/dl or SCr increase of 50% over baseline in patients with baseline SCr 1.5–3.0 mg/dl.
- ^h eGFR < 30 after CABG surgery.

Table 4

ormance

	Derivation			Internal Validation			External Validation			Level of Validation	
	Sample Size	AUC/c-statistic (95% CI)	H-L	Sample Size	Method	AUC/c-statistic (95% CI)	H-L	Cohort (ref)	Sample Size	AUC/c-statistic (95% CI)	H-L
42,773	42,773	0.76 ^d	NR	42,773	100-sample bootstrap	NR	NR	[24]	8,797	0.72	p=0.28
				3,795 ^b	Prospective validation	NR	NR	[26]	22,589	0.78	NR
								[25]	2,037	0.71	p=0.4
								[23]	2,566	0.68 (0.59, 0.75)	NR
								[23]	6,814	0.7 (0.66, 0.74)	NR
15,838	15,838	0.81 (0.78, 0.83)	NR	15,839	Split sample validation	0.82 (0.8, 0.85)	NR	[23]	2,566	0.81 (0.74, 0.86)	NR
								[23]	6,814	0.80 (0.76, 0.83)	NR
								[27]	1,642	0.82 (0.74, 0.9)	NR
								[28]	1,780	0.86 (0.81, 0.9)	p=0.17 ^c
								[31]	3,508	0.662 (0.646, 0.678)	NR
								[30]	12,096	0.86 (0.84, 0.88) ^d	p=0.2
										0.81 (0.79, 0.83) ^e	p=0.7
444,524	444,524	0.84 ^f 0.83 ^g	NR	86,009	Independent sample	0.83 ^g	p=0.07	[23]	2,566	0.75 (0.66, 0.83)	NR
								[23]	6,814	0.78 (0.74, 0.81)	NR
								[30]	12,096	0.81 (0.78, 0.86) ^d	p=0.6
										0.76 (0.73, 0.80) ^e	p=0.4
10,751	10,751	0.81 (0.78, 0.84)	p=0.27	10,751	200-sample bootstrap	NR	NR	[23]	6,814	0.78 (0.74, 0.81)	NR
								[28]	1,780	0.82 (0.76, 0.87)	p=0.32 ^c
								[29]	1,421	0.73 (0.62, 0.81)	NR
								[30]	12,096	0.79 (0.77, 0.82) ^d	NR
2,381	2,381	0.84	p=0.84	2,420	Split Sample validation	0.80	NR			0.75 (0.72, 0.77) ^e	NR
											1

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Derivation	Internal Validation			External Validation		Level of Validation
	Prospective validation	200-sample bootstrap	NR	NR	NR	
603	0.843 (0.78, 0.89)	0.847 (0.79, 0.9)	p=0.237	NR	NR	1
8,363	0.72 (0.68, 0.75)	0.847 (0.79, 0.9)	NR	NR	NR	0

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formance on derivation cohort, AUC reported from logistic regression model.

Validation of risk algorithm created by recursive partitioning on an independent sample.

values after logistic regression.

tested on Mayo Clinic cohort for postoperative AKI-RRT or

come of severe AKI, defined by an increase in SCr level to > 2.0 mg/dl and a 2-fold increase compared to the preoperative baseline SCr level or RRT.

all STS model, and the

S model.