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Project Title: Intraoperative prediction of cardiac surgery-associated acute kidney injury.

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SUMMARY: (no more than 250 words single spaced)

Rationale: Acute kidney injury (AKI) is a potentially fatal complication of cardiac surgery. Its pathogenesis is incompletely understood, and no specific treatments are presently available. Current models for prediction of cardiac surgery-associated AKI (CSA-AKI) are insufficient, particularly in patients without pre-existing kidney dysfunction. The inability to predict CSA-AKI is a major barrier to prevention and early treatment.

Objective: To identify the perioperative variables that can improve Thakar risk score prediction of CSA-AKI.

Methods: A prospective, observational cohort (n=289) of adult cardiac surgery patients was recruited. CSA-AKI was defined using the 2012 KDIGO serum creatinine criteria. The area under the Receiver Operating Characteristic (AUC) curve was calculated for the Thakar score alone, and for the Thakar score plus different intraoperative variables to identify improvements in discrimination.

Results: The Thakar score alone gave an AUC of 0.721 (95%CI=0.619-0.824). Nadir hematocrit during the operative period statistically improved model discrimination for post-operative AKI, as did hematocrit at initiation of cardio-pulmonary bypass (AUC=0.770, 95%CI=0.682-0.857, p=0.031). Experiencing a period of ≥ 25 minutes with MAP <55 mmHg predicted CSA-AKI (AUC=0.729, 95%CI=0.630-0.829, p=0.034). Other measures of arterial blood pressure dynamics, urine output, duration of procedure, blood transfusion and fluid balance did not improve model discrimination.

Conclusions: Nadir hematocrit and hematocrit at initiation of CPB appear to be good predictors of CSA-AKI, and may provide a target for early intervention. Intraoperative hemodynamics are generally poorly predictive of CSA-AKI; however, a period of at least 25 minutes with MAP <55 mmHg does contribute to prediction of CSA-AKI.



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Introduction

Acute kidney injury

Acute kidney injury (AKI) is an important complication of cardiac surgery associated with significantly increased morbidity¹⁻⁴, mortality^{1,2,4-10} and healthcare costs⁵. A recent systematic review and meta-analysis found the incidence of AKI to be 18% following cardiac surgery, with 2% of all patients undergoing cardiac surgery requiring renal replacement therapy (RRT)⁴. The overall mortality for cardiac surgery which is typically between 2-3%^{6,11}. When cardiac surgery-associated AKI (CSA-AKI) necessitates renal replacement therapy, 30-day mortality rates have been reported as high as 60%^{9,10}. The mildest stage of CSA-AKI (RIFLE-R) increases 30-day mortality by two-fold⁵, with mortality increasing as severity increases⁷. Even slight increases (0 to 0.5 mg/dL [0 to 44.2 μmol/L]) in serum creatinine post-operatively can cause increased 30-day mortality⁶. Not only is CSA-AKI strongly associated with mortality in the immediate post-operative period, but it also confers increased risk of mortality for up to 10 years after the surgery¹², with the greatest risk in the first 3 years⁸. Morbidity associated with CSA-AKI includes longer ICU and hospital length of stay², increased rates of infection¹³, dysfunction in multiple other organ systems^{2-4,14}, and long-term kidney dysfunction¹.

Pathophysiology of CSA-AKI

The pathogenesis of CSA-AKI is incompletely understood. Current working hypotheses have proposed that CSA-AKI is secondary to acute tubular necrosis^{15,16} caused by the cumulative result of minor intraoperative ischemic insults¹⁶⁻²⁰, systemic inflammation^{15,21-23}, and oxidative stress^{18,22,24,25}. The tubule is particularly vulnerable to reduced blood flow, given the low oxygen tension of the renal medulla under normal physiologic conditions, and so ischemia is thought to be a dominant mechanism of CSA-AKI^{15,26}. Postulated contributors to ischemic injury during cardiac surgery include reduced arterial pressure^{27,28}, hemodilution^{19,28,29}, hemolysis^{18,20,24,30}, microthrombi formation²⁶, and endothelial dysfunction^{17,23,31} (contributed to by the lack of pulsatile blood flow on CPB, by pro-inflammatory cytokines, and by the effect of increased free hemoglobin and iron in plasma). Mean arterial pressure (MAP) may be an important determinant of ischemia. The blood pressure perfusing the kidneys is subject to a great degree of autoregulatory control; however, a minimum systemic arterial pressure is required to allow adequate perfusion. This lower limit of autoregulation varies between individuals, and has been reported in a study of cerebral autoregulation to be between 43 and 90 mmHg (mean value of 66 mmHg)³². The minimum adequate pressure during CPB has been thought to be 50-60 mmHg^{28,33,34}, which may not be sufficient for all patients. Cardiopulmonary bypass (CPB) induces inflammatory cytokines and activates complement, leading to a systemic inflammatory response. Ensuing activation of leukocytes and infiltration into tissues may cause cytotoxic damage to a variety of organs, including the kidneys.

Hemodilution and hemolysis are both associated with CPB, and may contribute to diminished delivery of oxygen to the kidneys^{18-20,24,28-30,35}. Hemodilution is largely attributable to the fluid used to prime the bypass pump for initiation of CPB, which consists of 1-2L of isotonic crystalloid. The synthetic environment of the CPB apparatus may trigger hemolysis, as may the action of the pump. Hemolysis contributes to renal injury by reducing the oxygen carrying capacity of the blood, by contributing to systemic oxidative stress by release of iron species, and by formation of casts within the nephron²⁰.

Nephrotoxins administered prior to or during surgery may also contribute to CSA-AKI^{16,36}. Recognized nephrotoxins include aminoglycoside antibiotics^{37,38}, intravenous radiocontrast³⁸, NSAIDs³⁸, aminocaproic acid, tranexamic acid, ACE inhibitors and angiotensin receptor

blockers³⁹. Transfusion of blood products, particularly packed red blood cells and albumin, has also been associated with CSA-AKI^{26,28,40,41}.

The pathophysiologic progression of CSA-AKI has been theorized to occur in four phases (Figure 1)⁴². The initiation phase occurs during the surgery¹⁶. Renal function may resolve at this point or may continue to decline through an extension phase. Whether a patient will progress into this phase depends on the duration and severity of the perfusion disturbance; patient susceptibility, including previous renal dysfunction; and the presence of aggravating factors such as nephrotoxic agents or blood transfusion^{15,16,43}. Previous research in warm ischemia suggests a threshold of 25 minutes before significant risk of kidney injury arises⁴⁴. A plateau in renal function (i.e. glomerular filtration rate) characterizes the maintenance phase, which lasts for several days post-operatively before the recovery phase begins.

The pathophysiology of each stage is unique and potentially amenable to treatment, but the initiation phase is the ideal point for diagnosis and treatment to occur as minimal permanent damage occurs in this phase¹⁶. The initiation phase of CSA-AKI is thought to be related to hypo perfusion, representing decreased metabolic function due to transient ischemia without significant cell death. As the extension phase involves tubular necrosis, it is much less readily reversible.

Treatment of CSA-AKI

Despite a great deal of investigation over recent years, no specific, effective treatments are presently available for CSA-AKI. Furosemide is ubiquitously used for volume overload^{16,26,45}, but does not reverse CSA-AKI, and may even aggravate renal injury^{45,46}. Renal replacement therapy by hemodialysis or peritoneal dialysis may be used for severe AKI, following the same indications as in other settings (i.e. acidemia, electrolyte imbalance, fluid overload, uremic symptoms not amenable to other therapy)⁴⁵; however, its role is only supportive and it does not treat the underlying injury.

Animal models consistently demonstrate the potential to treat or prevent CSA-AKI with a variety of pharmaceutical approaches⁴⁷⁻⁵¹. Unfortunately, these approaches have been largely unsuccessful in human studies⁵²⁻⁵⁸. The failure of recent attempts to elucidate therapy for CSA-AKI may be due to an incomplete understanding of the pathophysiology^{54,59}, or may be due to our present inability to diagnose AKI in the potentially reversible initiation phase.

Conversely, several measures have been found to mitigate the risk of CSA-AKI in the perioperative period. Avoidance of radiocontrast and nephrotoxic antibiotics attenuates damage^{16,26,45}, selection of anaesthetic agents for renoprotection may provide benefit^{60,61}, and optimization of fluid status and cardiac output improve renal outcomes^{45,62}. Randomized trials and systematic reviews of a several novel treatment and prevention approaches are ongoing^{54,63-67}.

Diagnosis of AKI

Diagnosis of CSA-AKI is the same as for other forms of AKI. Currently, several diagnostic definitions exist for AKI, which have been applied to research and practice in the cardiac surgery setting. These include the AKIN, RIFLE, and most recently the KDIGO guidelines criteria, which are an amalgamation of the former two⁴⁵. These definitions rely on quantification of either decreasing urine output or increasing serum creatinine.

Urinary criteria applied CSA-AKI lead to overdiagnosis, and so are generally considered to be clinically unhelpful following cardiac surgery^{68,69}. This is likely because the urine output following

cardiac surgery is a reflection of many parameters apart from renal damage, including fluids administered, diuretics administered and alterations in the renin-angiotensin-aldosterone axis over the course of the procedure.

Serum creatinine criteria are widely accepted^{45,70-72}; however, creatinine takes several days to reach diagnostic thresholds⁷². Therefore creatinine-based diagnosis may not identify CSA-AKI until into the maintenance phase, at which point the opportunity to attempt preventive measures has passed.

Novel diagnostics for AKI based on a variety of protein and RNA biomarkers for renal tubular damage have been previously described however have not yet effectively translated into clinical practice^{70,71,73-76}. Many of these are able to diagnose CSA-AKI significantly earlier than serum creatinine, typically within 6-24 hours after surgery. Several barriers to widespread adoption of these new diagnostic tests remain, including significant costs, uncertainty about when to order these tests (i.e. how to identify those at significant risk of CSA-AKI) and how to interpret the results (i.e. how to determine positive predictive value)⁷⁵.

Prediction of CSA-AKI

Accurate prediction of CSA-AKI using pre- and/or intraoperative risk factors would serve several important clinical goals. Stratifying patients by risk would inform implementation of greater reno-protective efforts and more careful surveillance of renal function for patients at highest risk. Accurate risk assessment could improve pretest probabilities for novel diagnostic tests of CSA-AKI, thereby improving the reliability of early diagnosis. Risk stratification could also be used to select patients for inclusion in trials of novel diagnostics or therapeutics.

A myriad of pre- and/or intraoperative risk factors for CSA-AKI have been identified. The most well-validated of these include age, frailty, diabetes, gender, baseline renal dysfunction, higher disease severity scores, use of vasopressors or inotropes, duration of surgery, hypoperfusion, low hematocrit, transfusion of blood products, prior cardiac surgery, type of surgery (CABG, valve or combined), and poor cardiac output after surgery, among others^{35,72,77-79}. Based on these factors, a number of predictive models have been described for CSA-AKI, and have been the subject of recent review^{77,80-84}. These include models from the Continuous Improvement in Cardiac Surgery Study¹⁰, the Thakar score (also called the Cleveland Clinic score)⁹, the Simplified Renal Index⁸⁵, the Acute Kidney Injury following Cardiac Surgery (AKICS) score⁸⁶, the Multicenter Study of Perioperative Ischemia score⁸⁷, and the Society of Thoracic Surgeons score⁸⁸.

The best-validated and most predictive model for CSA-AKI is the Thakar score (Table 1)^{77,80-84}. Originally developed and validated specifically for the prediction of RRT after cardiac surgery, it has since been validated for prediction of less severe forms CSA-AKI as well⁸⁰⁻⁸². The Thakar score uses preoperative variables to calculate a score out of 17, with a higher score corresponding to increased risk of CSA-AKI. In validation studies, the Thakar score produced an area under the receiver operator characteristic curve (AUC) between 0.662 and 0.86⁷⁷, with better prediction for RRT and poorer prediction for all CSA-AKI^{80,82}.

Overall, current models for prediction of CSA-AKI are insufficient, and perform particularly poorly in patients without kidney dysfunction at baseline. The inability to predict which patients will develop CSA-AKI is a major barrier to prevention and early treatment.

Study Objective

To identify the perioperative variables that can improve prediction of CSA-AKI.

Hypotheses

The ability of the Thakar score to predict CSA-AKI can be improved by the addition of key intraoperative variables, which include mean systemic blood pressure, blood product transfusion, fluid balance, urine output, and/or perioperative hematocrit.

Methods

The University of Manitoba Human Research Ethics Board and the Saint Boniface General Hospital Research Review Committee approved our research protocol, and all patients provided informed consent.

Study design

We employed an observational prospective cohort design. All adult patients scheduled for elective cardiac surgery at a tertiary care centre (Saint Boniface General Hospital, Winnipeg, Canada) were considered for inclusion. Patient recruitment occurred between June 2012 and July 2014. Exclusion criteria included age < 18 years, chronic kidney disease of stage V or greater (MDRD eGFR < 15 mL/min/1.73m²), currently on dialysis for any indication, previous kidney transplant, or off-pump procedure.

Data collection

Data were abstracted from patient charts as well as from the Manitoba Cardiac Surgery Database for the duration of hospital stay from time of entry to the OR to hospital discharge. All data were collected according to routine clinical practice. By using standardly collected data, the implementation of a modified risk score, if successfully demonstrated, would not generate any additional cost by virtue of using existing infrastructure. Baseline data and demographics were recorded during the pre-surgical clinic visit and/or on admission to hospital. Mean arterial pressure was monitored via an arterial catheter and recorded by the anesthetist at 5 minute intervals. Data on hematocrit from intraoperative arterial blood gas panels were abstracted at the time of arterial line placement, on initiation of CPB, one hour following the commencement of CPB, and at arrival to postoperative ICU. Surgery duration was recorded in the intraoperative record. Pump time and cross clamp time were recorded in the perfusion record. Use of blood products was recorded in a transfusion log. Volume inputs were recorded by the anaesthesiologist and perfusionist. Urine outputs for the entire operative period as well as outputs specific to the period while on CPB were recorded intraoperatively by nursing staff.

Calculated variables include the Thakar score (Table 1), average MAP, variance of the MAP, acute drop in MAP (defined as the largest decrease between consecutive measurements), change in MAP (difference between the highest and lowest values), MAP<90, MAP<65, and MAP<40 (defined as 25 minutes or longer with a MAP < 90, 65 and 40 respectively). The 25 minute time point was selected based on evidence from a study of hilar clamping for partial nephrectomy which found significantly higher negative outcomes after ischemia of this duration⁴⁴. Urine outputs were evaluated as the gross volume measured and as well were standardized into rates of urine output by dividing volumes by the durations of the operative and CPB periods.

Creatinine was measured at arrival to ICU and in the morning of each post-operative day along with other routine bloodwork.

Primary outcome

Acute kidney injury (AKI) was defined according to the 2012 KDIGO guidelines for increase in serum creatinine (rise in serum creatinine $\geq 26.5 \mu\text{M}$ within 48 hours, or serum creatinine $\geq 150\%$ baseline within 7 days). We did not include oliguria in our definition of CSA-AKI.

Statistical analyses

In order to derive most optimal predictive model for CSA-AKI, we employed a statistical approach wherein all variables under investigation were assessed by whether they could improve upon the predictive power of the Thakar score. The Hosmer and Lemeshow method was used to create a logistic regression model, which was then used to generate a Receiver Operator Characteristic curve for the Thakar score only risk model. New models were then generated by adding our variables of interest to the base Thakar risk model, and were evaluated by change in the C-statistic, which equals the area under the Receiver Operator Characteristic curve (AUC), to identify improvements in model discrimination.

Models were compared for the entire study cohort, as well as for the subgroup of patients who did not have documented pre-existing kidney dysfunction (baseline creatinine $<106 \mu\text{mol/L}$ & eGFR $\geq 60 \text{ ml/min}$).

Results

Our final cohort included 289 adult cardiac surgery patients with complete clinical data (Figure 2 and Table 2). CSA-AKI occurred at a rate of 12.1% (n=35) in the overall cohort, and at a rate of 7.5% (n=16) in the subgroup without prior kidney dysfunction.

The Thakar score alone gave an AUC of 0.721 (95%CI=0.619-0.824; Table 3) in the entire cohort and 0.596 (95%CI=0.433-0.759) in the subset without baseline kidney dysfunction. The mean Thakar score in patients who developed CSA-AKI was 3.34 ± 2.10 , compared to 1.77 ± 1.51 in those who did not develop CSA-AKI ($p < 0.001$).

Nadir hematocrit in the operative period (from entrance to OR to arrival at ICU) conferred the greatest improvement to AUC in both the overall cohort (AUC=0.783, 95%CI=0.696-0.869, $p=0.0025$) and the subset without pre-existing renal dysfunction (AUC=0.741, 95%CI=0.618-0.865, $p=0.0107$). Patients who developed CSA-AKI had a mean nadir hematocrit of 0.2472 ± 0.0321 , while those who did not had a mean of 0.2828 ± 0.0426 ($p < 0.001$).

Hematocrit at initiation of cardio-pulmonary bypass (CPB) was the only specific time point to statistically improve model discrimination in the overall cohort (AUC=0.770, 95%CI=0.682-0.857, $p=0.0311$) as well as in the subgroup without prior kidney dysfunction (AUC=0.730, 95%CI= 0.603-0.857, $p=0.0349$). Hematocrit 1 hour into CPB and at arrival to the ICU improved prediction in the overall cohort, but not in the subset without prior renal dysfunction.

Whether or not a patient underwent a period of 25 minutes or greater with MAP $< 55 \text{ mmHg}$ improved model discrimination in both the overall cohort (AUC=0.729, 95%CI=0.630-0.829, $p=0.0339$) and in the subset without prior renal dysfunction (AUC=0.615, 95%CI=0.458-0.772, $p=0.0214$).

Measurement of the total intraoperative urine output did not improve prediction of CSA-AKI on its own or when standardized for OR duration. Likewise, the urine output specific to the period on CPB did not improve model discrimination, even when standardized for duration of CPB.

Other measures of arterial blood pressure dynamics, duration of procedure, blood transfusion and fluid balance did not improve model discrimination (see Table 3).

Discussion

Nadir hematocrit, defined in this study as the lowest value among the four time points examined (arrival to OR, initiation of CPB, 1 hour into CPB, and arrival at ICU), is a strong predictor of CSA-AKI. In fact, the addition of nadir hematocrit to the Thakar score in patients without pre-existing kidney dysfunction improved the AUC to 0.741 (95%CI=0.618-0.865), which is comparable to what the Thakar score achieved in the overall cohort (AUC=0.721, 95%CI=0.619-0.824). Thus, the nadir hematocrit can rectify a key failing of the Thakar score, namely its inability to accurately predict CSA-AKI in the absence of baseline kidney dysfunction.

Decreased hematocrit is thought to reflect hemodilution, hemolysis and operative blood loss, as well as preoperative anemia, and is routinely monitored during cardiac surgery. Interestingly, hematocrit on arrival to the OR did not improve model discrimination in our cohort. This suggests that preoperative management of anemia cannot replace careful intraoperative assessment and management of hematocrit. The current recommendations are to correct hematocrit below 22-24% by transfusion of packed red blood cells^{29,92}.

This finding is also in line with a theoretical understanding of CSA-AKI as an ischemia-reperfusion injury. Recent research has found nadir hemoglobin and both preoperative and post-operative anemia to be important predictors of CSA-AKI^{19,28,93,94}. As well, hematocrit variation during surgery has been associated with CSA-AKI, and proposed as a quality indicator of operative blood management⁹⁵. Hematocrit may reflect pre-existing anemia, fluid status, CPB-related hemodilution, hemolysis, operative blood loss, etc., all of which may be important contributors to CSA-AKI and potential targets for intervention.

Intraoperative hemodynamics are insufficient predictors of CSA-AKI. This is congruent with the findings of similar studies^{33,89,90}, including analysis by our group in a previous cohort. We designed our analysis of MAP to align with a variety of past data examining renal ischemia. Previous studies had examined average MAP over the entire surgery and time below 50 mmHg or 40 mmHg, failing to find an effect on CSA-AKI. We expanded this work by including novel calculated MAP variables, including 25-minute intervals below putative renal vascular autoregulatory thresholds and several measurements of MAP variation. A 25 minute period with MAP <55 mmHg did show a statistically significant improvement CSA-AKI prediction in both the overall cohort and the subset without prior renal dysfunction as compared to the Thakar score alone. The effect size, however, was small in the overall cohort (producing an AUC of 0.729, cf. 0.721 for Thakar score alone), and somewhat larger in the subset of patients without prior renal dysfunction (AUC=0.615, cf. AUC=0.596 for Thakar score alone). Only with this added layer of sophistication was MAP a contributor to the prediction of CSA-AKI.

An improvement in model discrimination based on whether patients experienced a 25 minute period with MAP <75 mmHg also reached statistical significance only in the subset of patients without prior renal dysfunction. Given that there is no plausible reason why a period of MAP below 75 mmHg would increase risk of CSA-AKI while periods below 70, 65, and 60 mmHg do not, it seems unlikely that this finding represents a true or meaningful effect.

It remains possible that MAP has its greatest effect on AKI in specific circumstances. One study²⁸ found that MAP became a predictor of CSA-AKI only for a subgroup of patients with lower hemoglobin concentrations. Another study found that a decrease in MAP intraoperatively compared to pre-operation was predictive of CSA-AKI, while other measures of intraoperative MAP were not⁹¹. It is conceivable that MAP may interact in meaningful ways with other risk factors.

Volume of crystalloid input was not predictive of CSA-AKI, despite the fact that it should also contribute to hemodilution. This is potentially due to minimal variation in fluid inputs between patients. Likewise, we did not find significant effects of blood product administration on CSA-AKI. A recent study found that red blood cell (RBC) transfusion, previously considered to be a risk factor for CSA-AKI, does not confer significant risk if transfusions are given at hemoglobin concentrations < 8 mg/dL (i.e. when they are truly needed to prevent ischemic injury)²⁸. Curiously, the addition of platelet transfusion as a variable to the Thakar model resulted in a significantly lower AUC (=0.575, 95%CI=0.410-0.740, p= 0.0294) compared to Thakar alone. The findings that RBC or platelet transfusions do not predict CSA-AKI in our cohort suggest that current practices for transfusion at our centre are performing well.

The specific segment of the ROC curve most changed by the addition of hematocrit to the Thakar score is in the range of sensitivity between 0.75 and 1.00. This is the true in both the overall cohort (Figure 3) and especially in the subgroup without baseline kidney dysfunction (Figure 4). Improvement in this portion of the curve is even more encouraging than the improvement in C statistic, as predictive models are essentially used like screening tests, which in order to be clinically useful should have maximum sensitivity.

The Thakar score relies heavily on the presence or absence of baseline kidney dysfunction, awarding 2 points for a serum creatinine of 107 to <186 μ M (1.2 to <2.1 mg/dl) and 5 points for a serum creatinine \geq 186 μ M (2.1 mg/dl). Clearly baseline kidney dysfunction is a key predictor of CSA-AKI; however, the reliance of the Thakar score on this variable leaves it largely ineffective for predicting CSA-AKI in patients who do not have baseline kidney dysfunction. To our knowledge, ours is the first study to take a detailed look at prediction of CSA-AKI in patients who do not present with renal dysfunction. New evidence suggests that different therapies may be effective for depending on the specific risk factors and AKI severity at play. Specifically, Wetz⁶⁷ found that bicarbonate infusions reduced CSA-AKI in patients at low risk, but conferred no benefit to high risk patients. If this holds true in future studies, then analyzing risk factors for specific subgroups of patients and prediction of AKI severity may be important in guiding selection of preventive measures and treatment approaches.

Clinical implications

Lower hematocrit during CPB confers risk for CSA-AKI, and correction of low hematocrit may provide a target for early intervention. The failure of hematocrit at arrival to OR to predict CSA-AKI suggests that preoperative screening and treatment for anemia will not prevent CSA-AKI. Conversely, careful maintenance of hematocrit through the intraoperative period, especially at the initiation of CPB, may reduce risk of CSA-AKI. As well, higher hematocrit targets may be justified, especially in patients with other risk factors for CSA-AKI. CPB apparatus should be selected for low priming volume to limit hemodilution³⁵.

Predictive models of CSA-AKI based on clinical variables should be implemented in practice to inform patients of their risk of this important complication, and to guide care for high and low risk patients. Using predictive models avoids many of the pitfalls that plague attempts at implementation of novel biochemical tests⁷⁵. Data are already routinely collected, there is no need to worry about costs and reimbursement, development of standardized testing and reporting procedures for clinical labs, or training medical personnel to interpret results of a new test.

Routine monitoring of intraoperative MAP should be continued, and sustained (i.e. 25 minutes or longer) periods of MAP <55 mmHg should be avoided.

Research implications

The relationship between hematocrit, arterial pressure and the pathogenesis of CSA-AKI requires further investigation. The threshold value of hematocrit at which risk increases requires further investigation, and may in fact vary widely between individuals based on susceptibility to ischemia. If this proves to be the case, then more specific measures of renal ischemia will be required. Measurements of arterial pressure may not reflect what is occurring at the level of the kidney, and more detailed measurements of hemodynamics at the organ level, for example by catheterization of the renal vasculature, may not ultimately be practical for clinical monitoring of kidney status during cardiac surgery. Future research should shift focus away from renal perfusion in favour of examining markers of renal ischemia. Biomarkers of tubular damage may serve this purpose if they can be developed into useful point of care tests. Near-infrared spectroscopy may also be a useful tool for detecting renal ischemia⁹⁶, as may measurement of renal resistive index by translumbar doppler⁹⁷ or transesophageal echo⁹⁸.

Continued refinement and validation of predictive models based on clinical variables is merited, and attempts should be made to combine these with emerging biomarkers and physical approaches for accurate preoperative risk stratification and intraoperative or early postoperative diagnosis of CSA-AKI. Several analyses have found that biomarkers perform synergistically with one another^{71,73,76,99,100}, and combinations of clinical and biochemical parameters may prove synergistic as well. Unique advantages exist for approaches aimed at preoperative risk assessment, intraoperative risk assessment, and early diagnosis, and future studies of all of these approaches in CSA-AKI are urgently needed.

Strengths and limitations

Our study has several key strengths. Our analysis examined key clinical variables with a level of sophistication not seen in past studies. The variables selected are still routinely measured ones however, which makes our findings readily applicable to clinical practice. Moreover, our group was able to collect urine and serum samples at key points throughout the perioperative period, and in a future analysis we will be able to further improve on this predictive model by the addition of novel biomarkers.

Our study also has limitations. Power was limited in by its small size, increasing the likelihood that true effects were missed. We performed multiple exploratory analyses, which may have increased risk of false positive associations as well. Our study population was on average a lower risk population, and our results may not apply to higher risk patients. Our results therefore, should be considered hypothesis generating, and validation in a broader cohort of cardiac surgery patients is required.

Conclusions

Nadir hematocrit and hematocrit at initiation of CPB appear to be good predictors of CSA-AKI. Intraoperative hemodynamics are generally poorly predictive of CSA-AKI; however, a period of at least 25 minutes with MAP <55 mmHg does contribute to prediction of CSA-AKI.

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Tables and Figures

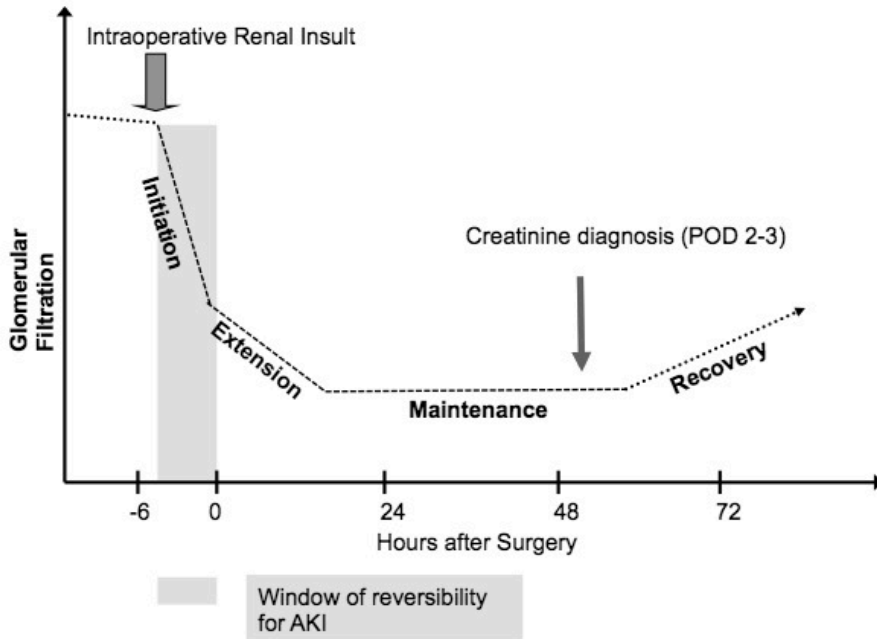


Figure 1. Pathological progression of AKI through four stages. Adapted from⁴².

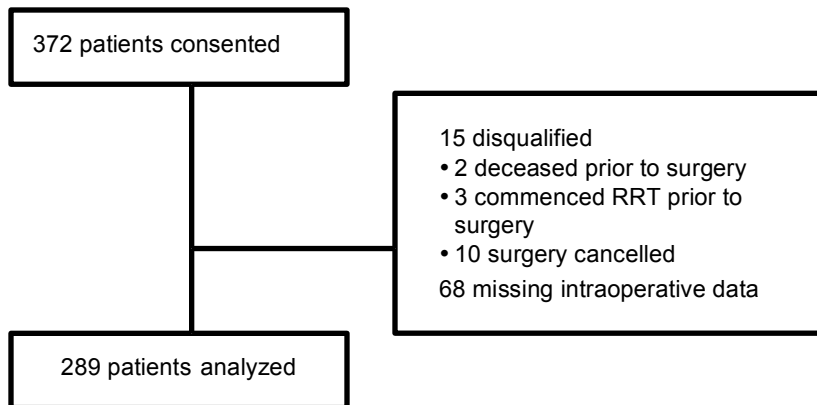


Figure 2. Development of cohort.

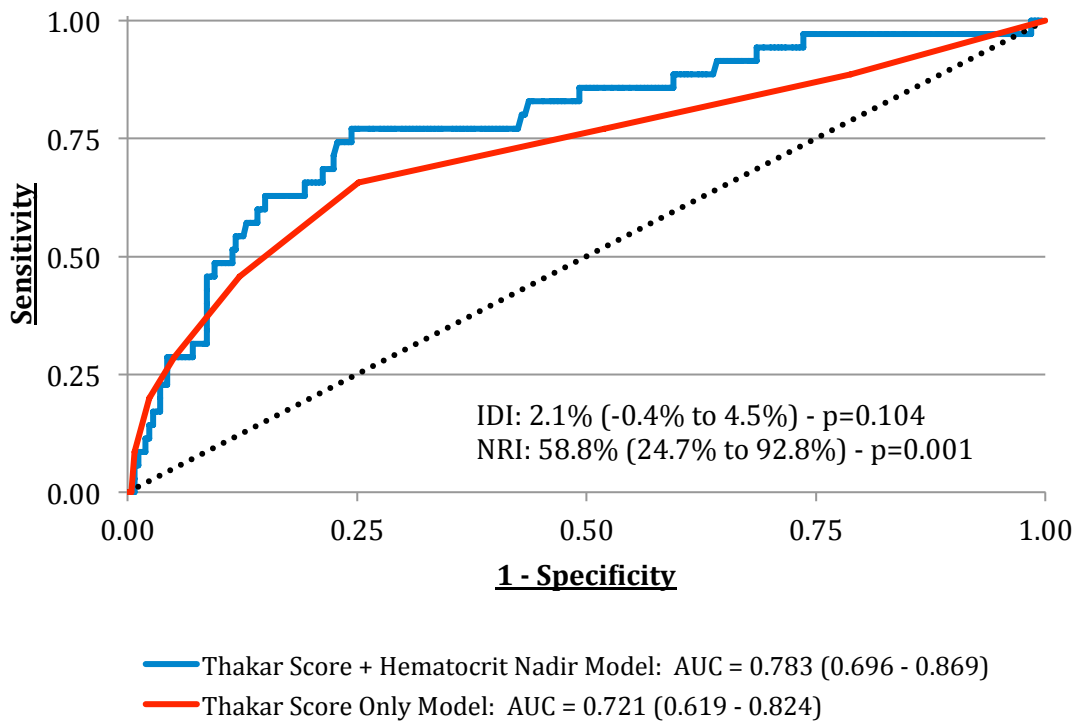


Figure 3. Comparison of Receiver Operator Characteristic (ROC) curves for the Thakar score only and the Thakar score + hematocrit nadir in the full cohort (n=289)

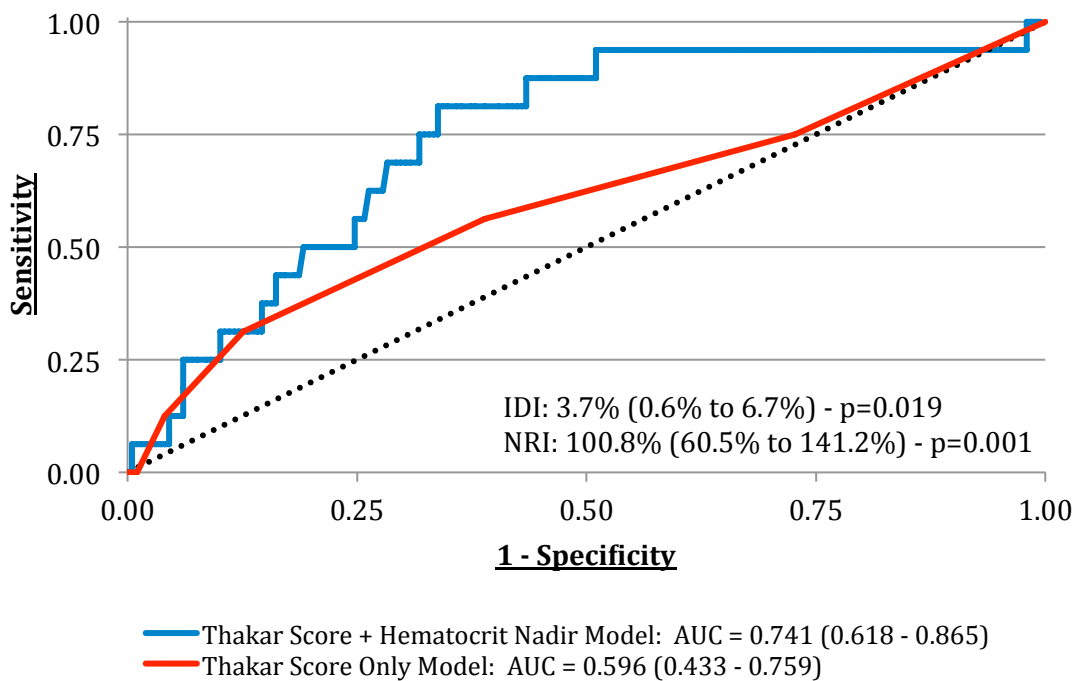


Figure 4. Comparison of Receiver Operator Characteristic (ROC) curves for the Thakar score only and the Thakar score + hematocrit nadir in the subset of patients without kidney dysfunction at baseline (n=214).

Table 1. Thakar score.

Risk Factor	Points
Female gender	1
Congestive heart failure	1
Left ventricular ejection fraction <35%	1
Preoperative use of intra-aortic balloon pump	2
Chronic obstructive pulmonary disease	1
Insulin-requiring diabetes	1
Previous cardiac surgery	1
Emergency surgery	2
Surgery type: Coronary artery bypass grafting only	0
Valve repair/replacement only	1
Coronary artery bypass grafting + valve	2
Any other cardiac surgery	2
Preoperative creatinine: 107 to <186 μ M (1.2 to <2.1 mg/dl)	2
$\geq 186 \mu$ M (≥ 2.1 mg/dl)	5
Maximum score	17

Table 2. Selected baseline characteristics of the full cohort.

	Non-AKI	AKI	P
No.	254	35	
Age (y)	65.5 (9.5)	69.0 (10.9)	0.0458*
Female (%)	23.2	31.4	0.2966
Previous CABG	2.8	5.7	0.2988
Previous cardiac intervention	9.8	14.3	0.3834
Comorbid conditions (%)			
Diabetes mellitus	29.1	57.1	0.0017*
COPD	7.5	5.7	1.0000
Heart Failure	7.5	22.9	0.0085*
Myocardial infarction	37.0	31.4	0.5780
Valve disease	37.8	57.1	0.0418*
Arrhythmia	17.3	31.4	0.0638
Hypertension	69.7	82.9	0.1156
ICD	2.0	5.7	0.2029
Peripheral artery disease	7.1	14.3	0.1739
Cerebrovascular accident	5.1	11.4	0.1356
Transient ischemic attack	4.3	2.9	1.0000
Type of surgery (% CABG)	62.6	54.3	0.3587
euroSCORE II	2.55 (3.80)	3.98 (3.28)	0.0349*
Presurgery kidney function			
Baseline serum creatinine (μ mol/L)	88.7 (26.9)	119.8 (51.9)	<0.0001*
eGFR (mL/min/1.73m ²)	80.9 (22.4)	59.7 (21.3)	<0.0001*
Within surgery variables			
OR duration (min)	287 (99)	305 (124)	0.3299
Clamp time (min)	75 (50)	81 (42)	0.4987
Pump time (min)	107 (48)	125 (54)	0.0415*
Urine output (mL)	451 (312)	391 (275)	0.2806
>2 inotropes during surgery (%)	12.2	20.0	0.0079*
Blood transfusion during surgery (%)	45.7	65.7	0.1458

*significant at $p < 0.05$.

Table 3. Areas under the Receiver Operator Characteristic curves for predictive models of CSA-AKI created by combining the Thakar score with various clinical variables.

	Full cardiac surgery cohort (n=289)			Patients without pre-existing renal dysfunction (n=214)		
	Area Under ROC Curve	(95% CI)	P-Value (Compared to Thakar Only)	Area Under ROC Curve	(95% CI)	P-Value (Compared to Thakar Only)
Thakar Score	0.721	0.619 - 0.824	-	0.596	0.433 - 0.759	-
<i>Duration</i>						
Thakar + OR Time	0.722	0.620 - 0.825	0.8950	0.626	0.482 - 0.770	0.5785
Thakar + Cross Clamp Time	0.731	0.628 - 0.833	0.1596	0.609	0.445 - 0.772	0.4111
Thakar + Pump Time	0.728	0.624 - 0.832	0.3684	0.614	0.464 - 0.765	0.6959
<i>Inputs/Outputs</i>						
Thakar + Anesthesia Input	0.731	0.627 - 0.835	0.1831	0.622	0.456 - 0.787	0.3899
Thakar + Perfusion Input	0.737	0.633 - 0.842	0.3670	0.653	0.479 - 0.826	0.3640
Thakar + Perfusion Output	0.739	0.637 - 0.839	0.0519	0.633	0.474 - 0.792	0.2017
<i>Transfusion</i>						
Thakar + Red Blood Cell Transfusion	0.751	0.650 - 0.851	0.0652	0.680	0.507 - 0.852	0.0659
Thakar + Plasma Transfusion	0.720	0.615 - 0.824	0.5437	0.575	0.410 - 0.740	0.0294*
Thakar + Platelet Transfusion	0.723	0.620 - 0.826	0.6890	0.590	0.434 - 0.747	0.8427
Thakar + Albumin	0.728	0.626 - 0.831	0.3155	0.641	0.477 - 0.805	0.4369
<i>Hematocrit</i>						
Thakar + Hematocrit (Arrival OR)	0.744	0.641 - 0.847	0.2678	0.615	0.442 - 0.787	0.6429
Thakar + Hematocrit (Start of CPB)	0.770	0.682 - 0.857	0.0311*	0.730	0.603 - 0.857	0.0349*
Thakar + Hematocrit (1 hour)	0.761	0.667 - 0.855	0.0308*	0.697	0.556 - 0.837	0.0772
Thakar + Hematocrit (Arrival ICU)	0.748	0.648 - 0.847	0.0478*	0.684	0.541 - 0.828	0.1233
Thakar + Hematocrit Nadir	0.783	0.696 - 0.869	0.0025*	0.741	0.618 - 0.865	0.0107*
<i>Blood Pressure</i>						
Thakar + Average MAP	0.724	0.620 - 0.827	0.7709	0.608	0.454 - 0.763	0.7554
Thakar + MAP Range	0.728	0.625 - 0.831	0.5093	0.632	0.465 - 0.800	0.2486
Thakar + Acute drop in MAP	0.724	0.620 - 0.828	0.7676	0.600	0.437 - 0.763	0.9398
Thakar + 25min with MAP<75	0.722	0.619 - 0.825	0.7812	0.611	0.451 - 0.770	0.0476*
Thakar + 25min with MAP<70	0.726	0.622 - 0.829	0.5195	0.597	0.429 - 0.764	0.9605
Thakar + 25min with MAP<65	0.722	0.619 - 0.826	0.9025	0.596	0.433 - 0.758	0.9616
Thakar + 25min with MAP<60	0.720	0.616 - 0.824	0.7753	0.613	0.466 - 0.760	0.6750
Thakar + 25min with MAP<55	0.729	0.630 - 0.829	0.0339*	0.615	0.458 - 0.772	0.0214*
Thakar + MAP Standard Deviation	0.720	0.615 - 0.826	0.9126	0.611	0.441 - 0.781	0.4808
<i>Urine Output</i>						
Thakar + Bypass UO	0.723	0.619 - 0.827	0.8640	0.601	0.437 - 0.764	0.7855
Thakar + Total UO	0.725	0.622 - 0.827	0.6508	0.599	0.431 - 0.766	0.8791
Thakar + Bypass UO (Standardized by OR duration)	0.738	0.637 - 0.839	0.2806	0.611	0.449 - 0.772	0.6511
Thakar + Total UO (Standardized by OR duration)	0.729	0.629 - 0.829	0.3757	0.620	0.471 - 0.769	0.4240

*significant at p<0.05