Original Investigation

Contrast Induced Nephropathy in Patients Undergoing Endovascular Peripheral Vascular Intervention: Incidence, Risk Factors, and Outcomes[1] As Observed in the Blue Cross Blue Shield of Michigan Cardiovascular Consortium

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Running Title
CIN in PVI: When, Why and So What?

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Abstract

Background: The incidence, risk factors and outcomes associated with Contrast induced nephropathy (CIN) after Percutaneous Vascular Intervention (PVI) in contemporary medical practice are largely unknown.

Methods: A total of 13,126 patients undergoing PVI were included in the analysis. CIN was defined as an increase in serum creatinine from pre-PVI baseline to post-PVI peak Cr of ≥ 0.5 mg/dL.

Results: CIN occurred in 3% (400 patients) of the cohort, and 26 patients (6.5%) required dialysis. Independent predictors of CIN were high and low body weight, diabetes, heart failure, anemia, baseline renal dysfunction, critical limb ischemia and a higher acuity of the PVI procedure and a contrast dose that was greater than three times the calculated creatinine clearance (CCC) (adjusted OR 1.4, 95% CI: 1.1 to 1.8, p=0.003). CIN was strongly associated with adverse outcome including in-hospital death (adjusted OR 18.1, CI 10.7-30.6, p < 0.001), myocardial infarction (adjusted OR 16.2, CI 8.9-29.5, p < 0.001), transient ischemic attack/stroke (adjusted OR 5.5, CI 3.2-14.9, p=0.001), vascular access complications (adjusted OR 3.4, CI 2.3-5, p < 0.001), and transfusion (adjusted OR 7, CI 5.4-9, p < 0.001). Hospital stay was longer in patients who developed CIN vs. those who did not.

Conclusions: CIN is not an uncommon complication associated with PVI, can be reliably predicted from pre-procedural variables, including a contrast dose of greater than three times the CCC and is strongly associated with the risk of in-hospital death, MI, stroke, transfusion and increased hospital length of stay.

Background

Acute decline in renal function is a well-known complication after cardiac and radiologic procedures that require contrast administration (1, 2). Among patients undergoing percutaneous coronary intervention (PCI), contrast induced nephropathy (CIN) is associated with increased morbidity, mortality, and healthcare cost (3-6). In patients with abnormal renal function at baseline, the incidence of CIN can be as high as 42% (1, 7). CIN may lead to transient or permanent need for hemodialysis, especially for high risk patients (3, 8). Predictors of CIN in patients undergoing coronary intervention have been well characterized, and include chronic kidney disease, diabetes, anemia and hemodynamic instability (3-5, 9). CIN may also be related to the volume (10, 11) and type of contrast agent administered during the procedure, with high-osmolar contrast media carrying a greater risk (12), although CIN has been reported with both low osmolar and iso-osmolar contrast media administration (12, 13).

Patients with peripheral vascular disease are increasingly being treated with percutaneous vascular intervention (PVI). While CIN would be an expected complication in this cohort, there is paucity of data on prevalence, predictors and outcome of CIN in patients undergoing PVI.

This study was undertaken to determine the incidence of and risk factors for CIN, and assess the peri-procedural outcomes in patients who develop CIN after undergoing PVI.

Methods

The study cohort for this analysis included patients undergoing PVI who were included in the Blue Cross Blue Shield of Michigan Cardiovascular Consortium Vascular Interventions Collaborative (BMC2 VIC). BMC2 VIC is a regional, multihospital, multidisciplinary, physician-led collaboration among interventional cardiologists, interventional radiologists and vascular surgeons designed to assess and improve quality of care and outcomes of patients that undergo percutaneous peripheral vascular interventional (PVI) procedures (14, 15). Data on all patients undergoing PVI at the participating hospitals were collected using standardized data collection form. Baseline data included demographics, clinical presentation, comorbidities, procedural, and angiographic characteristics as well as medications used before, during and after the procedure, and in-hospital outcomes. All data elements have been prospectively defined, and the registry has been approved or the need for approval waived by IRBs at each of the participating institutions. The data were collected by a trained and dedicated staff member and forwarded to the coordinating center. An audit of all major outcomes including death, stroke, myocardial infarction, emergent vascular surgery, transfusion and CIN, and a random audit of 5% of cases irrespective of outcome is performed at each participating institution to ensure data quality.

Data were analyzed from 23052 consecutive PVI cases collected between January 1st 2010 and December 31st 2013. Patients with end stage renal failure on dialysis, renal transplant, and/or missing pre or post-procedural creatinine values were excluded, as were patients who underwent hybrid procedure defined as an open surgical and PVI during the same hospitalization. The final number of cases included for analysis was 13126.

CIN, the primary end point for this analysis, was defined as an increase in serum creatinine from baseline to post-PVI peak creatinine ≥ 0.5mg/dL (11). Peak creatinine was collected at least 24 hours post-procedure, but varied depending on the length of stay. Secondary end points include need for transfusion, myocardial infarction, TIA/stroke and in-hospital death. In-hospital death was defined as death from either cardiac or non-cardiac cause prior to discharge. Major adverse cardiac event (MACE) was defined as the composite of death, myocardial infarction, transient ischemic attack (TIA) or stroke prior to discharge.

Statistical Analyses

Baseline characteristics, in-hospital treatments, and in-hospital complications of patients who developed CIN were compared with those who did not develop CIN. For descriptive purposes, we present categorical data as frequencies and percentages. The differences between groups were compared using χ^2 or Fisher exact tests, as appropriate. Continuous variables were reported as mean ± standard deviation (SD), and differences were compared using independent t tests. We assessed the occurrence of CIN in patients based upon a ratio of contrast volume (CV) and calculated creatinine clearance (CCC), (CV/CCC) (11).

Two separate multiple logistic regression models were constructed to assess 1) the association between CIN and other adverse outcomes, and 2) the relationship between pre-procedural variables and CIN. For the first logistic regression model, different models were constructed for each adverse outcome using the predictor variables such as baseline characteristics (patient information and history), pre-procedural pharmacotherapy and

other clinically relevant variables in addition to CIN. Details can be found in Supplementary Table 1. From each constructed adverse outcome model, the exponential of the estimated CIN's coefficient and its 95% confidence interval were presented. Each model's Hosmer-Lemeshow p-value and area under a receiver operating characteristic curve (AUC) were reported as model assessment for model fitting and prediction performance, respectively.

In the second logistic regression model, the risk prediction model for CIN, we included the same pre-procedure predictor variables that were used in the adverse outcome models (see Supplement Table 1). In addition, we included a contrast volume variable to assess the impact of exceeding a contrast dose of 3X the calculated creatinine clearance (CCC), based on prior work (11) demonstrating an association between renal function adjusted contrast dose and occurrence of CIN among PCI patients. The CCC was calculated with the Cockcroft-Gault equation (19). The stepwise method based on Akaike information criteria (AIC) was applied for variable selection, and we presented all the variables that were selected. The Hosmer-Lemeshow p-value and AUC were reported as model assessment. All calculations were performed using a statistical software R version 3.0.2.

Results

A total of 13126 patients who underwent PVI during the study period were included in the analysis. The overall incidence of CIN was 3.0% (n=400). Baseline demographics and clinical characteristics of CIN and non-CIN groups are shown in Table 1. Patients who developed CIN were, in general, higher risk patients; they were older, were more

likely to have co-morbidities including diabetes, congestive heart failure (CHF) and cerebrovascular disease.

The indications for the PVI procedure and types of interventions performed are summarized in Table 1. Patients with critical limb ischemia (CLI) were noted to have significantly higher incidence of CIN. Similarly, patients who underwent below the knee PVI (most of whom had CLI) more often developed CIN, while there was no difference in CIN when PVIs were performed in other vascular beds. Pre-procedure medical therapy in patients who developed CIN compared to those who did not is also highlighted in Table 1 and was broadly similar.

CIN was associated with significant morbidity and mortality (Figure 1). Compared with patients who did not develop CIN, those with incident CIN had significantly increased rates of death, myocardial infarction, transient ischemic attack or stroke, composite MACE, vascular complications, and transfusion. Development of CIN was also associated with greater than three times longer hospitalization.

After adjusting for patient characteristics and pre-PVI pharmacotherapy, CIN remained a significant predictor of adverse in-hospital outcome associated with PVI (Figure 1). CIN was independently associated with post-PVI death, MACE, vascular access complication and transfusion.

The pre-PVI variables that were included in the developed post-PVI CIN risk model are shown in Table 2. Patient demographic and clinical factors that predicted the development of CIN included; a history of diabetes, anemia, CHF and a pre-procedural CCC < 60ml/min. Critical limb ischemia as an indication for the PVI procedure strongly predicted development of CIN (11). We further evaluated the impact of CV utilized and the interaction of CV and CCC. The risk of developing CIN was dramatically elevated in patients exceeding a CV to CCC ratio of 3 (adjusted OR: 1.4, 95% CI: 1.1 to 1.8, p = 0.003).

Discussion

Risk factors for the development of, and outcomes associated with CIN have been well documented in the setting of PCI; however, there have been few published data on CIN associated with PVI. This is the first reported, large registry-based analysis of CIN in patients undergoing PVI. The central findings of this study are summarized in Figure 2. We found that CIN after PVI occurs in 3% of cases. However, when CIN does occur, it is associated with an extremely poor in-hospital outcome, including a greater than 25 fold increased risk of death, an increased risk of MACE, transfusion, and an increased hospitalization duration. Predictors of CIN in this real-world, contemporary cohort included pre-PVI renal insufficiency, history of CHF, diabetes, anemia, and cerebrovascular disease. Patients with CLI as an indication for PVI and who undergo urgent or emergent PVI were also more likely to develop CIN. Use of higher volume of contrast normalized to baseline renal function was also strongly associated with CIN.

The health care implications of CIN are significant given the apparent relationship with patient morbidity, mortality and increased cost. Prior studies suggest that risk factors for acute renal insufficiency after contrast exposure include reduced baseline renal function, diabetes mellitus, heart failure, dehydration, previous diuretic use, hypoalbuminemia, increased age, and increased contrast volume (1, 16, 17). The incidence of acute renal insufficiency after PCI in patients with normal baseline renal function is approximately 2%; this rate increases to 20% to 30% in patients with a baseline creatinine greater than 2mg/dL (16, 18).

Chronic renal insufficiency (Cr > 1.5mg/dL or CCC < 60mL/min) has been consistently shown to increase the risk of CIN (3, 6, 16). Inadequate renal perfusion in the setting of CHF or hemodynamic instability is also associated with increased risk of CIN. While hemodynamic instability is not commonly a factor in PVI, other factors are similar and the presence of prior renal dysfunction, anemia, diabetes and total contrast volume impart an increased risk of CIN. In our analysis, CCC less than 60 mL/min was an important predictor of CIN with CCC less than 30 mL/min the strongest predictor of CIN.

Age is a well-recognized independent predictor of CIN in observational studies (19). In our study, patients who developed CIN were of older age as compared to patients who did not develop CIN. These findings have been previously documented, where the incidence of CIN in patients greater than 70 years who undergo cardiac catheterization is approximately 11% (6). However, in this cohort, age greater than 70 did not predict CIN on multivariable analysis. This finding is consistent with a previously published study that demonstrated the overall relative safety of PVI in elderly patients (20).

Diabetes mellitus is one of the strongest predictors of acute renal failure after coronary intervention (17), and is commonly found in patients requiring PVI. Anemia has also been identified as an independent risk factor in multivariable analysis, perhaps related to decreased oxygen delivery to tubular cells (21). In our study, both pre-procedure anemia and diabetes were noted to predict CIN. Hence, PVIs should be performed with extra caution in such patients and contrast dosing should be minimized.

In our study, the CV/CCC ratio was directly related to the risk of CIN. This ratio has been validated in a large cohort of patients undergoing percutaneous coronary intervention (11). Similar to the PCI cohort, we found that a CV/CCC of > 3 was associated with an increased risk of CIN.

The choice of the contrast media used may also influence the risk of CIN. However, most of the excessive risk is associated with use of high osmolar contrast and recent data suggest little difference in risk of CIN between most low osmolar and iso-osmolar contrast media (12, 13). Most PVIs in our cohort were performed with non-ionic, iso-osmolar contrast agents, with the balance of patients receiving non-ionic, low osmolar contrast. Given the preponderance of iso-osmolar contrast use in our study, it is likely that our study is underpowered to define the comparative renal safety of different contrast media for PVI.

Strategies at reducing CIN include optimal case selection and risk stratification (18, 22), optimal hydration (23), minimizing contrast volume (10) and use of non-ionic contrast

agents (Iodixanol or low-osmolar contrast) (12, 24). In addition, utilization of carbon dioxide angiography has been associated with lower risk of CIN (25) and adequate peripheral arterial vessel visualization (26). We hope that a better understanding of risk factors for CIN in this population will help physicians better risk stratify patients and optimize preventive therapies.

In this study, CIN was associated with prolonged in-hospital length of stay. The economic burden of contrast related nephropathy is high. Incremental in-hospital costs associated with CIN have been reported to be more than $10,000 based upon a length of stay differential between CIN and non-CIN patients of 3.75 days (27). Interestingly, in our study, the hospital length of stay of patients who suffered CIN post-PVI was 11.6 days and the incremental average length of stay with CIN in our cohort was 9.8 days suggesting that the cost differential is likely higher. Strategies designed to avoid contrast nephropathy, therefore, have the potential to not only improve outcome but to limit the economic burden associated with this complication.

CIN has not only been associated with increased morbidity, but increased in-hospital post procedure mortality. Rich et al (6) reported 183 patients with 70 or greater years of age undergoing cardiac catheterization- including patients with prior renal insufficiency (mean serum creatinine 1.3±0.7 mg/dL). In this study, 21/183 patients (11.5%) developed progressive renal dysfunction (serum creatinine elevation > 0.5mg/dL), which persisted in five of them (24%). In-hospital mortality was significantly higher in the CIN group than age and baseline serum creatinine matched controls. McCullough et al. (16) reported

an incidence of acute renal failure after coronary interventions of 14.5%. The in-hospital mortality rate for these patients was 7.1% but increased to 35.7% for patients who required dialysis. In our study, the mortality in patients who developed CIN was 40-fold greater than the non-CIN group (11.5 vs. 0.3%, respectively). Clearly, the strong association between CIN and mortality in this study mirrors that in the PCI literature, and merits further investigation.

Study Limitations

This study is an analysis of observational data and conclusions are subject to the limitations inherent in such reports. We found an association between CIN and adverse outcome but cannot determine if the relationship is causal or casual. We conducted our analysis on a consecutive cohort of PVI patients with before and after PVI serum creatinine values. Approximately 43% of the overall cohort was not included in the analysis, with the majority due no post-PVI serum creatinine value available. While there were no significant differences in characteristics between patients in whom before and after PVI serum creatinine values were and were not available, it is possible that the rates of CIN in the overall cohort are either underestimated or overestimated. Although, the mean length of stay in non-CIN group was 3.8 days, some patients may have developed CIN after discharge; therefore, CIN in this analysis is possibly under representing the true burden of CIN after PVI in this population.

Conclusions

CIN is not uncommon following PVI and is strongly associated with the risk of in-hospital death, MI, stroke, transfusion and increased length of stay. Clinical predictors of CIN include higher and lower body weight, diabetes, heart failure, anemia, baseline renal dysfunction, critical limb ischemia and a higher acuity of the PVI procedure. Exceeding a contrast volume of greater than three times the CCC was also strongly associated with CIN, and suggests the need to minimize contrast dose in patients undergoing PVI. Further studies are warranted to reduce CIN in patients undergoing PVI.

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Figure Legend:

Figure 1.Unadjusted and adjusted odds ratios and their 95% confidence intervals for adverse outcomes comparing CIN vs. non-CIN. Frequencies, percentages for outcomes and p-values are from unadjusted numbers. P-values for adjusted odds ratio are the same as

those of unadjusted, except TIA or Stroke has p-value of 0.001. The blue vertical line is at 1.

Figure 2. Pre-procedural and procedural risk factors for the development of acute kidney injury in this study. The development of acute kidney injury was strongly associated with adverse in hospital outcome.

Table 1. Baseline Clinical Characteristics in CIN and Non-CIN group

	CIN group (n=400) N (%)	Non-CIN group (n=12726) N (%)	p value
Age (SD) years	70.7 (±12.3)	69 (±11.4)	0.007
Female (%)	200 (50)	5815 (45.7)	0.093
BMI (SD)	29.3 (7.1)	28.4 (6.3)	0.01
CAD (%)	277 (69.2)	7857 (61.7)	0.002
Afib	93 (23.2)	1810 (14.2)	<0.001
Hyperlipidemia	336 (84)	11139 (87.5)	0.039
HTN (%)	381 (95.2)	11696 (91.9)	0.014
Anemia (%)	290 (72.5)	5410 (42.5)	< 0.001
Diabetes (%)	255 (63.7)	5764 (45.3)	<0.001
CHF (%)	2601 (20.4)	170 (42.5)	<0.001
CVD/TIA (%)	150 (37.5)	3707 (29.1)	<0.001
COPD	142 (35.5)	3563 (28)	0.001
Anemia (%)	290 (72.5)	5410 (42.5)	< 0.001
CCC < 30 mL/min	61 (15.2)	561 (4.4)	<0.001
Indication			
Claudication	224 (56)	9335 (73.4)	<.001
Critical Limb ischemia	260 (65)	5304 (41.7)	<.001
Location			
Upper extremity	9 (2.2)	420 (3.3)	0.316
Renal	14 (3.5)	329 (2.6)	0.262
Mesenteric	33 (8.2)	834 (6.6)	0.183
Lower extremity	348 (87)	11248 (88.4)	0.384

Aorto – iliac	100 (25)	3497 (27.5)	0.305
Femoral – popliteal	231 (57.8)	7345 (57.7)	1.0
Below knee	135 (33.8)	3047 (23.9)	<0.001
Pre-PVI Medicine			
Aspirin	304 (76)	10574 (83.1)	<.001
Clopidogrel	191 (47.8)	6228 (48.9)	0.648
Beta Blocker	285 (71.2)	8180 (64.3)	0.004
Ace Inhibitor	170 (42.5)	6031 (47.4)	0.06
Statin	279 (69.8)	9338 (73.4)	0.108
n-acetylcysteine	83 (20.8)	1331 (10.5)	<.001
Sodium Bicarbonate Infusion	39 (9.8)	776 (6.1)	0.006
Saline Infusion	95 (23.8)	2646 (20.8)	0.151

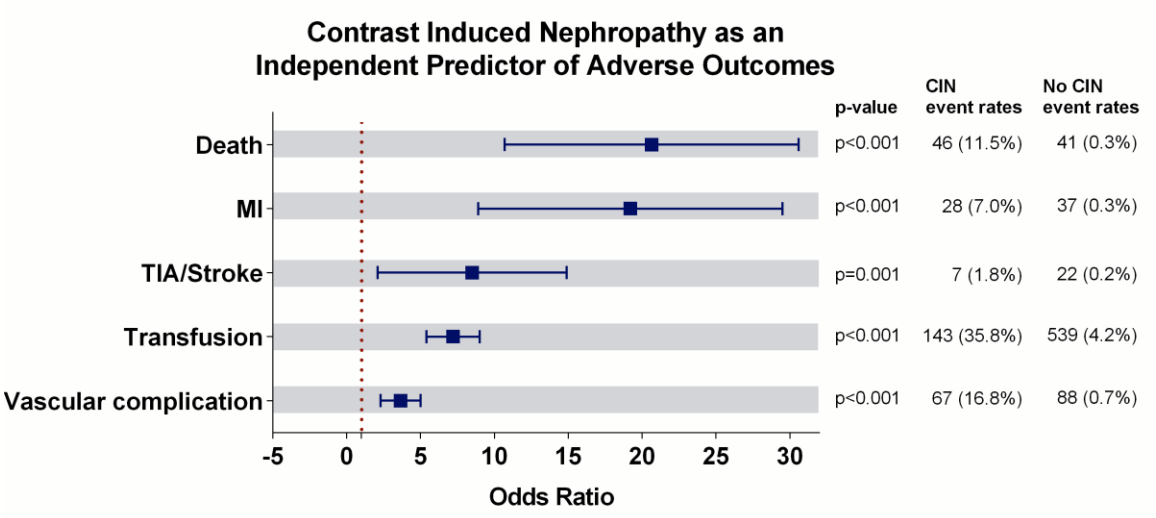
BMI = body mass index; CAD = coronary artery disease; Afib = atrial fibrillation; HTN = hypertension; CHF = congestive heart failure; CVD = cerebrovascular disease; TIA= transient ischemic attack; COPD= chronic obstructive pulmonary disease; CCC = calculated creatinine clearance.

Table 2. Pre-PVI predictors for the development of post-PVI CIN by stepwise logistic regression.

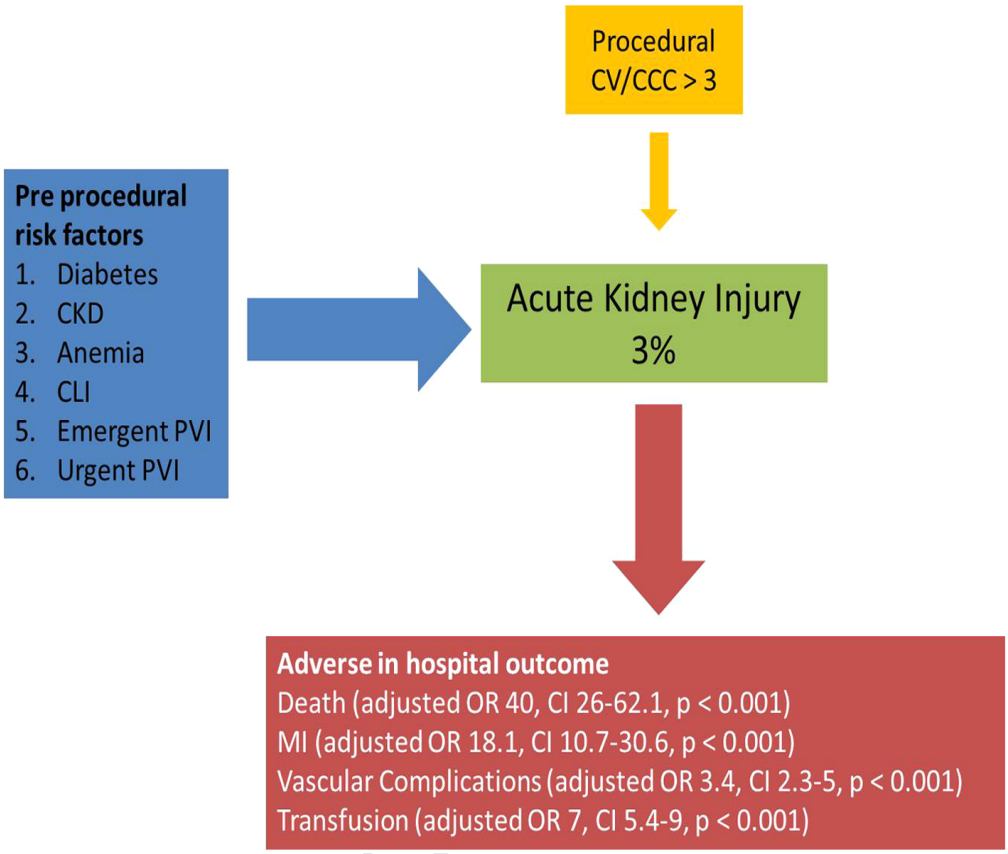
Name	Odds Ratio (95% CI)	P-value[1]
Creatinine Clearance < 30 mL/min[a]	3.1 (2.1, 4.4)	<.001
Creatinine Clearance 30 – 60 mL/min[a]	1.2 (1, 1.6)	0.112
Low BMI <18[b]	3.3 (1.2, 9)	0.024
High BMI >30[b]	4.3 (1.5, 12.2)	0.006
Pre Anemia	2 (1.6, 2.6)	<.001
Hyperlipidemia	0.8 (0.6, 1.1)	0.126
Diabetes	1.8 (1.4, 2.3)	<.001
Prior CHF	1.7 (1.3, 2.1)	<.001
COPD	0.7 (0.5, 0.9)	0.002
CVD or TIA	1.2 (1, 1.5)	0.123
Prior PCI	1.4 (1.1, 1.7)	0.013
Prior MI	1.3 (1, 1.6)	0.06
Prior CABG	0.7 (0.5, 0.9)	0.012
Aspirin (Pre procedure)	0.8 (0.6, 1)	0.101
Ace Inhibitor (Pre procedure)	0.8 (0.7, 1)	0.096
Critical Limb Ischemia	1.6 (1.2, 2.1)	<.001
Renal	1.8 (1.2, 2.7)	0.006
Status – Urgent[c]	3 (2.4, 3.9)	<.001
Status – Emergent[c]	7.7 (4.9, 12.2)	<.001
Contrast/CCC Ratio > 3[d]	1.4 (1.1, 1.8)	0.003
Model Assessment Measure		
Hosmer-Lemeshow P-value: 0.487; Area Under the ROC Curve (AUC): 0.786		

a. Reference is Creatinine clearance > 60 mL/min

b. Reference is Normal BMI (18 ≤ BMI ≤ 30)
c. Reference is Elective
d. Reference is Contrast/CCC ratio ≤ 3



Joic - Outcomes Plot JIC Fig 1 .



Joic central figure 2 .