

Association of Oral Sodium Phosphate Purgative Use with Acute Kidney Injury

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ABSTRACT

Oral sodium phosphate (OSP) is a commonly used purgative before colonoscopy. There have been numerous reports of acute phosphate nephropathy attributed to the use of OSP. This study evaluated the association between the use of OSP and acute kidney injury (AKI) in an observational, retrospective, cohort study. Of 9799 patients who underwent colonoscopy and had serum creatinine values recorded within 365 days before and after the procedure, AKI, defined as $\geq 50\%$ increase in baseline serum creatinine, was identified in 114 (1.16%). After adjustment for significant covariates in a multiple logistic regression model, the use of OSP was associated with increased risk for AKI (odds ratio 2.35; 95% confidence interval 1.51 to 3.66; $P < 0.001$) with an adjusted number need to harm of 81. Age was also independently associated with AKI in this cohort; therefore, until larger, prospective studies define the population at risk for acute phosphate nephropathy, the use of polyethylene glycol-based purgatives should be considered for older patients and possibly for those with comorbid medical conditions.

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Oral sodium phosphate (OSP) solution is commonly used for colorectal cleansing for colonoscopy. The total 90-ml dose contains approximately 10 g (111 mg/ml) of sodium and 11.5 g (4 mmol/ml) of phosphorous.¹ Its use is contraindicated in patients with preexisting renal disease because of the risk for developing renal failure or electrolyte disturbances.²

There are numerous reports of patients with previously normal renal function developing acute and chronic renal failure after the use of OSP bowel purgatives.^{3–10} Renal biopsies were performed in many of the reported cases and revealed nephrocalcinosis with intratubular deposition of calcium-phosphate.^{6–9} This new pathologic entity has been termed acute phosphate nephropathy (APN).⁶ The pathophysiology is not known, but the histopathology suggests that sodium phosphate ingestion leads to obstructive calcium-phosphate crystalluria followed by intratubular nephrocalcinosis.⁶ Advanced age, volume depletion, and the use of certain medications (nonsteroidal anti-inflammatory drugs

[NSAID], angiotensin-converting enzyme inhibitors [ACEI], angiotensin receptor blockers [ARB], and diuretics) have been suggested as possible risk factors for the development of APN after use of OSP purgatives.⁹

In May 2006, the Food and Drug Administration published an alert regarding the use of this medication.¹¹ They reported 20 additional cases of possible APN from their adverse event reporting system. They concluded that APN is a rare but serious event associated with the use of OSP. They reported that

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individuals who are at risk include those who are of advanced age, have kidney disease, have decreased intravascular volume, and use medications that affect renal perfusion or function.

Although there are cases of APN reported in the literature, millions of patients have received OSP. Without knowing the total number of exposed patients in a population, it is impossible to determine the associated risks. The objective of this study was to determine the frequency and risk of acute kidney injury (AKI) associated with OSP purgative use, compared with polyethylene glycol (PEG), the most commonly used alternative agent.

RESULTS

Study Population

A total of 16,826 patients received either a PEG- or an OSP-based purgative and had an endoscopic procedure (Table 1). Of these, 9799 (58%) patients had available creatinine values, obtained within a mean of 87.2 ± 77.2 d before and 126.0 ± 101.6 d after the procedure date. As expected, patients with available creatinine values were older, more likely to have comorbid conditions, and more likely to be taking prescribed medications. It is interesting that the OSP-treated group had a higher proportion of patients without laboratory values.

Of the patients with available laboratory values, nearly twice as many received an OSP purgative (Table 2), and significant differences were noted between the two purgative groups. Compared with patients who received OSP, patients who received PEG were older and more likely to have comorbid medical diseases (diabetes, hypertension, atherosclerotic cardiovascular disease (ASCVD), congestive heart failure (CHF),

proteinuria, and chronic kidney disease (CKD)]. They had a greater number of total physician visits and were more likely to be taking an ACEI, an ARB, or a diuretic. Patients who received PEG also had a higher preprocedure creatinine and shorter pre- and postprocedure creatinine intervals.

Primary Outcome

There were 114 cases of AKI out of 9799 patients, with a period prevalence of 1.16%. There were 83 (1.29%) AKI cases in the OSP group and 31 (0.92%) in the PEG group. On univariate analysis (Table 3), there was no significant difference in the risk for AKI with the use of OSP purgatives (odds ratio [OR] 1.41; 95% confidence interval [CI] 0.93 to 2.13; $P = 0.113$). Patients with AKI were significantly older and more likely to have diabetes, hypertension, CHF, and ASCVD. They were also more likely to be taking diuretics, ACEI, or ARB.

After adjustment for significant covariates (age [per year], diabetes, hypertension, ASCVD, ACEI or ARB use, diuretic use, and factors suspected to be associated with AKI [e.g., NSAID use, CHF, CKD, proteinuria, contrast exposure, OSP use]), OSP purgatives were found to be associated with increased risk for AKI (OR 2.35; 95% CI 1.51 to 3.66; $P < 0.001$) when compared with PEG (Table 4). Age (per year) (OR 1.06; 95% CI 1.04 to 1.08; $P < 0.001$) and CHF (OR 1.99; 95% CI 1.02 to 3.88; $P = 0.044$) were also significant. A receiver operating characteristic curve was done to test the predictive accuracy of the model with a resulting c statistic of 0.73 (95% CI 0.68 to 0.78; $P < 0.001$).

As a sensitivity analysis, alternative versions of the logistic regression model (version 1) were constructed to adjust for other potential confounders (Table 5). An alternative definition for renal injury (doubling of serum creatinine) was used as

Table 1. Patient demographics

Parameter	Patients without Laboratory Values (n = 7027; % or Mean ± SD)	Patients with Laboratory Values (n = 9799; % or Mean ± SD)	P
Age (yr)	57.7 ± 7.6	62.9 ± 9.5	<0.001
OSP purgative use	79.8	65.6	<0.001
Black race	10.2	19.0	<0.001
White race	46.4	54.1	<0.001
Male gender	58.3	54.1	<0.001
Diabetes	5.6	24.1	<0.001
Hypertension	30.8	64.0	<0.001
ASCVD	5.0	14.0	<0.001
CHF	1.0	3.5	<0.001
CKD ^a		9.6	
NSAID use	16.6	22.6	<0.001
ACEI or ARB use	11.0	29.4	<0.001
Diuretic use	9.9	24.5	<0.001
Contrast exposure		9.8	
Preprocedure creatinine (mg/dl)		1.01 ± 0.30	
Precreatinine interval (d)		87.2 ± 77.2	
Preprocedure eGFR (ml/min per 1.73 m ²)		86.0 ± 21.6	
Postprocedure creatinine (mg/dl)		1.03 ± 0.34	
Postcreatinine interval (d)		126.0 ± 101.6	

^aDefined as MDRD eGFR of <60 ml/min per 1.73 m².

Table 2. Comparison of patients by purgative type

Parameter	Purgative Type				P
	OSP (n = 6432)		PEG (n = 3367)		
	n	% or Mean ± SD	n	% or Mean ± SD	
Age (yr)		61.2 ± 8.7		66.2 ± 10.0	<0.001
Black race	961	14.9	903	26.8	<0.001
White race	3525	54.8	1780	52.9	0.070
Male gender	3493	54.3	1815	53.9	0.717
Diabetes	1151	17.9	1217	36.1	<0.001
Hypertension	3723	57.9	2554	75.9	<0.001
ASCVD	629	9.8	742	22.0	<0.001
CHF	115	1.8	224	6.7	<0.001
CKD ^a	393	6.1	552	16.4	<0.001
Proteinuria	285	4.4	234	6.9	<0.001
NSAID use	1520	23.6	696	20.7	0.001
ACEI or ARB use	1662	25.8	1223	36.3	<0.001
Diuretic use	1389	21.6	1010	30.0	<0.001
Contrast exposure	623	9.7	374	11.1	0.029
Colorectal cancer	125	1.9	69	2	0.760
Accrual period (d)		923.7 ± 430.3		983.1 ± 477.7	<0.001
No. of physician visits		10.4 ± 15.3		12.6 ± 19.3	0.001
Preprocedure creatinine (mg/dl)		0.98 ± 0.23		1.01 ± 0.40	<0.001
Precreatinine interval (d)		93.5 ± 79.5		75.0 ± 71.0	<0.001
Preprocedure eGFR (ml/min per 1.73 m ²)		88.0 ± 20.1		82.2 ± 23.8	<0.001
Postprocedure creatinine (mg/dl)		0.99 ± 0.28		1.11 ± 0.43	<0.001
Postcreatinine interval (d)		137.2 ± 104.3		104.6 ± 93.0	<0.001

^aDefined as MDRD eGFR of <60 ml/min per 1.73 m².

Table 3. Comparison of patients with and without AKI

Parameter	AKI (n = 114)		No AKI (n = 9685)		P
	n	% or Mean ± SD	n	% or Mean ± SD	
OSP purgative	83	72.8	6349	65.6	0.113
Age (yr)		68.7 ± 10.8		62.9 ± 9.4	<0.001
Black race	21	18.4	1843	19.0	1.000
White race	66	57.9	5239	54.1	0.450
Male gender	55	48.2	5253	54.2	0.219
Diabetes	39	34.2	2329	24.0	0.015
Hypertension	94	82.5	6183	63.8	<0.001
ASCVD	25	21.9	1346	13.9	0.020
CHF	12	10.5	327	3.4	0.001
CKD ^a	12	10.5	933	9.6	0.749
Proteinuria	10	8.8	509	5.3	0.134
NSAID use	28	24.6	2188	22.6	0.652
ACEI or ARB use	49	43.0	2836	29.3	0.003
Diuretic use	46	40.4	2353	24.3	<0.001
Contrast exposure	18	15.8	979	10.1	0.059
Colorectal cancer	2	1.8	192	2	1.000
Accrual period (d)		938.5 ± 461.9		944.2 ± 447.9	0.892
No. of physician visits		15.0 ± 20.8		11.1 ± 16.7	0.092
Preprocedure creatinine (mg/dl)		0.95 ± 0.35		1.02 ± 0.30	0.005
Precreatinine interval (d)		76.4 ± 68.0		87.3 ± 77.3	0.092
Preprocedure eGFR (ml/min per 1.73 m ²)		84.5 ± 25.1		86.0 ± 21.6	0.576
Postprocedure creatinine (mg/dl)		1.71 ± 1.00		1.02 ± 0.32	<0.001
Postcreatinine interval (d)		92.0 ± 85.9		126.4 ± 101.8	<0.001
Follow-up creatinine (mg/dl)		1.38 ± 0.60		1.07 ± 0.51	<0.001
Follow-up creatinine interval (d)		269.4 ± 280.4		283.0 ± 263.3	0.611

^aDefined as MDRD eGFR of <60 ml/min per 1.73 m².

Table 4. Multiple logistic regression model of factors associated with AKI^a

Covariates	OR	95% CI	P
OSP purgative	2.35	1.51 to 3.66	<0.001
Age (per year)	1.06	1.04 to 1.08	<0.001
Diabetes	1.38	0.91 to 2.09	0.131
Hypertension	1.68	0.98 to 2.88	0.060
ASCVD	1.19	0.74 to 1.92	0.483
CHF	1.99	1.02 to 3.88	0.044
CKD ^b	0.64	0.34 to 1.20	0.161
Proteinuria	1.34	0.69 to 2.63	0.390
NSAID use	1.03	0.67 to 1.60	0.889
ACEI or ARB use	1.10	0.72 to 1.67	0.660
Diuretic use	1.45	0.96 to 2.19	0.074
Contrast exposure	1.61	0.96 to 2.69	0.070

^aNo interaction noted among significant covariates. Hosmer-Lemeshow test, $P = 0.219$. Receiver operating characteristic c statistic 0.73 (95% CI 0.68 to 0.78; $P < 0.001$).

^bDefined as MDRD eGFR of <60 ml/min per 1.73 m².

the outcome variable with the same covariates in version 2. OSP purgative use remained significantly associated with increased risk for AKI (OR 3.52; 95% CI 1.13 to 10.93; $P = 0.030$) with a higher OR, despite a more “strict” definition of AKI. As expected, fewer cases of AKI ($n = 19$) resulted from the more “strict” definition, and there was a wider CI.

Patients who developed AKI had a significantly lower preprocedure creatinine (Table 3), although the difference in preprocedure estimated GFR (eGFR) was not statistically significant. Presumably, this represents laboratory artifact given the sensitive definition of AKI that was used. In addition, the postprocedure creatinine interval was significantly shorter in patients who developed AKI (Table 3) and could potentially confound results because of surveillance bias; however, when these variables were added to the regression model (version 3), OSP use remained independently associated with AKI.

To account for differences in patient “run-in” time, we added the number of physician visits and the number of accrual days to the model in version 4. When patients with preexisting renal disease or proteinuria (version 5), patients who were exposed to intravenous contrast (version 6), or patients who had a diagnosis of colorectal cancer (version 7) were excluded from the analysis, OSP use remained significantly associated with AKI. Given the substantial differences noted in the two comparison groups, propensity scores were calculated and added to the regression analysis (version 8), and after adjustment for propensity scores, OSP use remained significantly associated with AKI.

Follow-up

Of the 114 patients who developed AKI, follow-up creatinine values were available in 99 (87%) patients, with a mean follow-up of 269.4 ± 280.4 d. Follow-up creatinine values were significantly higher in patients who developed AKI with an equivalent follow-up interval (Table 3). Mean preprocedure, postprocedure, and follow-up creatinine values were $0.98 \pm$

0.34 , 1.78 ± 1.03 , and 1.38 ± 0.60 mg/dl, respectively. Among the patients with follow-up laboratory values available, creatinine had returned to baseline in only 16 (16%) patients. It is unknown whether any of these patients required renal replacement therapy during the study period, but there were no *International Classification of Diseases, Ninth Revision* (ICD-9) codes for ESRD or common procedural terminology (CPT) codes for dialysis therapy.

Safety

The unadjusted absolute risk increase of AKI with OSP purgative use was 0.38% with an unadjusted number needed to harm (NNH) of 263. Using the OR of 2.35 derived from the multivariate analysis and the PEG purgative (control) event rate of 0.93%, the adjusted NNH was found to be 81. Using the alternative definition of AKI (doubling of serum creatinine), the adjusted NNH was 298.

DISCUSSION

In the United States, approximately 14 million lower intestinal endoscopies are performed for colorectal cancer screening each year.¹² A significant number of these are performed using OSP purgatives, which have been reported to be equally safe, more effective, and better tolerated when compared with PEG-based purgatives¹³; however, reports of acute and chronic renal failure associated with OSP purgatives have questioned the safety of these medications.^{3–10}

More than 50 cases of AKI with OSP have been reported in the medical literature,^{3–11} and many of these are strengthened by biopsy-confirmed diagnosis of APN; however, several of the patients had factors (volume depletion^{3,10} preexisting renal disease,^{4,8,9} active colitis,^{4,8,10} higher than recommended dosage of OSP,^{4,5} bowel obstruction,⁷ and NSAID use.^{8,9}) that confound the association between AKI and OSP use. In our study, we attempted to reduce potential confounders by limiting our analysis to the screening colonoscopy population. We adjusted for NSAID use and preexisting renal disease, but we were unable to account for patient volume status at the time of the procedure. Of note, 393 patients with CKD received an OSP purgative despite its contraindication for use with renal disease; however, this was not a significant risk factor for AKI in our analysis.

We report a statistically significant increased risk for AKI with OSP purgative use in a screening colonoscopy population. The period prevalence of AKI with OSP was 1.29% during the 3.4-yr study period, and the adjusted NNH was 81. Our comparison groups were not equal (Table 2), but this reflects clinical practice at the time presumably related to the increased medical comorbidities and medication use in the PEG group. On univariate analysis, purgative type was not significantly associated with AKI, likely related to negative confounding.

Although the preprocedure eGFR, in contrast to preprocedure creatinine level, was not significantly associated with AKI,

Table 5. Summary of multiple logistic regression model versions (factors associated with AKI)

Model Version	OR (OSP)	95% CI	P	Model Description
1	2.35	1.51 to 3.66	<0.001	Original model ^a
2	3.52	1.13 to 10.93	0.030	Sensitivity analysis ^b
3	2.26	1.45 to 3.52	<0.001	Version 1 with addition of pre- and postcreatinine interval
4	2.44	1.57 to 3.81	<0.001	Version 1 with addition of accrual days and number of physician visits
5	2.86	1.71 to 4.81	<0.001	Version 1 with exclusion of patients with CKD or proteinuria
6	2.31	1.48 to 3.61	<0.001	Version 1 with exclusion of patients exposed to intravenous contrast
7	2.33	1.50 to 3.62	<0.001	Version 1 with exclusion of patients with colorectal cancer
8	2.71	1.48 to 5.00	0.001	Version 1 with addition of propensity scores

^aCovariates in all models (unless otherwise specified) include OSP use, age (per year), diabetes, hypertension, ASCVD, CHF, CKD, proteinuria, NSAID use, ACEI or ARB use, diuretic use, and contrast exposure.

^bAKI defined as doubling of serum creatinine; other covariates in model were the same as in version 1.

it is noteworthy that the mean serum creatinine level in the patients who developed AKI was 0.95 mg/dl. This is consistent with previous reports of patients with “normal” kidney function developing APN and that creatinine alone is not a reliable indicator of risk for AKI after OSP use.

In comparison with the largest case series,⁹ our population with AKI was slightly older and did not show the same predilection for white race or female gender. Both mean and presenting creatinine levels were lower in our population, and the pre- and postprocedure laboratory intervals were shorter. The series by Markowitz *et al.*⁹ had a longer follow-up period and overall worse outcomes to include a higher percentage of ESRD and a higher mean follow-up creatinine (mean 2.4 mg/dl; range 1.3 to 3.4 mg/dl). The worse outcomes in that series could reflect the natural progression of disease during the longer follow-up interval but may also result from selection in that all of their patients had a renal biopsy and likely represented the most severe cases of APN.

Although our outcomes were less severe, they were still clinically significant, because even small increases in creatinine have been shown to be associated with increased mortality.^{14–16} In our study, follow-up creatinine values in patients with AKI were significantly higher than the preprocedure creatinine, and only 16% of patients returned to their previous level of renal function. Follow-up creatinine values were also significantly higher when compared with patients without AKI, with an equivalent follow-up period (Table 3).

For each AKI definition used, age (per year) was independently associated with AKI. Gumurdulu *et al.*¹⁷ noted a positive correlation between age and serum phosphorous levels after OSP administration (Pearson $r = 0.705$, $P < 0.001$) in patients with relatively normal creatinine clearance (>70 ml/min); however, there was a greater increase in phosphorous in patients who were older than 56 yr ($P < 0.001$). They postulated that the greater rise in phosphorous in older patients was related to either the subclinical loss of renal function (increased tubular secretion of creatinine) or altered absorption from the increased intestinal transit time.

Limitations

Given that this is an observational retrospective study, we cannot comment on causality with regard to OSP and AKI. We attempted to exclude or adjust for known AKI risk factors in our multivariate analysis and sensitivity analyses, but there is the potential for additional unmeasured confounders, which might include differences in medication instructions before the procedure. Also, as mentioned, we could not account for the volume status of patients at the time of the procedure or when the laboratory work was done.

There was unavoidable selection bias in that patients who received an OSP-based purgative were less likely to have laboratory work done. Without laboratory values, we were unable to assess for the primary outcome; therefore, it is possible that many cases of AKI were missed. However, we believe that it is more likely that our reported risk estimates the upper limit of risk for this population, because the presumably lowest risk population had less frequent laboratory work and was excluded from analysis. Given this, our results may not be generalizable to the entire screening colonoscopy population.

It is also evident that laboratory monitoring differed substantially by purgative type. Patients who received PEG purgatives had shorter postprocedure laboratory intervals (Table 2) as did those who developed AKI (Table 3). This increase in monitoring likely reflects the increased comorbidity and medication use in these patients but also adds bias. As mentioned, episodes of AKI may have been missed in “healthier” patients as a result of decreased monitoring, but, again, we believe that our results define the upper limit of risk for this population.

We attempted to limit the analysis to screening colonoscopy patients, but it is possible that the endoscopies were not performed for screening. We were also unable to determine whether the patient actually received the prescribed purgative, but this is assumed given that they filled the prescription and underwent the procedure (procedures are routinely cancelled for inadequate preparation). We were unable to quantify the amount of purgative received, and patients may have received

additional doses of purgative if their preparation was inadequate. They also may have used other purgatives (*e.g.*, bisacodyl) in addition to the primary purgatives.

Medication use was defined by the pharmacy fill date, but we cannot confirm that patients were taking the medications as prescribed. In addition, although many NSAID are prescribed in our health care system, we cannot account for their over-the-counter use in this population, which could also lead to misclassification. Also, any misclassification in this study may not be random given the baseline differences in comparison groups.

Although the term AKI is used to describe patients who had a rise in serum creatinine value, it is possible that the interval change in creatinine was actually a slow progressive increase given the time interval between laboratory studies. In this regard, interval creatinine increase may be a more appropriate classification for creatinine change in studies of this type; however, because there is no standard definition regarding the time course of injury in outpatients, we elected to use the conventional terminology.

In summary, OSP use and older age were significantly associated with the development of AKI in this cohort of patients. Additional studies are needed to investigate further the pathophysiology of this disease, and larger, prospective studies are needed to define better the population at risk for APN. Until these studies are completed, use of PEG-based purgatives should be considered in older patients and possibly in patients with comorbid medical conditions. If OSP-based purgatives are used, then patients should be counseled on the potential risks associated with the use of this medication and screened for AKI and electrolyte abnormalities after the procedure.

CONCISE METHODS

Study Sample

We used the Composite Health Care System (I-CHCSTM), the electronic medical record of Department of Defense beneficiaries receiving healthcare in the national capital area, to identify all adults who were ≥ 50 yr and filled a prescription for an OSP- or PEG-based purgative from January 1, 2002, to May 31, 2006. Of note, all medications in this health care system are ordered electronically, and it is standard practice to prescribe several medications that are available as over-the-counter preparations (aspirin, NSAID, multivitamins, and OSP). Because the purgatives could have been used for reasons other than endoscopy, we also queried CPT codes for lower intestinal endoscopic procedures performed after the purgative was filled. The procedure date was used to determine the date of purgative exposure. From this population, we selected patients with creatinine values available both 365 d before and after purgative administration.

To reduce potential confounders, we attempted to limit the analysis to patients who had endoscopy for screening purposes. In addition to age < 50 , patients were excluded when the purgative was prescribed as an inpatient, was used for reasons other than endoscopy, or there was other evidence that the procedure was not performed for screening.

Outcome and Covariates

The primary outcome was AKI defined as an increase of $\geq 50\%$ in baseline serum creatinine. All serum creatinine values were extracted, and the pre- and postprocedure creatinine values closest to the procedure date were used to define AKI. The most recent creatinine value available was used to determine whether there was resolution of the renal injury.

Medical diagnoses were defined by the presence of at least two outpatient ICD-9 codes recorded before the purgative fill date (Appendix). Colorectal cancer was defined by the presence of two outpatient ICD-9 codes recorded before or after the colonoscopy date but before the postprocedure creatinine date to include cases diagnosed after the procedure. Because medical diagnoses depend on physician contacts, the total number of physician visits was extracted as were the number of days of available clinical data before the procedure (accrual period).

Medications were considered active when they were filled within 90 d before the procedure date. Patients were considered to have intravenous contrast exposure when they had CPT codes for cardiac catheterization, noncoronary angiography, or other radiologic study using intravenous contrast between the pre- and post-creatinine dates. Proteinuria was defined by the presence of at least 30 mg/dl protein (1+) on urinalysis dipstick before the procedure date. The Modification of Diet in Renal Disease (MDRD) equation was used to define ESRD and CKD as an eGFR of < 15 or < 60 ml/min per 1.73 m^2 , respectively.¹⁸ Values > 140 ml/min derived from the equation were considered not to be biologically plausible and were changed to missing values. Patients with ESRD were excluded from analysis.

Statistical Analyses

Oracle was used to extract data from the Integrated Clinical Database, a read-only image of the Composite Health Care System. SPSS 12.0 (SPSS, Chicago, IL) was used for statistical analysis. In univariate analysis, χ^2 testing was used for categorical variables, and *t* test was used for continuous variables with a normal distribution. α values were set at 0.05 (two-tailed). Alternative tests were used for special circumstances (Fisher exact test for categorical variables with violations of Cochran assumptions, the Wilcoxon rank sum test or Mann-Whitney test as alternatives for the *t* test for continuous variables without Gaussian distributions). Multiple logistic regression analysis was performed separately to assess factors independently associated with development of AKI. Variables suspected to be associated with AKI were included in the model, and factors with a $P < 0.05$ after multivariate analysis were considered to be independently associated with AKI. The predictive accuracy of the model was assessed using the concordance *c* index. Model fit was assessed using Hosmer-Lemeshow diagnostics.

Institutional Review

This research protocol was approved by the Walter Reed Army Medical Center Human Use Committee as an exempt review protocol.

APPENDIX: ICD-9 CODES USED TO DEFINE COMORBID MEDICAL CONDITIONS

Diabetes 250.xx, 362.0x
 Hypertension 401.xx, 402.xx, 403.xx
 ASCVD 414.xx, 443.xx, 440.9
 CHF 428.xx
 Colorectal cancer 153.x, 230.3

DISCLOSURES

None.

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