A Simple Risk Score for Prediction of Severe AKI after IV Cisplatin: Derivation and External Validation from a Contemporary Multicenter Cohort

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Introduction

- Cisplatin remains a first-line treatment option for numerous malignancies
- AKI is one of the most common toxicities caused by cisplatin
- Cisplatin-associated AKI (CP-AKI) increases susceptibility to extrarenal toxicities from cisplatin and jeopardizes eligibility for participation in clinical trials of other cancer therapies
- Accurate assessment of CP-AKI susceptibility can help clinicians weigh risks and benefits, dose-adjust, identify those who need more frequent monitoring, and allow researchers to enrich prospective cohorts
- Prior studies of risk factors for CP-AKI were limited by small sample size, lack of external validation, non-contemporary data, heterogeneous definitions of AKI, inclusion of biomarkers not readily available in clinical practice, and use of liberal definitions of AKI

We derived and externally validated a prediction model for moderate-to-severe CP-AKI using data from six large contemporary cohorts.

Methods and Materials

Study design

- Multicenter cohort study of adults treated with first dose of IV cisplatin at 6 major academic cancer centers in the US between 2006-2022
- Exclusion criteria: ESKD, missing baseline SCr, and missing a follow-up SCr in first 14 days following IV cisplatin

Primary Outcome

Moderate-to-severe CP-AKI, defined as ≥2-fold rise in SCr compared to baseline or receipt of kidney replacement therapy within 14d

Statistical analyses

- Patients divided into derivation cohort and external validation cohort (**Figure 1**)
- Multivariable logistic regression used to identify independent predictors of CP-AKI
- Continuous variables modeled with restricted cubic splines
- Development of a simple risk model (integer-based score) by evaluating continuous variables in categories and converting the covariate's odds ratio into an integer
- Patients split into low, moderate, high, and very high-risk groups
- C-statistic for primary model compared to prior models using DeLong Method

Results

Table 1: Baseline characteristics

Characteristic	Derivation Cohort (N=11,808)	Validation Cohort (N=13,321)
Demographics		
Age (years) – median (IQR)	59 (50-67)	60 (50-67)
Male sex – no. (%)	6966 (59.0)	7528 (56.5)
Race – no. (%)		
White	9529 (80.7)	10,114 (75.9)
Black	797 (6.7)	925 (6.9)
Asian/Pacific Islander	804 (6.8)	674 (5.1)
Other/Unknown	243 (2.1)	1106 (8.3)
Ethnicity – no. (%)		
Non-Hispanic	9560 (81.0)	10,358 (77.8)
Hispanic	711 (6.0)	1376 (10.3)
Body mass index – median (IQR)	26.7 (23.5-30.5)	27.0 (23.6-30.9)
Coexisting conditions		
Diabetes mellitus – no. (%)	1431 (12.1)	1896 (14.2)
Hypertension – no. (%)	2913 (24.7)	4486 (33.7)
COPD – no. (%)	1527 (12.9)	874 (6.6)
Current or former smoker – no. (%)	4792 (57.5)	4104 (30.8)
Congestive heart failure – no. (%)	91 (0.8)	376 (2.8)
Cirrhosis – no. (%)	67 (0.6)	183 (1.4)
Baseline eGFR (ml/min/1.73m^2)		
Median (IQR)	90 (75-101)	92 (77-104)
≥90 – no. (%)	5859 (49.6)	7197 (54.0)
60-89– no. (%)	4928 (41.7)	4996 (37.5)
45-59 – no. (%)	870 (7.4)	923 (6.9)
<45 – no. (%)	151 (1.3)	205 (1.5)
Laboratory Values – median (IQR)		
WBC count – per mm^3	7.1 (5.6-9.1)	7.1 (5.6-9.3)
Hemoglobin – g/dl	12.8 (11.4-14.0)	12.7 (11.2-14.0)
Platelet count – K/mm^3	255 (204-322)	245 (196-306)
Creatinine – mg/dl	0.9 (0.9-1.0)	0.8 (0.7-1.0)
Magnesium – mg/dl	2.1 (1.9-2.2)	2.0 (1.9-2.1)
Calcium – mg/dl	9.3 (9.0-9.6)	9.4 (9.0-9.7)
Albumin – g/dl	4.1 (3.7-4.4)	4.1 (3.7-4.3)
Chemotherapy		
Cisplatin (mg) – median (IQR)	90 (60-160)	70 (47-97)
Nephrotoxic chemo – no. (%)	1045 (8.8)	1044 (7.8)
Pemetrexed	675 (5.7)	282 (2.1)
Immune checkpoint inhibitors	139 (1.2)	186 (1.4)
Ifosfamide	257 (2.2)	543 (4.1)

Figure 1: Derivation and validation cohorts

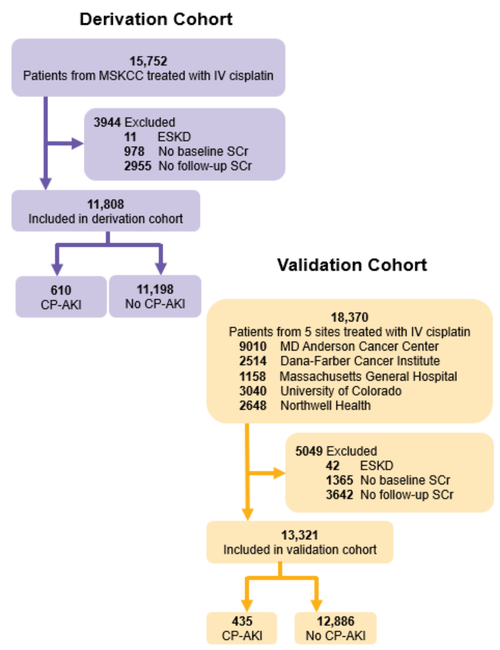


Figure 2: Risk factors and incidence of CP-AKI by risk score

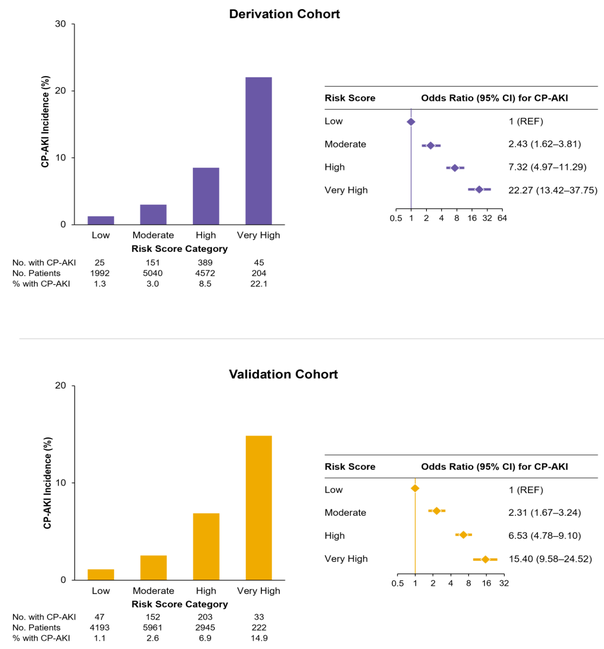


Figure 3: Incidence of CP-AKI by risk score category

Risk Factor	Odds Ratio (95% CI)	Score
Age (years)		
≤45	1 (REF)	0
46-60	2.93 (2.09–4.17)	2.5
61-70	4.13 (2.95–5.92)	3.5
>70	5.15 (3.52–7.67)	4.5
Hypertension	1.34 (1.12–1.61)	1
Diabetes	1.27 (1.00–1.60)	1
Smoker	1.19 (0.99–1.43)	1
Hemoglobin (g/dl)		
≥12.0	1 (REF)	0
<9.0	1.71 (1.13–2.54)	1.5
9.0-10.9	1.54 (1.20–1.96)	1.5
11.0-11.9	1.38 (1.06–1.77)	1
WBC count (per mm^3)		
≤12.0	1 (REF)	0
>12.0	1.61 (1.26–2.03)	1.5
Serum albumin (g/dl)		
>3.8	1 (REF)	0
3.3-3.8	1.28 (1.01–1.61)	1
<3.3	1.73 (1.30–2.29)	1.5
Serum Magnesium (mg/dl)		
≥2.0	1 (REF)	0
<2.0	1.62 (1.35–1.93)	1.5
Cisplatin dose (mg)		
≤50	1 (REF)	0
51-75	2.25 (1.54–3.35)	2
76-100	3.27 (2.16–5.00)	2.5
101-125	3.58 (2.24–5.73)	3
126-150	6.41 (4.34–9.65)	5.5
151-200	9.07 (6.24–13.50)	7.5
>200	12.02 (7.92–18.55)	10

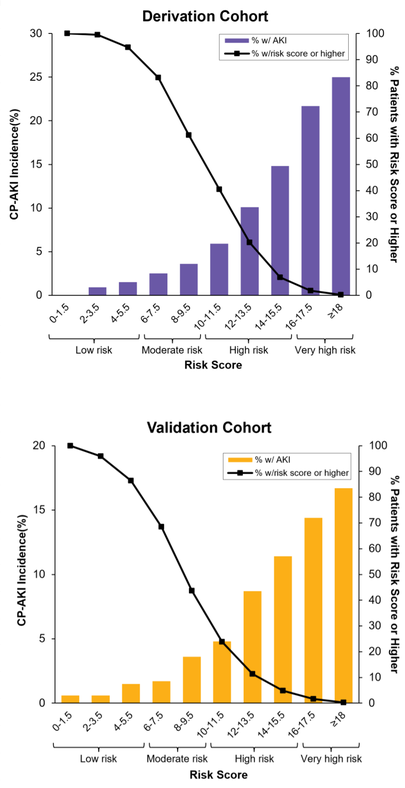
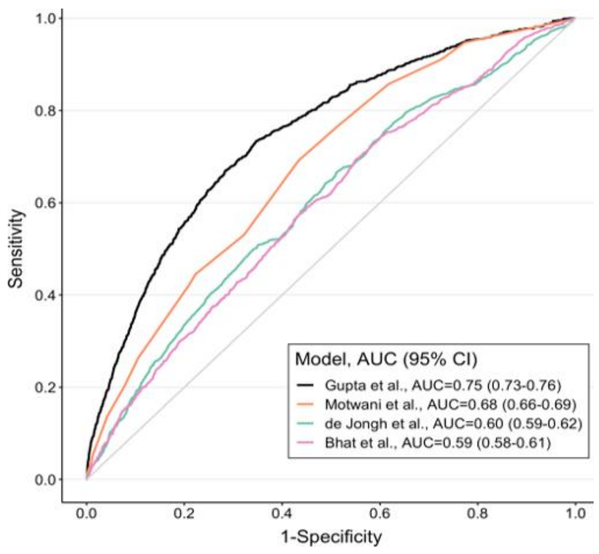
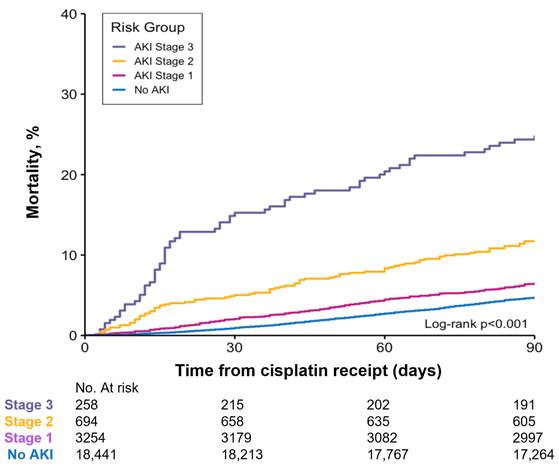


Figure 4: Performance of primary model compared to existing models



	Gupta et al.	Motwani et al.	De Jongh et al.	Bhat et al.
No. of patients	25,129	4481	400	233
Year of publication	2023	2018	2003	2015
Dates of cisplatin	2006-2022	2000-2016	1990-2001	2005-2011
Multicenter?	Y	Y	Y	N
External validation?	Y	N	N	N
Risk factors for CP-AKI				
Age	√	√	√	√
Sex			√	√
Race	√			√
Hypertension	√	√		√
Diabetes mellitus	√			√
Smoker	√		√	√
WBC count	√			
Hemoglobin	√			
Platelet count	√			
Serum creatinine	√			
Serum albumin	√	√	√	
Serum magnesium	√			
Cisplatin dose	√	√		

Figure 5: CP-AKI severity and survival



Conclusions

- In a multicenter cohort study of >25,000 adults treated with IV cisplatin, we identified key risk factors for severe AKI based on readily available variables.
- We derived and characterized a simple 9-component clinical prediction score for CP-AKI and externally validated it using data from 5 geographically-diverse hospitals across the US
- We demonstrated a strong, monotonic, and independent relationship between CP-AKI and death, underscoring the importance of identifying those at highest risk for CP-AKI.
- This model can help providers weigh the risks and benefits of administering cisplatin and will allow for enrichment of prospective studies designed to prevent CP-AKI.