Supplemental Appendix

Derivation and external validation of a simple risk score for predicting severe acute kidney injury after intravenous cisplatin: cohort study

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Supplemental Methods: Power Calculations

1) Sample size calculation for small optimism

$$S = \frac{0.1}{0.1 + 0.05 * 0.334} = 0.889$$

Assuming R^2 of approx. 0.134, expected optimism of 0.05, and max(R^2) of 0.334,(1) then:

$$n = \frac{50}{(0.889 - 1)ln\left(1 - \frac{0.134}{0.889}\right)} \approx 2757$$

2) Sample size Calculation for model validation, and allowing for estimation of observed/expected (O/E) outcome ratio:

With outcome proportion in the validation set of 0.033, assuming O/E=1 and a target CI width of 0.5,(2)

$$n = \frac{1 - 0.033}{0.033 \times (0.128^2)} \approx 1789$$

Supplemental Methods: Patient Survey

Summary:
Cisplatin is a chemotherapy that is good at treating cancer, but can hurt the kidneys. We looked at information from more than 24,000 patients who were treated with cisplatin. We identified risk factors that make kidney problems from cisplatin more likely. These risk factors include things like older age, high blood pressure, diabetes, and receiving larger doses of cisplatin.

We created a simple score to categorize patients as being at low, medium, high, or very high risk of kidney problems from cisplatin. If you're in the very high risk group, you have more than a 17-times higher risk of developing kidney problems from cisplatin than if you're in the lowest risk group. We are happy to give you your "score."

Please note that you do not have to answer any questions you do not want to and your decision to participate will not affect your present or future care. We want to know what you think about the above findings. Please answer the questions below. Each question is graded on a scale from 1 to 5, with "1" indicating the least important or least useful, and "5" indicating the most important or most useful.

How important are these findings for the scientific community?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Not Important Very Important

How important is it for patients with cancer to know about this information before getting cisplatin?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Not Important Very Important

How much would you want your cancer doctor to use this information when discussing the risks and benefits of cisplatin with you?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Not at all Very Much

How important is it to share these findings with patients with cancer?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Not Important Very Important

Is giving out flyers and pamphlets at the doctor's office is a good way to share this information with patients?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Not at all Very Much

Are patient advocacy and support groups a good way to share this information with patients?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Not at all Very Much

Are cancer societies a good way to share this information with patients?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Not at all Very Much

Is social medial (like Facebook or Twitter) a good way to share this information with patients?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Not at all Very Much

If you have any comments for suggestions on how this information should be incorporated into clinical practice or disseminated to the community, please provide them here:

Thank you for your participation!

Questions? Contact Dr. Shruti Gupta (sgupta21@bwh.harvard.edu) or Dr. David Leaf (deleaf@bwh.harvard.edu)

Table S1. ICD 9 and 10 Codes for Comorbidities

Comorbidity	ICD 9/10 Code	Description	ICD 9 or 10
Diabetes Mellitus	V12.21	History of gestational diabetes	9
	249*	Secondary diabetes mellitus	9
	250*	Type 1 diabetes mellitus & Type 2 diabetes mellitus, uncontrolled	9
	357.2	Neuropathy in diabetes	9
	362*	Diabetic retinopathy	9
	366.41	Diabetic cataracts	9
	E08*	Diabetes due to underlying condition	10
	E09*	Drug or chemical induced diabetes	10
	E10*	Type 1 diabetes mellitus	10
	E11*	Type 2 diabetes mellitus	10
	E13*	Other diabetes mellitus	10
Hypertension	401*	Essential hypertension	9
	402*	Hypertension with or without heart failure	9
	403*	Hypertensive chronic kidney disease	9
	404*	Hypertensive chronic kidney disease with or without heart failure	9
	405*	Renovascular hypertension	9
	437.20	Hypertension encephalopathy	9
	642*	Hypertension complicating pregnancy	9
	I12.9	Kidney with heart disease (see hypertension, cardiorenal)	10
	I13*	Cardiorenal (disease)	10
	I15*	Renovascular	10
	I16*	Hypertensive crisis	10
	I87*	Venous (chronic) idiopathic	10
	I11.0	With heart failure (congestive)	10
	O13*	Gestational (without significant proteinuria) (pregnancy-induced) (transient)	10
	O16*	Complicating pregnancy	10
	R03.0	Borderline	10
Congestive Heart Failure	398.91	Rheumatic heart failure	9
	402*	Hypertension with or without heart failure	9
	404*	Hypertensive chronic kidney disease with or without heart failure	9
	425.70	Metabolic cardiomyopathy	9
	428*	Congestive heart failure	9
	514.00	Pulmonary congestion/hypostasis	9
	I50*	Congestive heart failure	10
Chronic Obstructive Pulmonary Disease	490.20	Bronchitis (chronic)	9
	491.21	Obstructive pulmonary disease with (acute) exacerbation	9
	493.2	Asthma (chronic) (obstructive)	9
	496	Diffuse obstructive (chronic)	9
	J44*	Pulmonary chronic obstructive	10
Cirrhosis	571*	Cirrhosis of liver	9
	K70*	Alcoholic	10
End-Stage Renal Disease (ESRD)	585*	Chronic end-stage renal disease	9
	N18.6	End-stage renal disease (ESRD)	10
	N28.9	Renal (functional) (pelvis) end-stage (failure)	10
	I12.0	End-stage renal (ESRD) due to hypertension	10
Smoking	V15.82	History of tobacco use	9
	305.1	Tobacco use disorder	9
	649*	Tobacco use in pregnancy	9
	989.84	Toxic effect of tobacco	9
	O99*	Smoking (tobacco) complicating pregnancy	9
	Z77.22	Contact with and exposure to environmental tobacco smoke	10
	Z71.6	(acute) (chronic)	10
	Z72.0	Tobacco abuse counseling	10
		Tobacco abuse	10

*Includes all codes with the preceding numeric identifiers

Table S2. Baseline Characteristics by Outcome Status

Characteristic	Derivation Cohort		Validation Cohort	
	AKI (N=608)	No AKI (N=11,158)	AKI (N=421)	No AKI (N=12,530)
Demographics				
Age (years) – median (IQR)	63 (56-69)	59 (50-67)	62 (53-69)	60 (50-67)
Male sex – no. (%)	362/608 (59.5)	6573/11,158 (58.9)	240/421 (57.0)	7100/12,530 (56.7)
Race – no. (%)				
White	508/608 (83.6)	8987/11,158 (80.5)	309/421 (73.4)	9574/12,530 (76.4)
Black	62/608 (10.2)	731/11,158 (6.6)	55/421 (13.1)	825/12,530 (6.6)
Asian/Pacific Islander	16/608 (2.6)	787/11,158 (7.1)	12/421 (2.9)	634/12,530 (5.1)
Other/Unknown	22/608 (3.6)	653/11,158 (5.9)	45/421 (10.7)	1497/12,530 (11.9)
Ethnicity – no. (%)				
Non-Hispanic	505/608 (83.1)	9027/11,158 (80.9)	310/421 (73.6)	9755/12,530 (77.9)
Hispanic	26/608 (4.3)	682/11,158 (6.1)	39/421 (9.3)	1298/12,530 (10.4)
Body mass index – median (IQR)	27.6 (24.3-31.6)	26.7 (23.5-30.4)	28.2 (24.6-32.8)	27.0 (23.5-30.8)
Coexisting conditions				
Diabetes mellitus – no. (%)	103/608 (16.9)	1323/11,158 (11.9)	86/421 (20.4)	1747/12,530 (13.9)
Hypertension – no. (%)	200/608 (32.9)	2700/11,158 (24.2)	192/421 (45.6)	4131/12,530 (33.0)
Chronic obstructive pulmonary disease – no. (%)	101/608 (16.6)	1415/11,158 (12.7)	31/421 (7.4)	821/12,530 (6.6)
Current or former smoker – no. (%)	405/608 (66.6)	6357/11,158 (57.0)	138/421 (32.8)	3910/12,530 (31.2)
Congestive heart failure – no. (%)	7/608 (1.2)	84/11,158 (0.8)	19/421 (4.5)	352/12,530 (2.8)
Cirrhosis – no. (%)	2/608 (0.3)	65/11,158 (0.6)	7/421 (1.7)	173/12,530 (1.4)
Baseline eGFR (ml/min/1.73m^2)[a]				
Median (IQR)	91 (76-101)	90 (75-101)	93 (77-107)	92 (77-103)
≥90 – no. (%)	316/608 (52.0)	5528/11,158 (49.5)	231/421 (54.9)	6781/12,530 (54.1)
60-89 – no. (%)	246/608 (40.5)	4662/11,158 (41.8)	148/421 (35.2)	4696/12,530 (37.5)
45-59 – no. (%)	36/608 (5.9)	829/11,158 (7.4)	34/421 (8.1)	864/12,530 (6.9)
<45 – no. (%)	10/608 (1.6)	139/11,158 (1.2)	8/421 (1.9)	189/12,530 (1.5)
Laboratory Values				
WBC count – x10^9/L, median (IQR)	7.5 (5.8-9.9)	7.1 (5.6-9.1)	7.5 (5.8-10.3)	7.1 (5.6-9.2)
Hemoglobin – g/L, median (IQR)	126 (109-139)	128 (114-140)	119 (102-134)	127 (113-140)
Platelet count – x10^9/L, median (IQR)	253 (200-333)	255 (204-321)	243 (185-322)	245 (197-306)
Creatinine – µmol/L, median (IQR)	70.7 (61.9-88.4)	79.6 (61.9-88.4)	69.8 (55.7-86.6)	72.5 (61.0-86.6)
Magnesium – mmol/L, median (IQR)	0.9 (0.8-0.9)	0.9 (0.8-0.9)	0.8 (0.7-0.9)	0.8 (0.8-0.9)
Calcium – mmol/L, median (IQR)	2.3 (2.2-2.4)	2.3 (2.2-2.4)	2.3 (2.1-2.4)	2.3 (2.2-2.4)
Albumin – g/L, median (IQR)	40 (35-43)	41 (37-44)	39 (33-42)	41 (37-43)
Chemotherapy				
Cisplatin Dose (mg) – median (IQR)	140 (80-190)	85 (60-160)	100 (64-160)	70 (46-94)
Nephrotoxic chemotherapy – no. (%)[b]	65/608 (10.7)	1978/11,158 (8.8)	49/421 (11.6)	972/12,530 (7.8)
Pemetrexed	45/608 (7.4)	628/11,158 (5.6)	12/421 (2.9)	250/12,530 (2.0)
Immune checkpoint inhibitors	13/608 (2.1)	126/11,158 (1.1)	11/421 (2.6)	175/12,530 (1.4)
Cetuximab	0/608 (0.0)	0/11,158 (0.0)	1/421 (0.2)	45/12,530 (0.4)
Ifosfamide	10/608 (1.6)	247/11,158 (2.2)	26/421 (6.2)	515/12,530 (4.1)

Table Legend:

[a]eGFR was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration equation (3)

[b]Receipt of concomitant nephrotoxic chemotherapy was assessed within 30 days prior to cisplatin receipt, and included pemetrexed, immune checkpoint inhibitors (pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, ipilimumab, and cemiplimab), cetuximab, and ifosfamide.

Missing data: In the overall cohort (n=24,717), ethnicity was missing in 3075 (12.4%), body mass index in 3889 (15.7%), smoking in 1,639 (6.6%), WBC count in 275 (1.1%), hemoglobin in 270 (1.1%), platelet count in 470 (1.9%), serum magnesium in 6577 (26.6%), serum calcium in 3356 (13.6%), serum albumin in 1938 (7.8%), cisplatin dose in 83 (0.3%), and immune checkpoint inhibitors in 5 (<0.1%).

Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; WBC, white blood cell.

Table S3. Equations for CP-AKI Models

Model	Equation
Primary Model	$(-3.686659 + \{0.04421425Age + 0.0000183485(Age - 30)_+^3 - 0.0002163227(Age - 51)_+^3 + 0.0004394909(Age - 59)_+^3 - 0.0002907307(Age - 66)_+^3 + 0.0000492141(Age - 76)_+^3\}$ $- \{0.2525115Mg - 5.801969(Mg - 1.7)_+^3 + 29.89521(Mg - 1.9456)_+^3 - 43.75054(Mg - 2.1)_+^3 + 18.23788(Mg - 2.2)_+^3 + 1.419414(Mg - 2.432)_+^3\}$ $- \{0.04471118\text{Hgb} - 0.009984642(Hgb - 9.1)_+^3 + 0.07499566(Hgb - 11.6)_+^3 - 0.1355953(Hgb - 12.8)_+^3 + 0.08595369(Hgb - 13.9)_+^3 - 0.01536942(Hgb - 15.5)_+^3\}$ $+ \{0.01993736WBC - 0.003237126(WBC - 3.8)_+^3 + 0.02176998(WBC - 5.8)_+^3 - 0.03178413(WBC - 7.1)_+^3 + 0.01411246(WBC - 8.8)_+^3 - 0.0008611787(WBC - 14.5)_+^3\}$ $- \{0.4990617Alb - 0.02681548(Alb - 3)_+^3 + 4.312953(Alb - 3.8)_+^3 - 13.50495(Alb - 4.1)_+^3 + 10.66724(Alb - 4.3)_+^3 - 1.448432(Alb - 4.7)_+^3\}$ $+ \{0.04708185Cisplatin - 0.00001028397(Cisplatin - 38)_+^3 + 0.00002391644(Cisplatin - 65)_+^3 - 0.00001521614(Cisplatin - 90)_+^3 + 0.000002039042(Cisplatin - 150)_+^3 - 0.0000004553695(Cisplatin - 220)_+^3\}$ $+ \{0.00397566Plt - 0.0000005145004(Plt - 137)_+^3 + 0.00000222745(Plt - 210)_+^3 - 0.000002459005(Plt - 255)_+^3 + 0.0000007631055(Plt - 312)_+^3 - 0.00000001705063(Plt - 488)_+^3\}$ $- \{4.626802BaselineSCr + 94.00696(BaselineSCr - 0.6)_+^3 - 187.9561(BaselineSCr - 0.7)_+^3 + 232.7567(BaselineSCr - 0.9)_+^3 - 153.7796(BaselineSCr - 1.0)_+^3 + 14.97206(BaselineSCr - 1.3)_+^3\}$ $+ 0.2739952Htn + 0.2528551Diabetes)$
Secondary Outcome #1	$(-2.490598 + \{0.04000223Age + 0.00000006298178(Age - 30)_+^3 - 0.00002418857(Age - 51)_+^3 + 0.00005872481(Age - 59)_+^3 - 0.00003965045(Age - 66)_+^3 + 0.000005051239(Age - 76)_+^3\}$ $+ \{0.06689548Mg - 1.359371(Mg - 1.7)_+^3 - 4.58897(Mg - 1.9456)_+^3 + 34.63995(Mg - 2.1)_+^3 - 35.6609(Mg - 2.2)_+^3 + 6.969292(Mg - 2.432)_+^3\}$ $- \{0.03856351\text{Hgb} - 0.005212778(Hgb - 9.1)_+^3 + 0.07172748(Hgb - 11.6)_+^3 - 0.1880601(Hgb - 12.8)_+^3 + 0.1633668(Hgb - 13.9)_+^3 - 0.0418214(Hgb - 15.5)_+^3\}$ $+ \{0.07928039WBC - 0.01212509(WBC - 3.8)_+^3 + 0.05110061(WBC - 5.8)_+^3 - 0.05636264(WBC - 7.1)_+^3 + 0.01793802(WBC - 8.8)_+^3 - 0.0005508973(WBC - 14.5)_+^3\}$ $- \{0.613374Alb + 0.3375341(Alb - 3)_+^3 - 2.411267(Alb - 3.8)_+^3 + 3.335702(Alb - 4.1)_+^3 - 1.012722(Alb - 4.3)_+^3 - 0.2492469(Alb - 4.7)_+^3\}$ $+ \{0.0353438Cisplatin - 0.000006688326(Cisplatin - 38)_+^3 + 0.0000158907(Cisplatin - 65)_+^3 - 0.00001065217(Cisplatin - 90)_+^3 + 0.000001985695(Cisplatin - 150)_+^3 - 0.0000005359009(Cisplatin - 220)_+^3\}$ $- \{0.03891557\text{BMI} + 0.001334993(BMI - 19.55852)_+^3 - 0.005182263(BMI - 23.85243)_+^3 + 0.00565021(BMI - 26.7063)_+^3 - 0.001884502(BMI - 29.97543)_+^3 + 0.00008155498(BMI - 37.90634)_+^3\}$ $- \{1.034175BaselineSCr - 22.52534(BaselineSCr - 0.6)_+^3 + 54.79238(BaselineSCr - 0.7)_+^3 - 76.86693(BaselineSCr - 0.9)_+^3 + 45.4636(BaselineSCr - 1.0)_+^3 - 0.8637109(BaselineSCr - 1.3)_+^3\}$ $+ 0.2538455Htn + 0.1266644Diabetes + 0.09053564Smoking)$
Secondary Outcome #2	$(-4.153904 + \{0.02410884Age + 0.00005252085(Age - 30)_+^3 - 0.0006015845(Age - 51)_+^3 + 0.001132983(Age - 59)_+^3 - 0.0006637052(Age - 66)_+^3 + 0.00007978621(Age - 76)_+^3\}$ $+ \{0.05743622Mg - 15.30692(Mg - 1.7)_+^3 + 75.33083(Mg - 1.9456)_+^3 - 109.4739(Mg - 2.1)_+^3 + 47.02194(Mg - 2.2)_+^3 + 2.428062(Mg - 2.432)_+^3\}$ $- \{0.4181957\text{Hgb} + 0.0123466(Hgb - 9.1)_+^3 - 0.06520753(Hgb - 11.6)_+^3 + 0.09086393(Hgb - 12.8)_+^3 - 0.04377594(Hgb - 13.9)_+^3 + 0.00577293(Hgb - 15.5)_+^3\}$ $+ \{0.1589295WBC - 0.02967569(WBC - 3.8)_+^3 + 0.1497068(WBC - 5.8)_+^3 - 0.1889221(WBC - 7.1)_+^3 + 0.07247453(WBC - 8.8)_+^3 - 0.003583471(WBC - 14.5)_+^3\}$ $+ \{0.02870776Cisplatin - 0.000002161638(Cisplatin - 38)_+^3 + 0.000003402058(Cisplatin - 65)_+^3 - 0.0000009506496(Cisplatin - 90)_+^3 - 0.0000001473776(Cisplatin - 150)_+^3 - 0.0000001423929(Cisplatin - 220)_+^3\}$ $+ \{0.005083972Plt - 0.0000007825818(Plt - 137)_+^3 + 0.000003303735(Plt - 210)_+^3 - 0.000003514574(Plt - 255)_+^3 + 0.0000009951348(Plt - 312)_+^3 - 0.000000001713566(Plt - 488)_+^3\}$ $- \{1.883519BaselineSCr + 39.80574(BaselineSCr - 0.6)_+^3 - 90.60196(BaselineSCr - 0.7)_+^3 + 152.0967(BaselineSCr - 0.9)_+^3 - 114.4718(BaselineSCr - 1.0)_+^3 + 13.17128(BaselineSCr - 1.3)_+^3\}$ $+ 0.3425585Htn)$
Secondary Outcome #3	$(7.557475 + \{0.01868734Age - 0.0000003677806(Age - 30)_+^3 - 0.00007915008(Age - 51)_+^3 + 0.0002756448(Age - 59)_+^3 - 0.0002690292(Age - 66)_+^3 + 0.00007290223\ (Age - 76)_+^3\}$ $- \{0.6482215Mg + 1.194161(Mg - 1.7)_+^3 + 1.281955(Mg - 1.9456)_+^3 - 7.189057(Mg - 2.1)_+^3 + 3.832321(Mg - 2.2)_+^3 + 0.8806202(Mg - 2.432)_+^3\}$ $- \{0.1256361\text{Hgb} - 0.00345172(Hgb - 9.1)_+^3 - 0.004177308(Hgb - 11.6)_+^3 + 0.05755815(Hgb - 12.8)_+^3 - 0.07314031(Hgb - 13.9)_+^3 + 0.02321119(Hgb - 15.5)_+^3\}$ $+ \{0.2446413WBC - 0.02500308(WBC - 3.8)_+^3 + 0.119387(WBC - 5.8)_+^3 - 0.1472926(WBC - 7.1)_+^3 + 0.05593524(WBC - 8.8)_+^3 - 0.003026611(WBC - 14.5)_+^3\}$ $- \{0.83535Alb - 0.1959481(Alb - 3)_+^3 - 1.746562(Alb - 3.8)_+^3 + 14.64228(Alb - 4.1)_+^3 - 17.20088(Alb - 4.3)_+^3 + 4.501108(Alb - 4.7)_+^3\}$

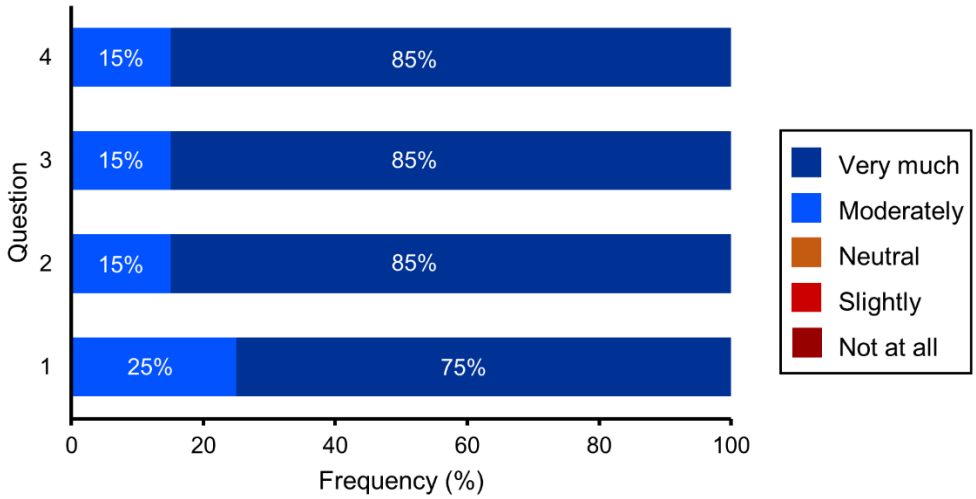
	$-\{0.01668694Cisplatin + 0.00000428506(Cisplatin - 38)_+^3 - 0.000008179878(Cisplatin - 65)_+^3 + 0.000003476913(Cisplatin - 90)_+^3 + 0.0000005143064(Cisplatin - 150)_+^3 - 0.00000009640148(Cisplatin - 220)_+^3\}$ $-\{0.09689629BMI + 0.001743043(BMI - 19.55852)_+^3 - 0.005918177(BMI - 23.85243)_+^3 + 0.005785523(BMI - 26.7063)_+^3 - 0.001715514(BMI - 29.97543)_+^3 + 0.000105126(BMI - 37.90634)_+^3\}$ $-\{0.00575309Plt + 0.00000001980788(Plt - 137)_+^3 + 0.0000003956919(Plt - 210)_+^3 - 0.0000008248991(Plt - 255)_+^3 + 0.0000004275374(Plt - 312)_+^3 - 0.00000001813806(Plt - 488)_+^3\}$ $-\{2.71515BaselineSCr + 14.59871(BaselineSCr - 0.6)_+^3 - 21.01498(BaselineSCr - 0.7)_+^3 + 17.96645(BaselineSCr - 0.9)_+^3 - 15.98897(BaselineSCr - 1.0)_+^3 + 4.438785(BaselineSCr - 1.3)_+^3\}$ $+ 0.1552521Htn)$

Secondary Outcome #1 is defined according to modified KDIGO AKI staging as any of the following occuring in the first 14 days following IV cisplatin: absolute increase in SCr of ≥26.5 µmol/L mg/dl compared to baseline, relative increase in SCr ≥1.5-fold compared to baseline, or receipt of KRT.
Secondary Outcome #2 is severe CP-AKI, defined as ≥3-fold rise in SCr or receipt of KRT within 14 days following IV cisplatin.
Secondary Outcome #3 is MAKE90, defined as death within 90 days, KRT within 90 days, or persistent kidney dysfunction (increase in SCr ≥100% compared to baseline) at day 90 post-cisplatin.

Abbreviations: Alb, albumin; BMI, body mass index; CP-AKI, cisplatin-associated acute kidney injury; eGFR, estimated glomerular filtration rate; Hgb, hemoglobin; Htn, hypertension; KDIGO, Kidney Disease Improving Global Outcomes; KRT, kidney replacement therapy; MAKE, major adverse kidney event; Mg, magnesium; Plt, platelets; SCr, serum creatinine; WBC, white blood cell.

Figure S1. Patient Survey Results

A. Importance of Findings



Q1: How important are these findings for the scientific community?
Q2: How important is it for patients with cancer to know about this information before getting cisplatin?
Q3: How much would you want your cancer doctor to use this information when discussing the risks and benefits of cisplatin with you?
Q4: How important is it to share these findings with patients with cancer?

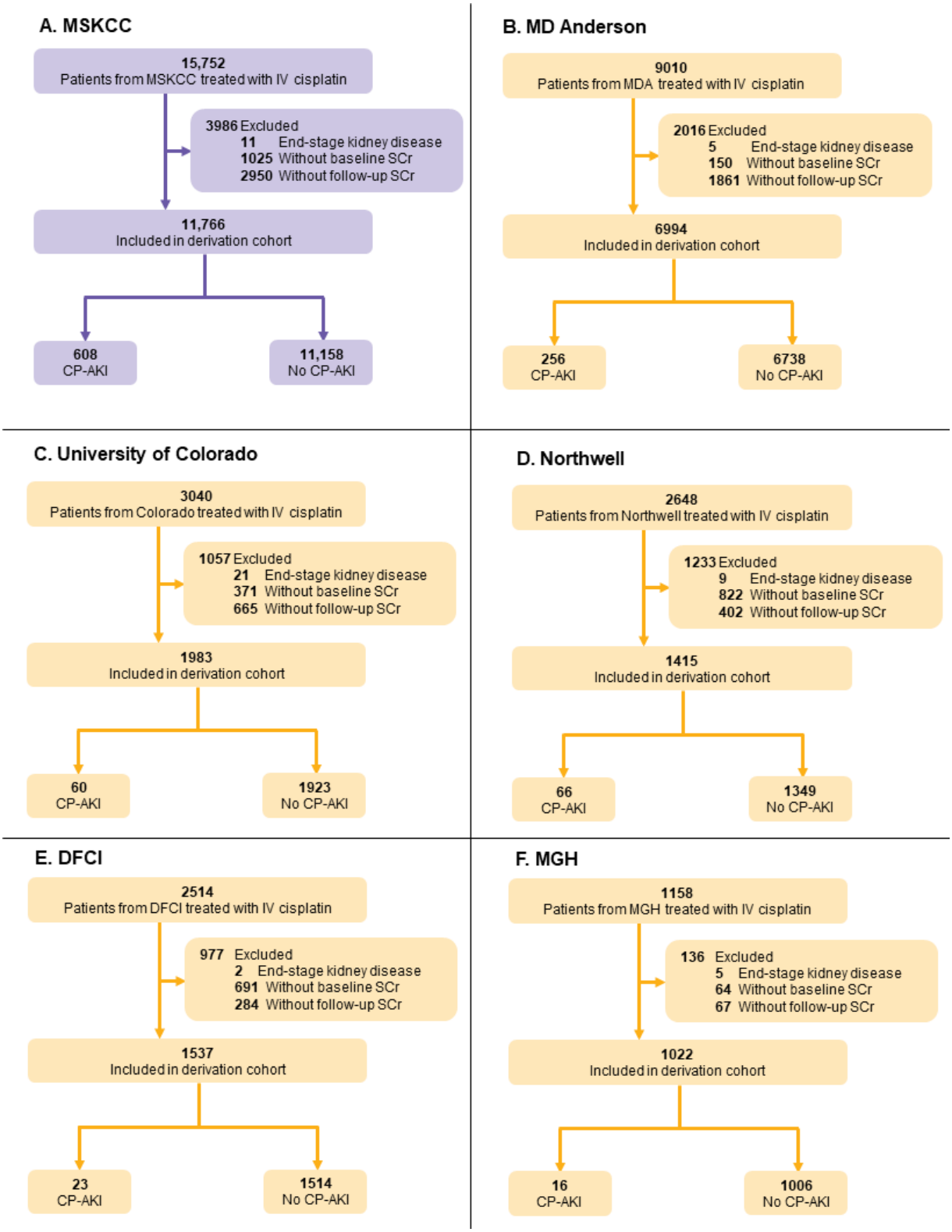
B. Modes of Dissemination of Information

Most Favorable to Least Favorable:

1. Cancer Societies, Q7 (Average = 3.9, Median = 4)
2. Patient Advocacy and Support Groups, Q6 (Average = 3.4, Median = 3) (Tie)
3. Social Media, Q8 (Average = 3.4, Median = 3) (Tie)
4. Flyers and Pamphlets at the Doctor's Office, Q5 (Average = 3.2, Median = 3)

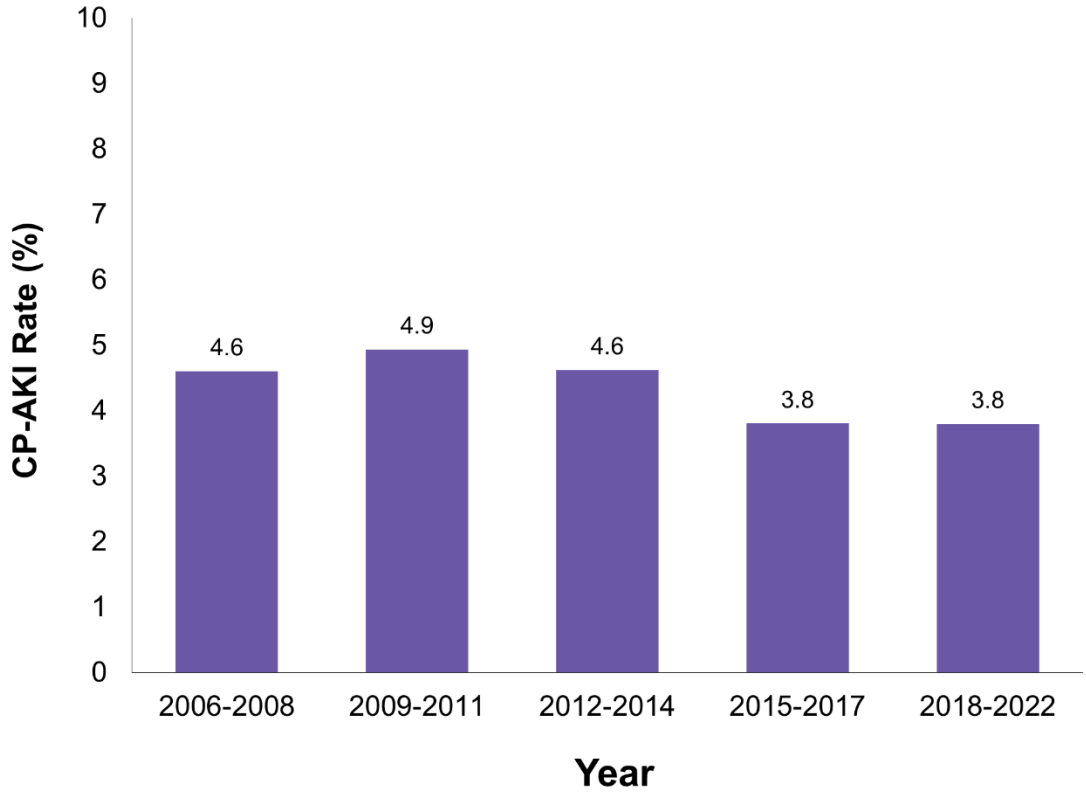
5=very much; 4=moderately; 3=neutral; 2=slightly; 1=not at all

Figure S2. Flow Diagram Depicting Study Population for the Derivation and Validation Cohorts, by Site



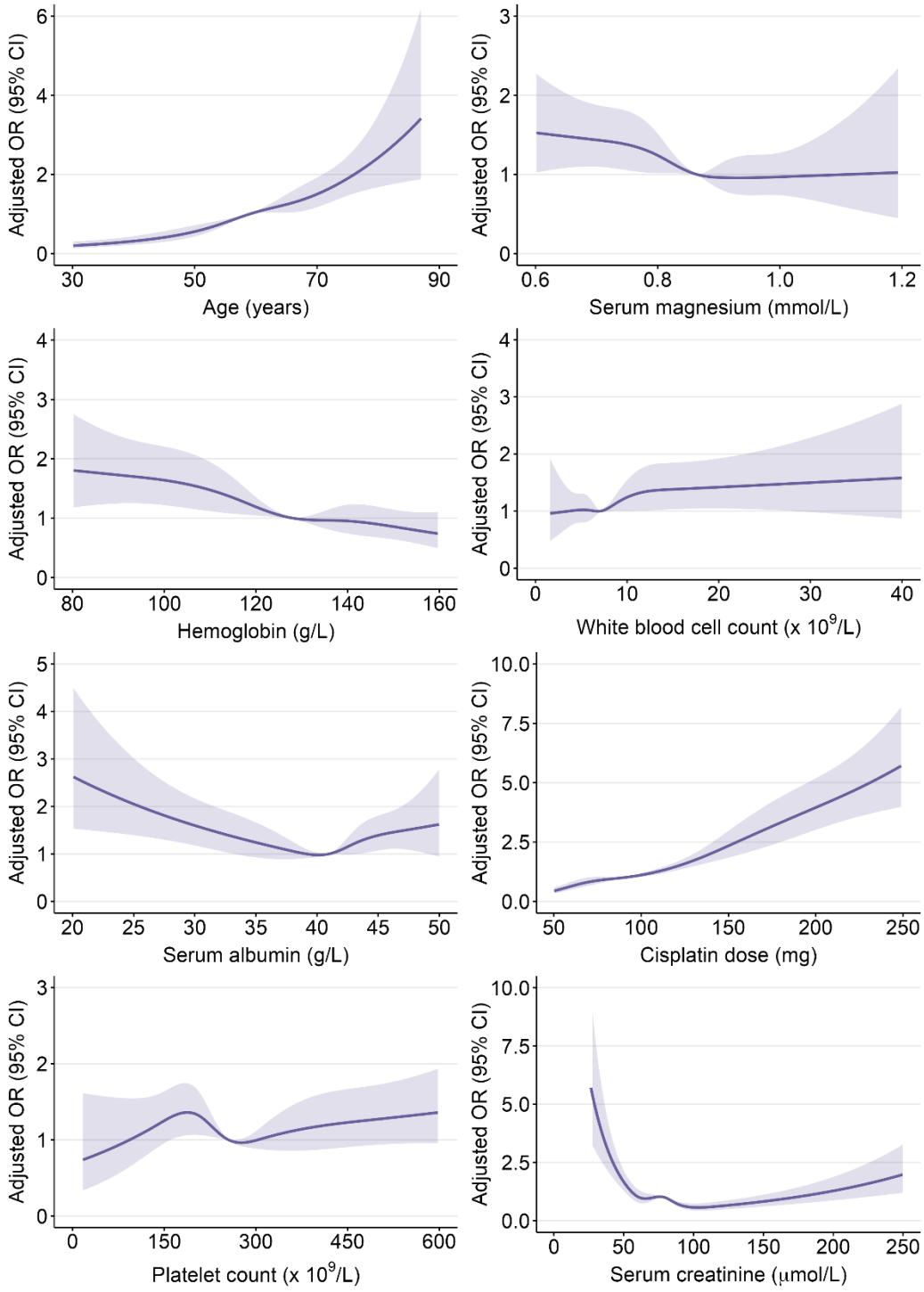
Abbreviations: CP-AKI, cisplatin-associated acute kidney injury; DFCI, Dana-Farber Cancer Institute; MGH, Massachusetts General Hospital; MSKCC, Memorial Sloan Kettering Cancer Center; SCr, serum creatinine.

Figure S3. Incidence of CP-AKI by Year



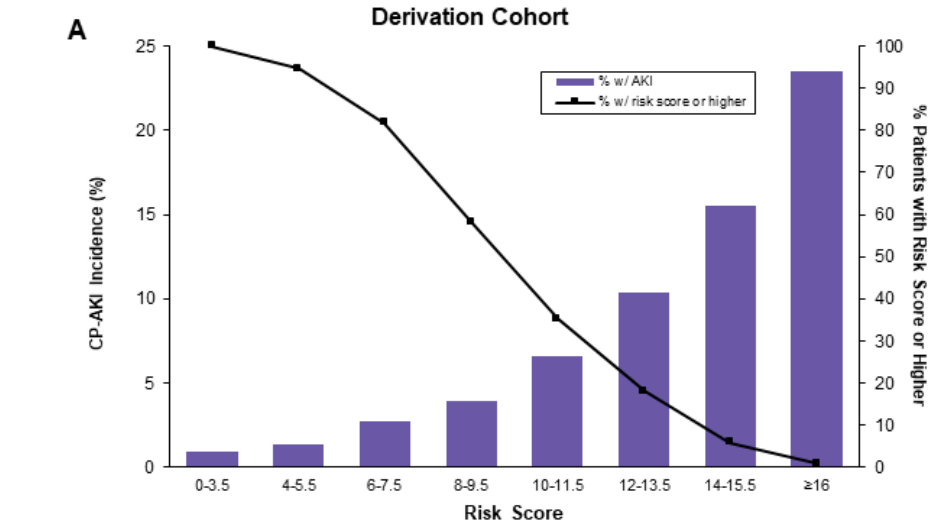
Data are shown for the overall cohort (n=24,717)
Abbreviations: CP-AKI, cisplatin-associated acute kidney injury.

Figure S4. Partial Effect Plots for Restricted Cubic Splines

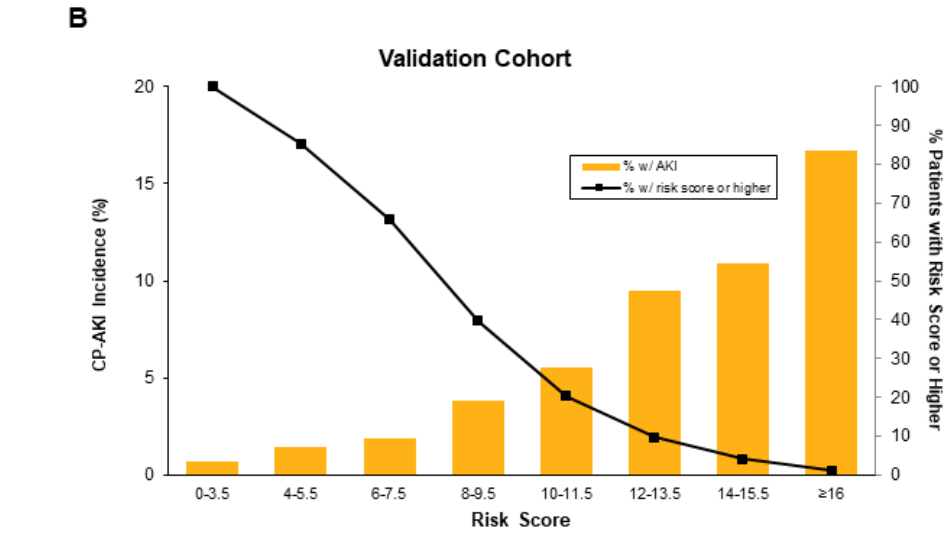


Partial effect plots for restricted cubic splines for continuous variables included in primary model. The odds ratio for each variable was adjusted for the median values of other variables in the model.
Abbreviations: CI, confidence interval; OR, odds ratio.

Figure S5. CP-AKI and Risk Score Characteristics



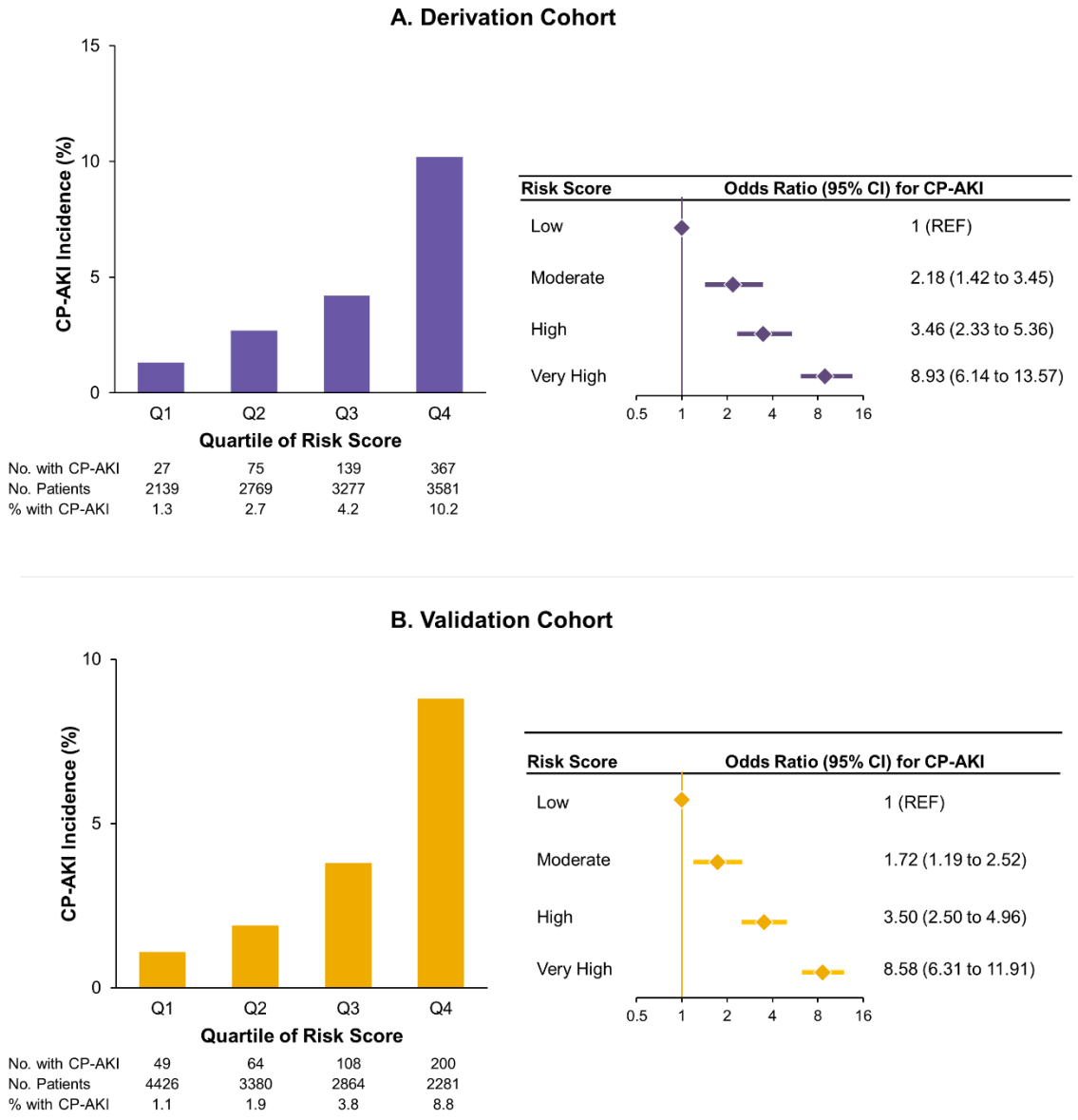
No. w/ AKI	6	21	75	108	133	147	91	27
No. Pts	637	1502	2769	2720	2018	1420	585	115
% w/ AKI	0.9%	1.4%	2.7%	4.0%	6.6%	10.4%	15.6%	23.5%
Sensitivity*	100.0%	99.0%	95.6%	83.2%	65.5%	43.6%	19.4%	4.4%
Specificity*	0.0%	5.7%	18.9%	43.1%	66.5%	83.4%	94.8%	99.2%
PPV*	5.2%	5.4%	6.0%	7.4%	9.6%	12.5%	16.9%	23.5%
NPV*	99.1%	98.7%	97.9%	97.2%	96.4%	95.6%	95.0%	94.8%



No. w/ AKI	13	36	64	96	76	69	42	25
No. Pts	1910	2516	3380	2512	1372	725	386	150
% w/ AKI	0.7%	1.4%	1.9%	3.8%	5.5%	9.5%	10.9%	16.7%
Sensitivity*	100.0%	96.9%	88.4%	73.2%	50.4%	32.3%	15.9%	5.9%
Specificity*	0.0%	15.1%	34.9%	61.4%	80.7%	91.0%	96.3%	99.0%
PPV*	3.3%	3.7%	4.4%	6.0%	8.1%	10.8%	12.5%	16.7%
NPV*	99.3%	98.9%	98.6%	98.0%	97.6%	97.1%	96.9%	96.7%

Depicts the percentage of patients with CP-AKI within each risk score category, and the sensitivity/specificity and positive predictive value/negative predictive value for each risk score category, in the DC (Panel A) and VC (Panel B). Bars (left axes) show the proportion with CP-AKI and lines (right axes) show the percentage of patients with the risk score or higher.
Abbreviations: CP-AKI, cisplatin-associated acute kidney injury; NPV, negative predictive value; PPV, positive predictive value.

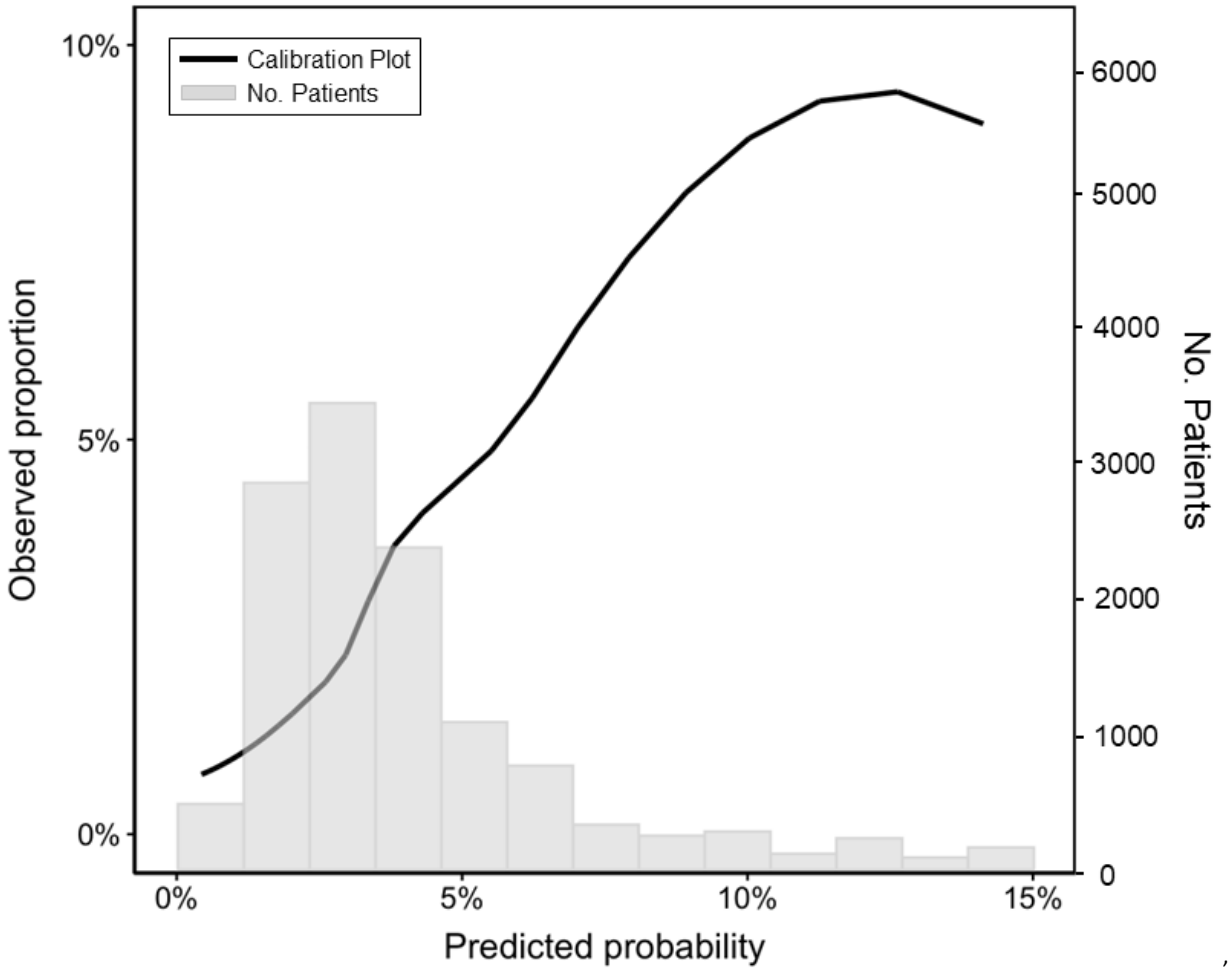
Figure S6. Incidence of CP-AKI According to Risk Score in Quartiles in the Derivation and Validation Cohorts



1st quartile: 0-5.5 points; 2nd quartile: 6-7.5 points; 3rd quartile: 8-10 points; 4th quartile: ≥10.5 points

Abbreviations: CP-AKI, cisplatin-associated acute kidney injury; DC, derivation cohort; OR, odds ratio; REF, reference group; VC, validation cohort.

Figure S7. Model Calibration in the Validation Cohort



The calibration plot shows the predicted versus observed proportion of CP-AKI. Slope: 0.98; Intercept: -0.15.
Abbreviations: No, number

Figure S8. Decision Curves

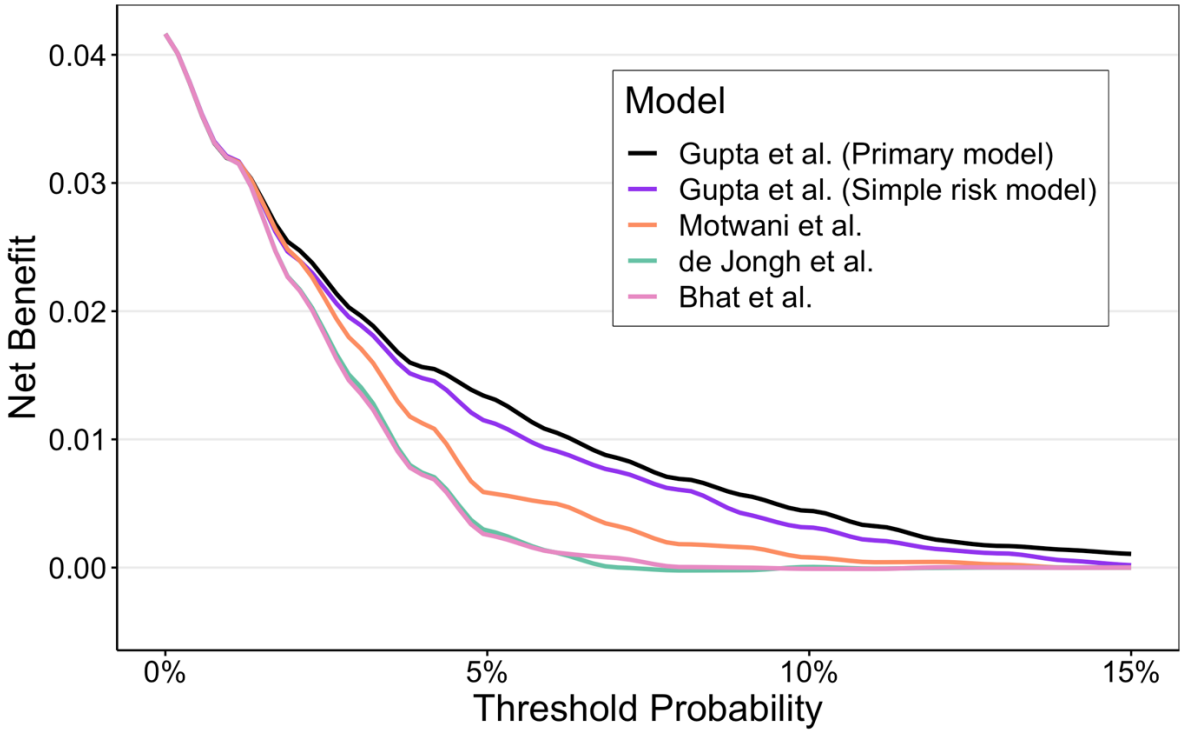
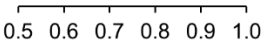


Figure S9. Discrimination of Primary Model in Additional Analyses and Secondary Outcomes

	No. of events/ No. of patients (%)	AUC (95% CI)	Forest Plot of AUC (95% CI)
Primary Outcome (↑SCr ≥100% or KRT within 14d)			
Derivation Cohort	608 / 11766 (5.2)	0.76 (0.74 to 0.78)	
Validation Cohort	421 / 12951 (3.3)	0.72 (0.70 to 0.75)	
Overall	1029 / 24717 (4.2)	0.75 (0.73 to 0.76)	
Simplified Model*	1029 / 24717 (4.2)	0.73 (0.71 to 0.74)	
Additional Analyses**			
Additional analysis #1	1133 / 24717 (4.6)	0.75 (0.73 to 0.76)	
Additional analysis #2	838 / 22220 (3.8)	0.76 (0.74 to 0.78)	
Additional analysis #3	1186 / 29676 (4.0)	0.73 (0.72 to 0.76)	
Additional analysis #4	481 / 12707 (3.8)	0.74 (0.72 to 0.76)	
Additional analysis #5	578 / 12405 (4.7)	0.73 (0.71 to 0.76)	
Secondary Outcome (↑SCr ≥50%, 0.3 mg/dl rise within 14d, or KRT within 14d)			
Derivation Cohort	2738 / 11766 (23.3)	0.72 (0.71 to 0.73)	
Validation Cohort	1737 / 12951 (13.4)	0.68 (0.66 to 0.69)	
Overall	4475 / 24717 (18.1)	0.71 (0.70 to 0.72)	
Secondary Outcome (↑SCr ≥200% or KRT within 14d)			
Derivation Cohort	154 / 11766 (1.3)	0.80 (0.77 to 0.84)	
Validation Cohort	132 / 12951 (1.0)	0.67 (0.62 to 0.71)	
Overall	286 / 24717 (1.2)	0.74 (0.71 to 0.77)	
Secondary Outcome (MAKE90)			
Derivation Cohort	892 / 9667 (9.2)	0.81 (0.79 to 0.82)	
Validation Cohort	949 / 10065 (9.4)	0.78 (0.77 to 0.80)	
Overall	1841 / 19732 (9.3)	0.79 (0.78 to 0.81)	



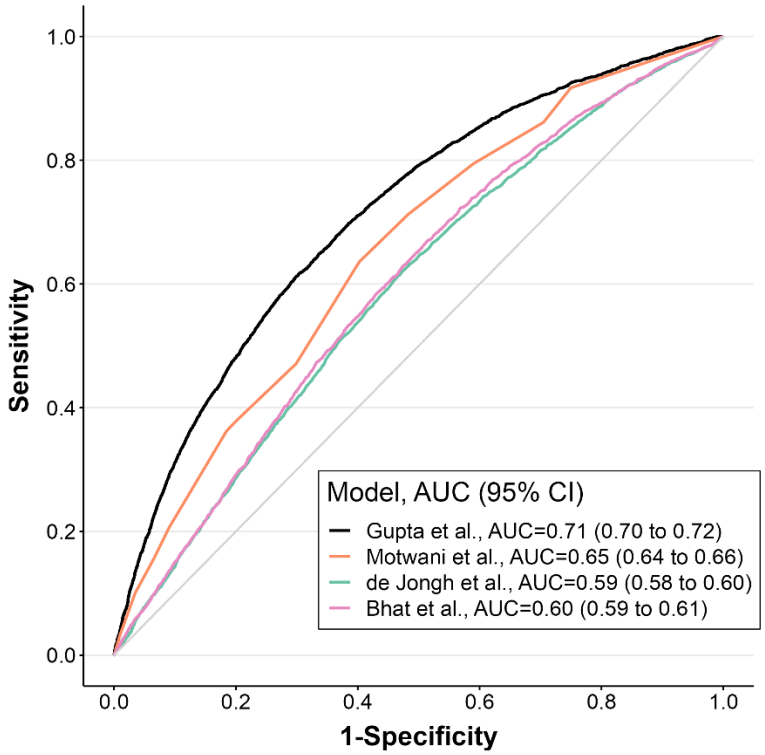
*Refers to model in which continuous variables were categorized.

**Additional analyses refer to #1: outcome is composite of CP-AKI or death in the first 14 days following cisplatin administration; #2: outcome is CP-AKI in the 10 days following cisplatin administration; #3: outcome is CP-AKI in the 21 days following cisplatin administration; #4: analysis is limited to patients treated with cisplatin in 2016 or later; #5: complete case analysis rather than use of multiple imputation for missing data.

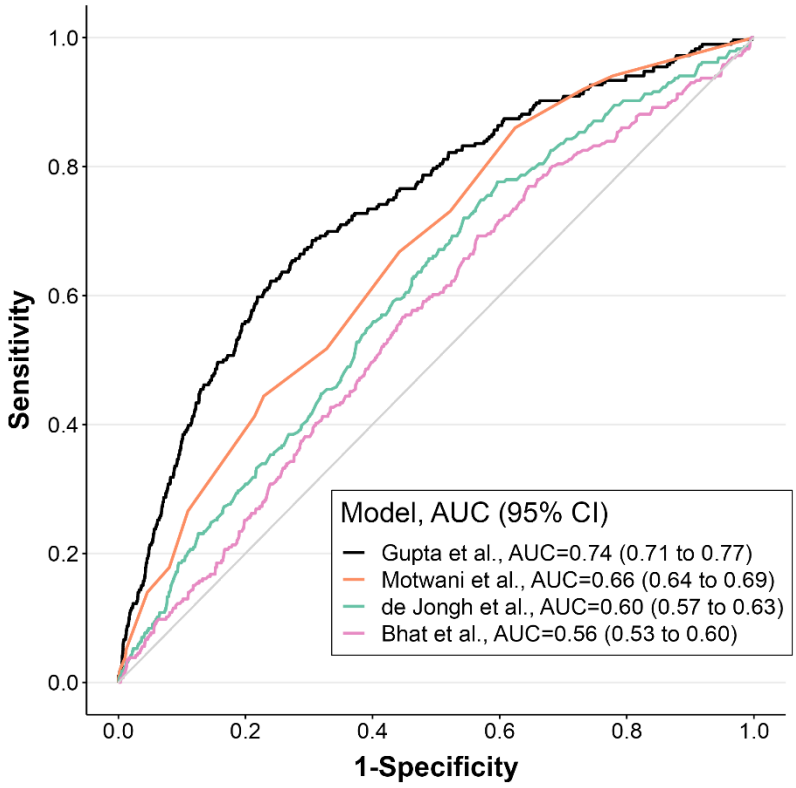
Abbreviations: AUC, area under the curve; CI, confidence interval; d, day; KRT, kidney replacement therapy; MAKE, major adverse kidney event; SCr, serum creatinine.

Figure S10. C-Statistics for Secondary Outcomes

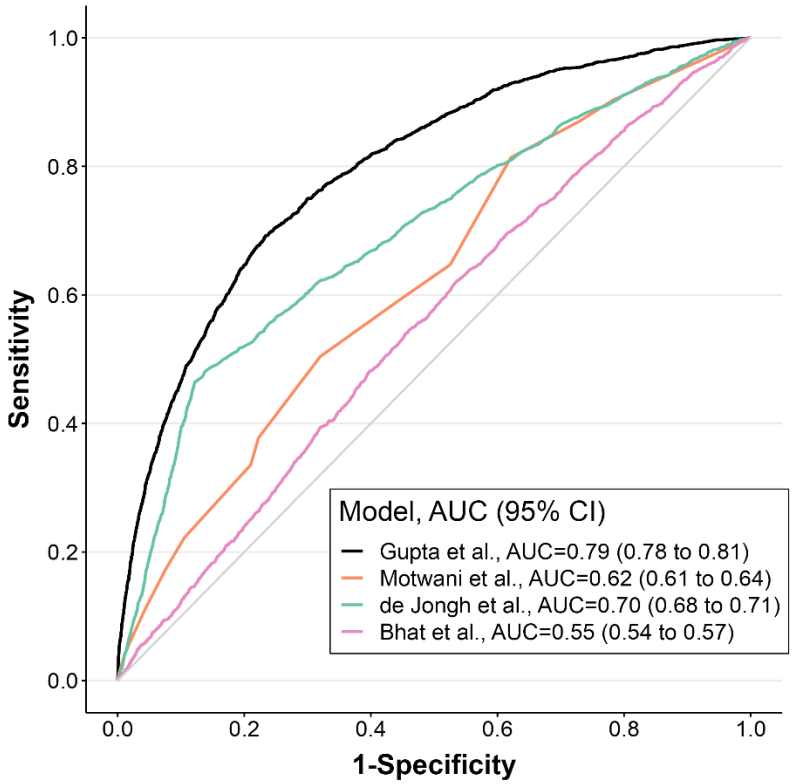
A



B

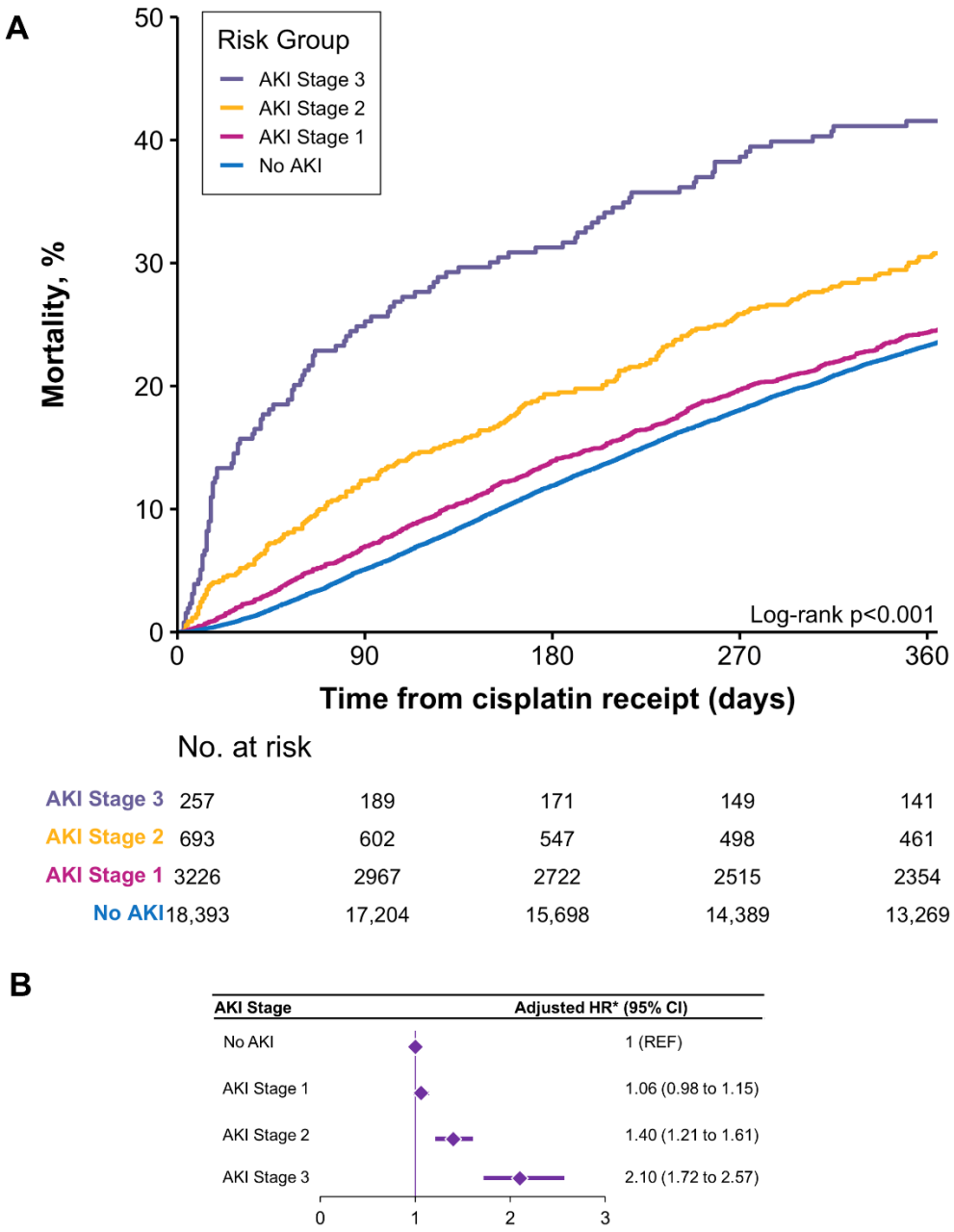


C



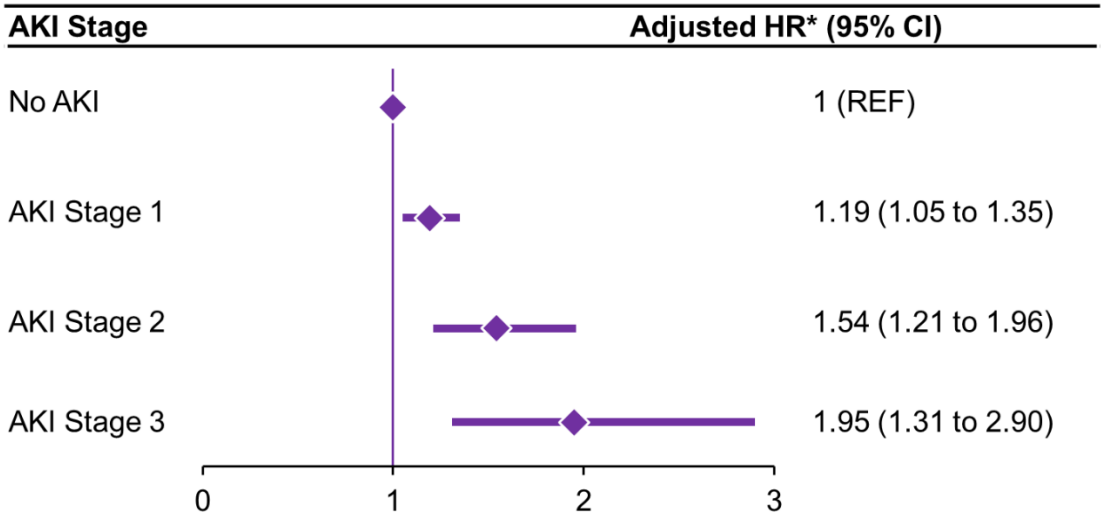
Panel A shows CP-AKI, defined according to modified KDIGO AKI staging as any of the following occuring in the first 14 days following IV cisplatin: absolute increase in SCr of ≥26.5 µmol/compared to baseline, relative increase in SCr ≥1.5-fold compared to baseline, or receipt of KRT. Panel B shows severe CP-AKI, defined as ≥3-fold rise in SCr or receipt of KRT within 14 days following the first dose of IV cisplatin. Panel C shows MAKE90, defined as death within 90 days, KRT within 90 days, or persistent kidney dysfunction (increase in SCr ≥100% compared to baseline) at day 90 post-cisplatin.
Abbreviations: AUC, area under the curve; CI confidence interval; KRT, kidney replacement therapy; MAKE, major adverse kidney event; SCr, serum creatinine

Figure S11. CP-AKI Severity and 1-Year Survival



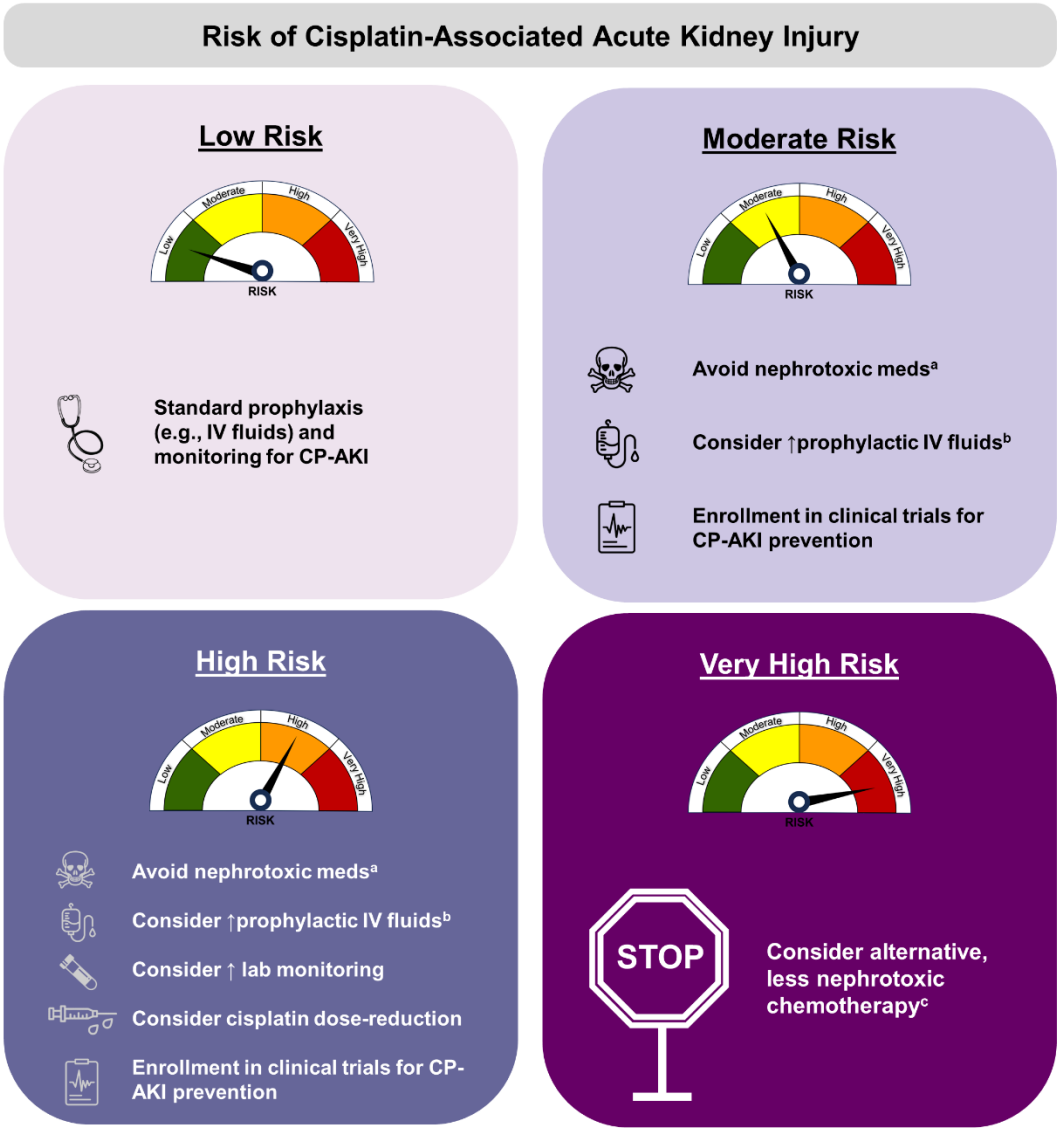
Panel A shows the cumulative incidence of death in the first year following cisplatin administration according to CP-AKI stage. CP-AKI severity was categorized into four groups: no AKI, AKI stage 1 (an increase in SCr ≥26.5 µmol/ or a 1.5-1.9-fold rise in SCr), AKI stage 2 (2-2.9-fold rise in SCr) or AKI stage 3 (≥3-fold rise in SCr or KRT), each assessed within 14 days following cisplatin administration. Panel B shows a multivariable Cox model for 1-year survival according to CP-AKI stage (n=22,850). The model was adjusted for age, male sex, body mass index, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, smoking, serum creatinine, white blood cell count, hemoglobin, platelet count, serum magnesium, serum albumin, cisplatin dose, and concomitant nephrotoxic chemotherapy (binary variable that included receipt of pemetrexed, cetuximab, ifosfamide, immune checkpoint inhibitors within 30 days prior to cisplatin administration).
Abbreviations: CI, confidence interval; CP-AKI, cisplatin-associated acute kidney injury; HR, hazard ratio; KRT, kidney replacement therapy; SCr, serum creatinine

Figure S12. MAKE365



MAKE365 is defined as any death or KRT in the first 365 days or persistent kidney dysfunction (doubling of SCr) at day 365. Models were adjusted for age, sex, body mass index, hypertension, diabetes mellitus, COPD, smoking, baseline SCr, WBC count, hemoglobin, platelet count, serum magnesium, serum albumin, cisplatin dose, and concomitant nephrotoxic chemotherapy (receipt of pemetrexed, cetuximab, ifosfamide, or immune checkpoint inhibitors within 30 days prior to cisplatin administration). Abbreviations: AKI, acute kidney injury; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; KRT, kidney replacement therapy; MAKE, major adverse kidney vent; SCr, serum creatinine; WBC, white blood cell count

Figure S13. Expert Recommendations for CP-AKI



[a]For example, non-steroidal anti-inflammatory drugs, IV contrast.
[b]For example, consider additional IV fluids on the day *after* cisplatin receipt (in addition to IV fluids on the day of cisplatin receipt).
[c]For example, carboplatin.

Note: recommendations are based on expert opinion of the co-authors and have not been validated in clinical practice.

Supplemental References

1. Riley RD, Ensor J, Snell KIE, Harrell FE, Martin GP, Reitsma JB, et al. Calculating the sample size required for developing a clinical prediction model. BMJ. 2020;368.
2. Riley RD, Debray TPA, Collins GS, Archer L, Ensor J, van Smeden M, et al. Minimum sample size for external validation of a clinical prediction model with a binary outcome. Stat Med. 2021;40(19).
3. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. N Engl J Med. 2021;385(19).