Target Trial Emulation in Onconephrology

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BRIGHAM HEALTH
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Disclosures

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Consulting

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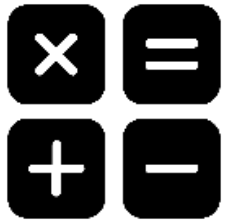
Learning Objectives



Apply the principles of target trial emulation to observational studies

Identify and appraise the data supporting:

- Glucarpidase for HDMTX-AKI
- Rasburicase for TLS
- IV magnesium for cisplatin-AKI

The Two Flavors of Clinical Research

RCTs

Gold standard for establishing efficacy BUT:

- Expensive
- Slow
- Often underpowered
- Often have limited generalizability

Observational Studies

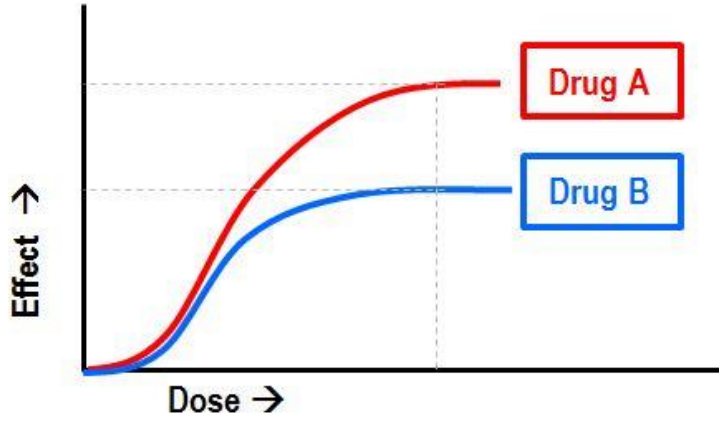
Subject to residual confounding (correlation ≠ causation) BUT:

Can inform clinical decision making when data from RCTs are unavailable

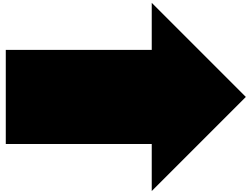
How do we make the most out of observational studies?

Target Trial Emulation (TTE)

TTE is a causal inference methodology that incorporates features of RCT design to minimize bias in the analysis of observational data



Step 1:
Imagine what your ideal RCT would look like



Step 2:
Collect and analyze your observational data in a way that emulates the target trial as closely as possible

The NEW ENGLAND JOURNAL of MEDICINE

FUNDAMENTALS OF PUBLIC HEALTH

Methods of Public Health Research — Strengthening Causal Inference from Observational Data

Miguel A. Hernán, M.D., Dr.P.H.

October 7, 2021

"Causal inference involves specifying a causal question and answering it. The question is articulated in the form of the target-trial protocol, which incorporates:

- **Eligibility criteria**
- **Treatment assignment**
- **Start and end of follow-up**
- **Outcomes**
- **Data-analysis plan."**

-Miguel Hernán

JAMA Guide to Statistics and Methods

Target Trial Emulation
A Framework for Causal Inference From Observational Data

Miguel A. Hernán, MD, DrPH; Wei Wang, PhD; David E. Leaf, MD, MMSc

December 12, 2022

"Emulating randomization generally requires data on prognostic factors that are associated with treatment decisions. If all such confounders were correctly measured and adjusted for, there would be no difference between a randomized trial and an observational analysis emulating it."

-Miguel Hernán

Four Key Principles of Target Trial Emulation

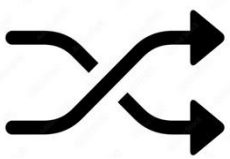
1. Use similar eligibility criteria as you would for the corresponding RCT

2. Use the same "time zero" for both groups to avoid immortal time bias

> "A ridiculous example of immortal time bias would be if ICU patients were offered tea and crumpets (T&C) on ICU day 3. Subsequent analysis would likely find that T&C recipients have lower mortality than T&C non-recipients." –Ho et al., Anaesthesia, 2012

3. Adjust for <u>detailed</u> baseline confounders to emulate random treatment assignment

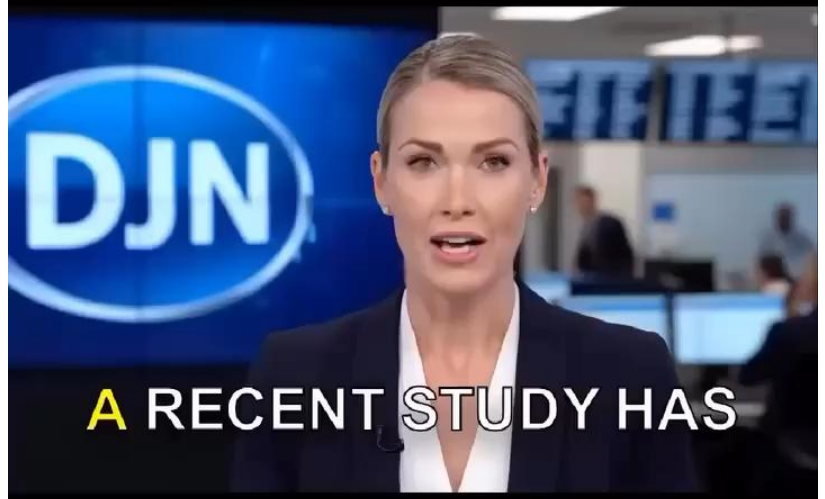
- Regression
- Matching
- IPW



4. Analysis by intention-to-treat (compare effect of being assigned to treatment "A" vs. "B" at baseline, regardless of potential crossover later on)

Improvement Crew

Finally, some hardcore science 😭



“A recent study has found that birthdays are good for your health. Researchers found that people with more birthdays live longer than those who have fewer.”

Four Key Principles of Target Trial Emulation

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> "A ridiculous example of immortal time bias would be if ICU patients were offered tea and crumpets (T&C) on ICU day 3. Subsequent analysis would likely find that T&C recipients have lower mortality than T&C non-recipients." –Ho et al., Anaesthesia, 2012

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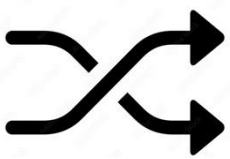

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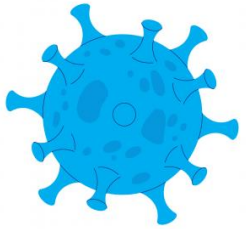
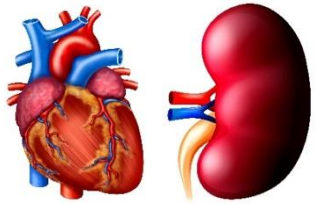
Application of Target Trial Emulation



COVID-19

Identify therapies that improve survival in critical illness

- Tocilizumab
- Anticoagulation
- ECMO
- Prone Ventilation



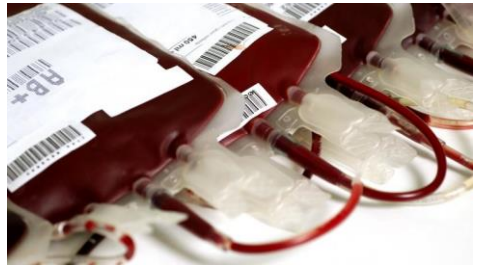
CSA-AKI

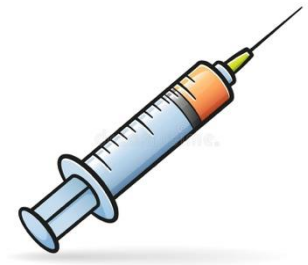
Identify perioperative medications that affect cardiac surgery–associated AKI

- NSAIDs
- Del Nido Cardioplegia
- Vasopressin

Babesiosis

Examine the effect of RBC exchange transfusion on acute organ injury





Onconephrology

Identify therapies that improve kidney outcomes in cancer patients

Shruti Gupta

- **Glucarpidase for MTX-AKI**
- **Rasburicase for TLS**
- **IV Mg for Cisplatin-AKI**
- **Mannitol for Cisplatin-AKI**
- **Eculizumab for HSCT-TMA**
- **GC Duration for ICI-AKI**

Glucarpidase and MTX-AKI

Background on HDMTX, AKI, and Glucarpidase

HDMTX remains a cornerstone of treatment for lymphoma and leukemia involving the CNS

AKI is one of the most common (~10%) and consequential toxicities

Glucarpidase is a recombinant bacterial enzyme (originally derived from *Pseudomonas*) that rapidly cleaves and inactivates MTX

Despite glucarpidase's potent biochemical effects, no study had examined its clinical efficacy in patients with HDMTX toxicity

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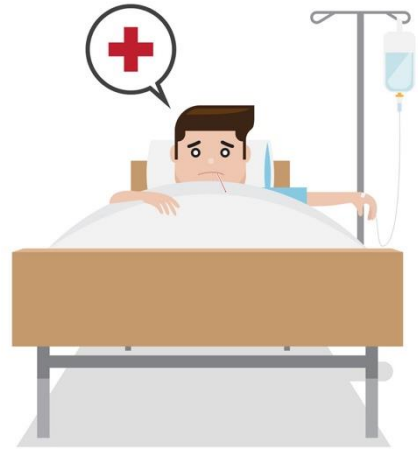


Biochemical Effect

Improved Outcomes

blood®
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Glucarpidase for treatment of high-dose methotrexate toxicity

Shruti Gupta,[1-3,*] Sarah A. Kaunfer,[1,*] Kevin L. Chen,[4] Julie-Alexia Dias,[4] Anitha Vijayan,[5,6] Arun Rajasekaran,[7] Jason M. Prosek,[8] Huong L. Truong,[9,10] Anthony Wood,[11,12] Claude Bassil,[13] Amanda D. Renaghan,[14] Chintan V. Shah,[15] Jingjing Zhang,[16] Ilya Glezerman,[17,18] Christopher Carlos,[19] Katherine Kelly,[20] Christopher J. Passero,[21] Jan Drappatz,[22] Ala Abudayyeh,[23] Daniel Sanghoon Shin,[24] C. John Sperati,[25] Bradley J. Yelvington,[26] Swetha R. Kanduri,[27] Javier A. Neyra,[7,28] Daniel Edmonston,[29] Anushree C. Shirali,[30] Anip Bansal,[31] Abdallah Geara,[32] Zain Mithani,[33] Susan L. Ziolkowski,[34] Arash Rashidi,[35] Jonathan Jakubowski,[5] Ashwini Pujari,[7] David A. Bond,[36] Emily Dotson,[37] Sarah Wall,[36] John Patton,[36] Jason N. Barreto,[9] Sandra M. Herrmann,[38] Mohammad S. Sheikh,[38] Rachid Baz,[12] Jamie Lee,[12] Nicholas Lucchesi,[14] Michael Kolman,[15,39] Muhammad Ahsan Rasheed,[16] Afsheen Afzal,[17,18] Dasol Kang,[17,18] Amrita Mahesh,[19] Raymond K. Hsu,[19] Anthony Nicolaysen,[40] Kibrewessen Tefera,[40] Claire Schretlen,[25,41] Ryan M. Miller,[26] Juan Carlos Velez,[27] Alexander H. Flannery,[42] Abinet M. Aklilu,[29,43] Shuchi Anand,[34] Soniya Chandrasekhara,[44] Vicki Donley,[35] Ashka Patel,[45] Jian Ni,[46] Shobana Krishnamurthy,[1] Rafia Ali,[1] Osman A. Yilmam,[1] Sophia L. Wells,[1] Jessica L. Ortega,[1] Olivia L. Green-Lingren,[1] Rebecca K. Leaf,[3,47] Meghan E. Sise,[3,48] Lakshmi Nayak,[3,49,50] Ann S. LaCasce,[3,50] Nelson Leung,[38] and David E. Leaf[1,3]

TTE: Efficacy of Glucarpidase vs No Glucarpidase in MTX-AKI

Overview

Multicenter cohort study of 708 adults with MTX-AKI from **28 major cancer centers** across the U.S.

Data Collection

Manual chart review, >400 data elements/patient

Primary Exposure

Receipt vs. no receipt of glucarpidase within 96h of MTX initiation

Primary Outcome

Kidney recovery at discharge

Statistical Analysis

- **"Sequential" TTE framework**
- MV adjustment for demographics, comorbidities, labs, 24h MTX levels, and AKI severity

Covariates adjusted for in multivariable models

Demographics
- Age
- Sex
- Race

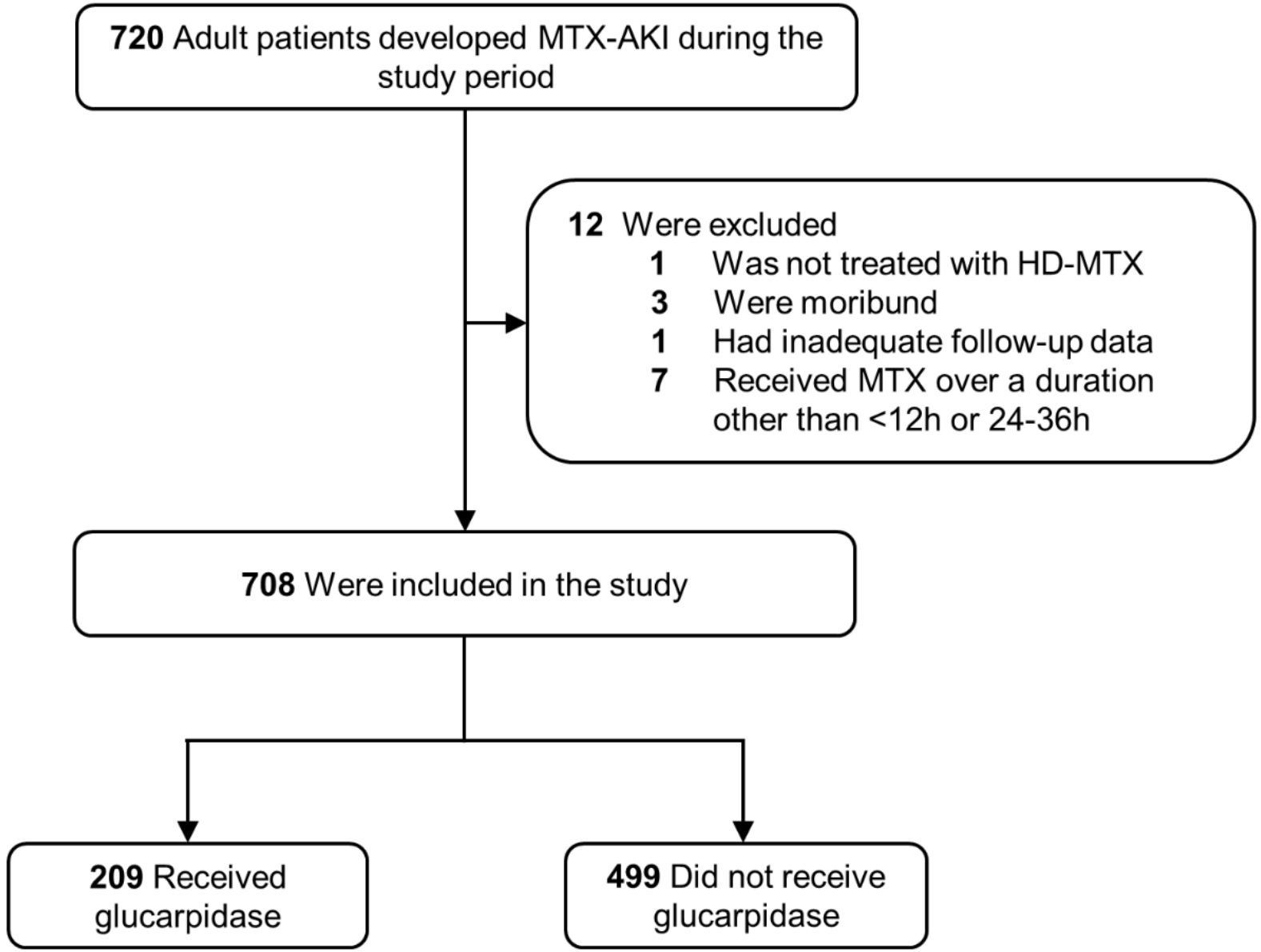
Comorbidities
- Hypertension
- Diabetes mellitus
- CHF
- CAD
- COPD
- Chronic liver disease
- BMI

Baseline labs
- SCr
- WBC count
- Hemoglobin
- Albumin
- LDH
- Urine pH

Malignancy type
- Primary CNS lymphoma
- ALL
- Other leukemia/lymphoma
- Osteosarcoma/other solid tumor

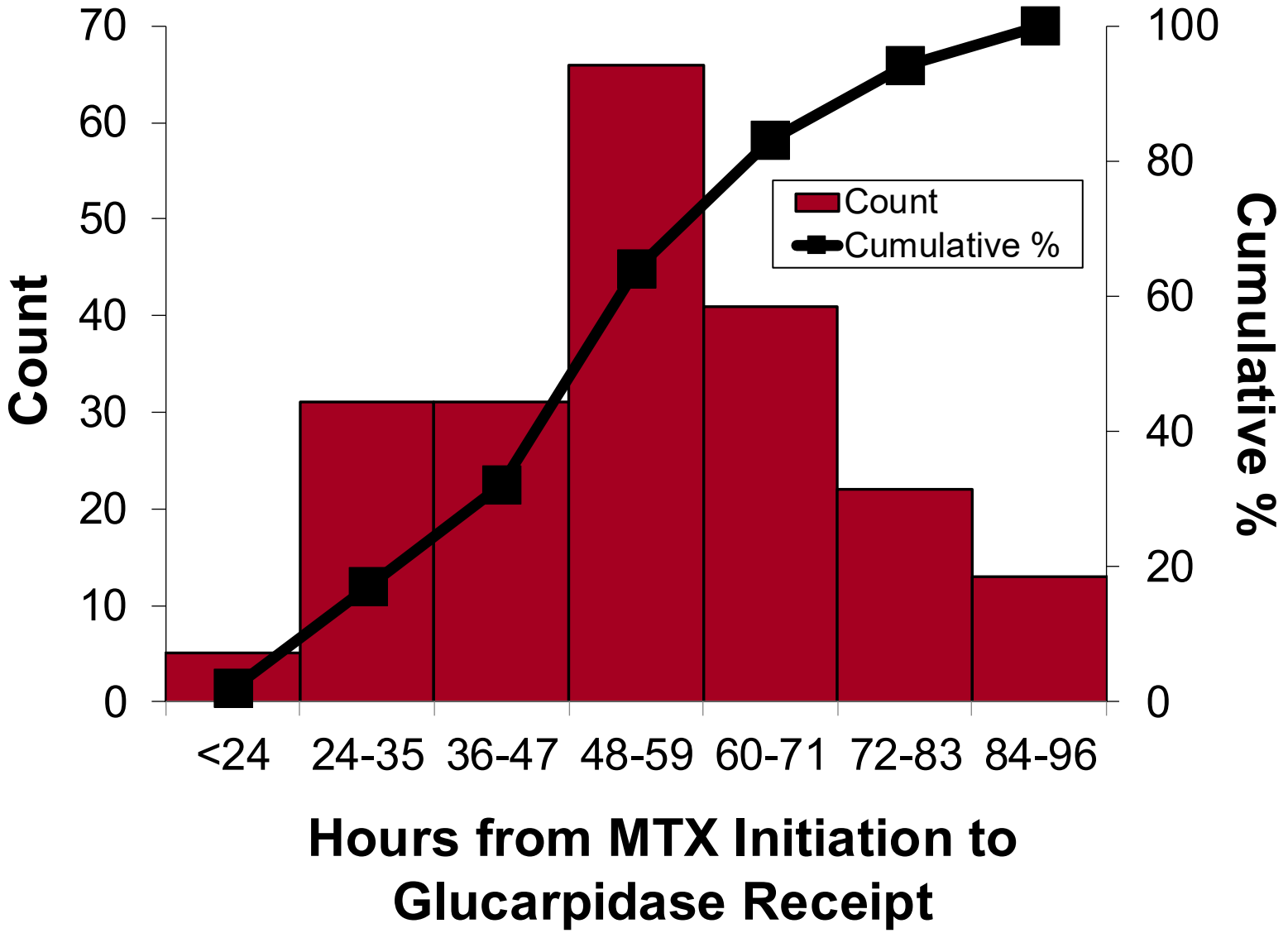
MTX treatment
- Other chemo
- MTX dose
- MTX infusion duration
- CNS prophylaxis vs. treatment
- IV fluids
- Leucovorin dose

Other
- 24h Plasma MTX level
- Max fold-change in SCr

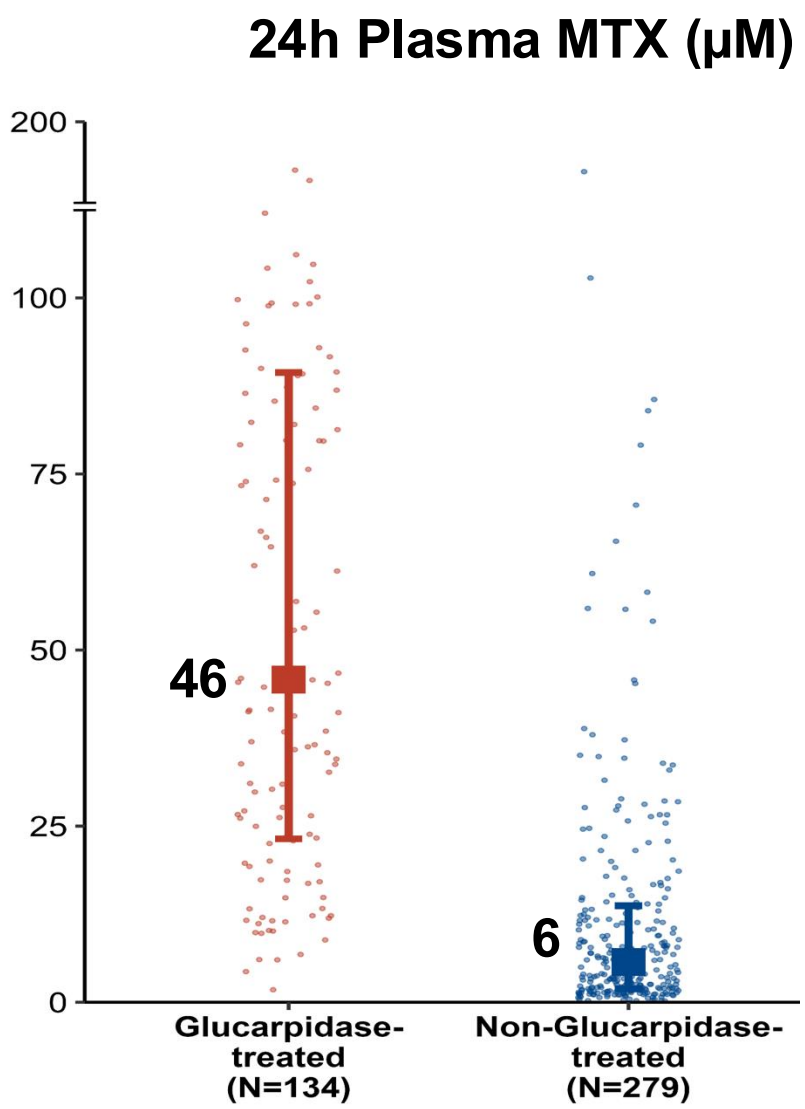

720 Adult patients developed MTX-AKI during the study period
12 Were excluded
1 Was not treated with HD-MTX
3 Were moribund
1 Had inadequate follow-up data
7 Received MTX over a duration other than <12h or 24-36h
708 Were included in the study
209 Received glucarpidase
499 Did not receive glucarpidase

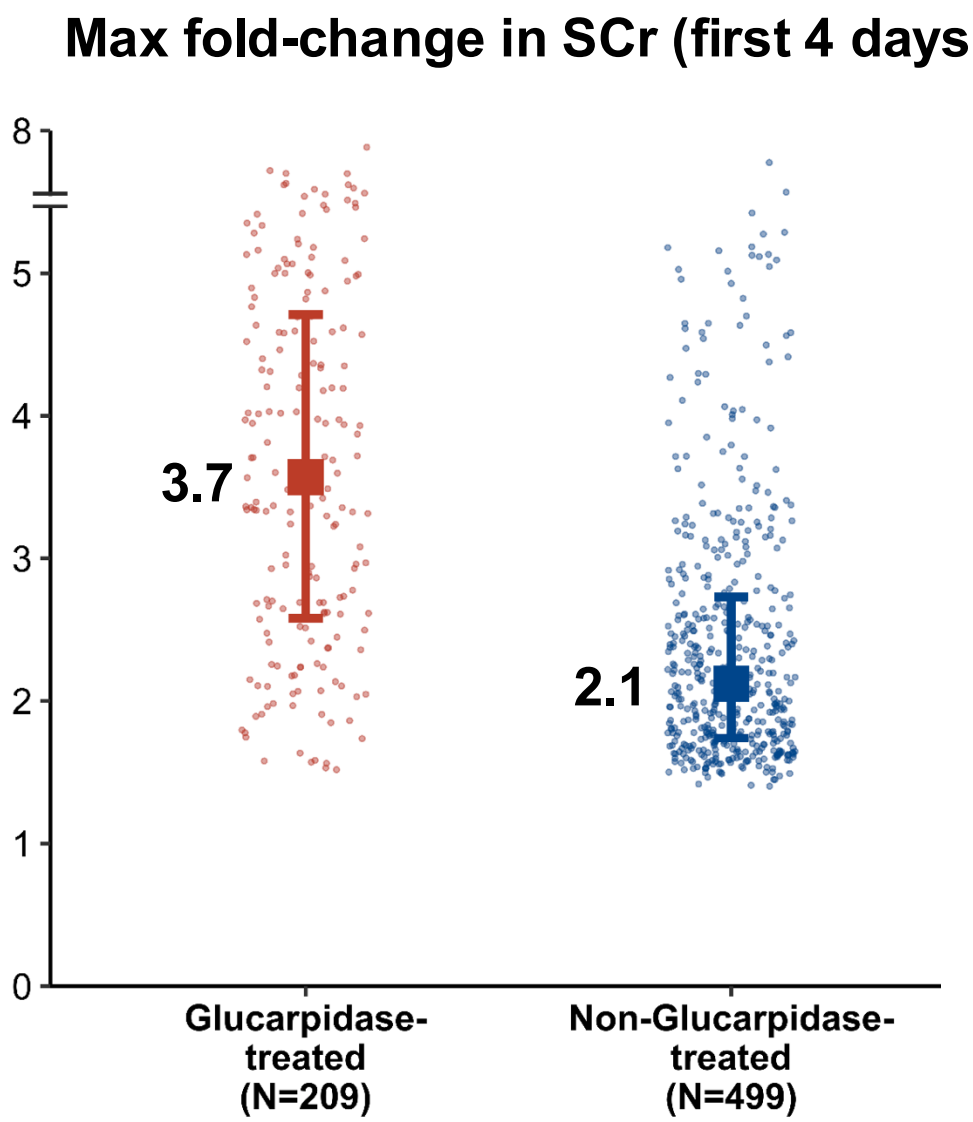
Timing of Glucarpidase Receipt relative to MTX Initiation

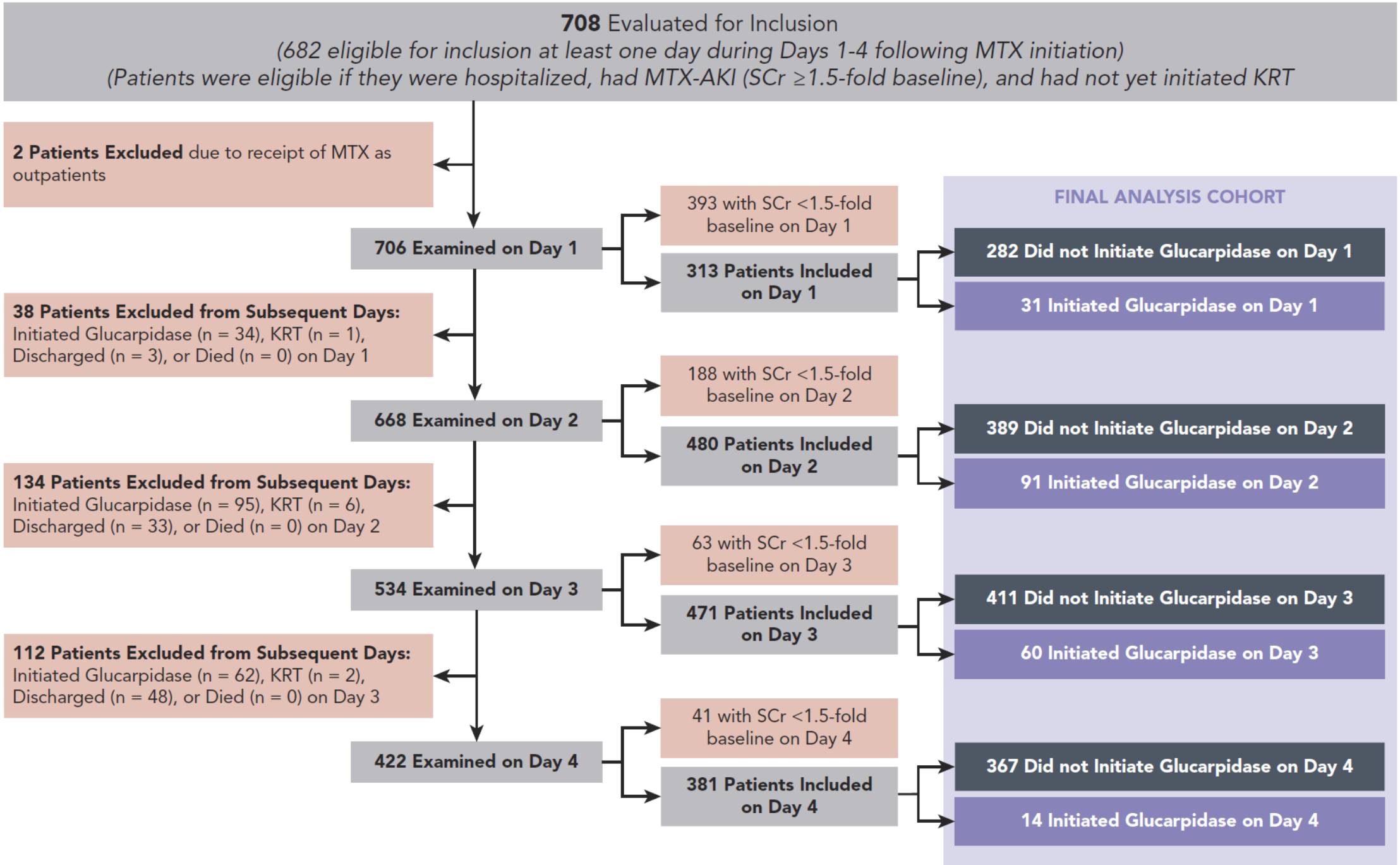
Glucarpidase administered at median of 54 hours (IQR, 44– 66) following MTX initiation

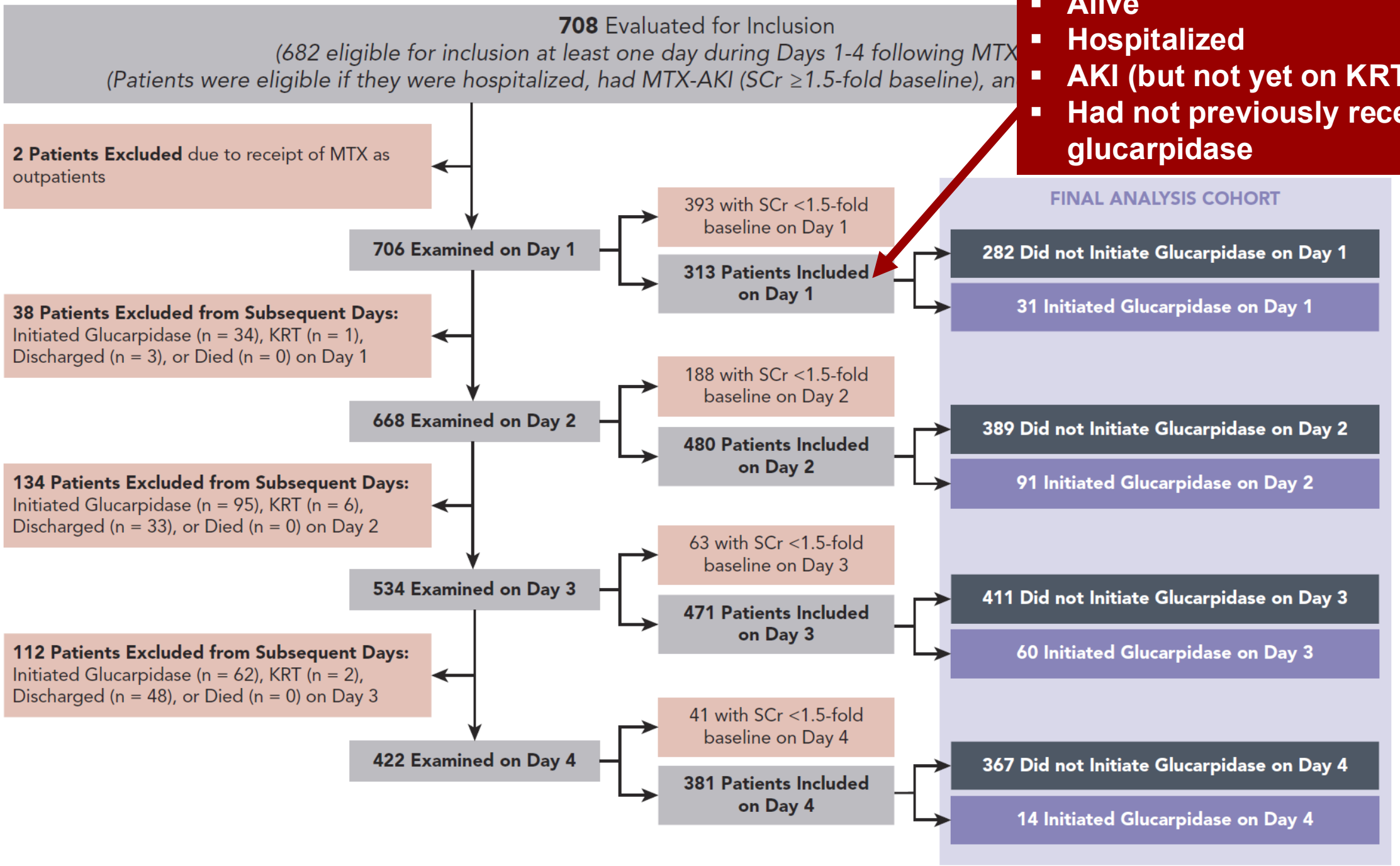


Glucarpidase-treated patients had ↑24h MTX levels and ↑AKI severity compared to controls





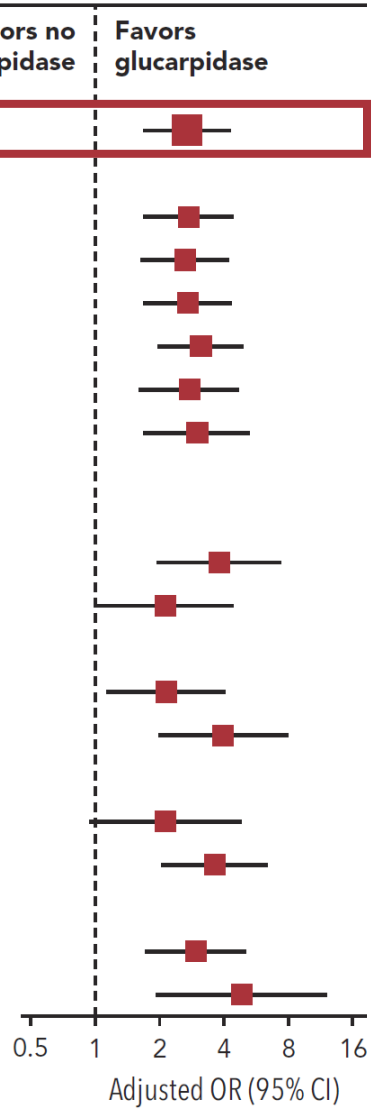

708 Evaluated for Inclusion
(682 eligible for inclusion at least one day during Days 1-4 following MTX initiation)
(Patients were eligible if they were hospitalized, had MTX-AKI (SCr ≥1.5-fold baseline), and had not yet initiated KRT
2 Patients Excluded due to receipt of MTX as outpatients
706 Examined on Day 1
393 with SCr <1.5-fold baseline on Day 1
313 Patients Included on Day 1
38 Patients Excluded from Subsequent Days: Initiated Glucarpidase (n = 34), KRT (n = 1), Discharged (n = 3), or Died (n = 0) on Day 1
668 Examined on Day 2
188 with SCr <1.5-fold baseline on Day 2
480 Patients Included on Day 2
134 Patients Excluded from Subsequent Days: Initiated Glucarpidase (n = 95), KRT (n = 6), Discharged (n = 33), or Died (n = 0) on Day 2
534 Examined on Day 3
63 with SCr <1.5-fold baseline on Day 3
471 Patients Included on Day 3
112 Patients Excluded from Subsequent Days: Initiated Glucarpidase (n = 62), KRT (n = 2), Discharged (n = 48), or Died (n = 0) on Day 3
422 Examined on Day 4
41 with SCr <1.5-fold baseline on Day 4
381 Patients Included on Day 4
FINAL ANALYSIS COHORT
282 Did not Initiate Glucarpidase on Day 1
31 Initiated Glucarpidase on Day 1
389 Did not Initiate Glucarpidase on Day 2
91 Initiated Glucarpidase on Day 2
411 Did not Initiate Glucarpidase on Day 3
60 Initiated Glucarpidase on Day 3
367 Did not Initiate Glucarpidase on Day 4
14 Initiated Glucarpidase on Day 4



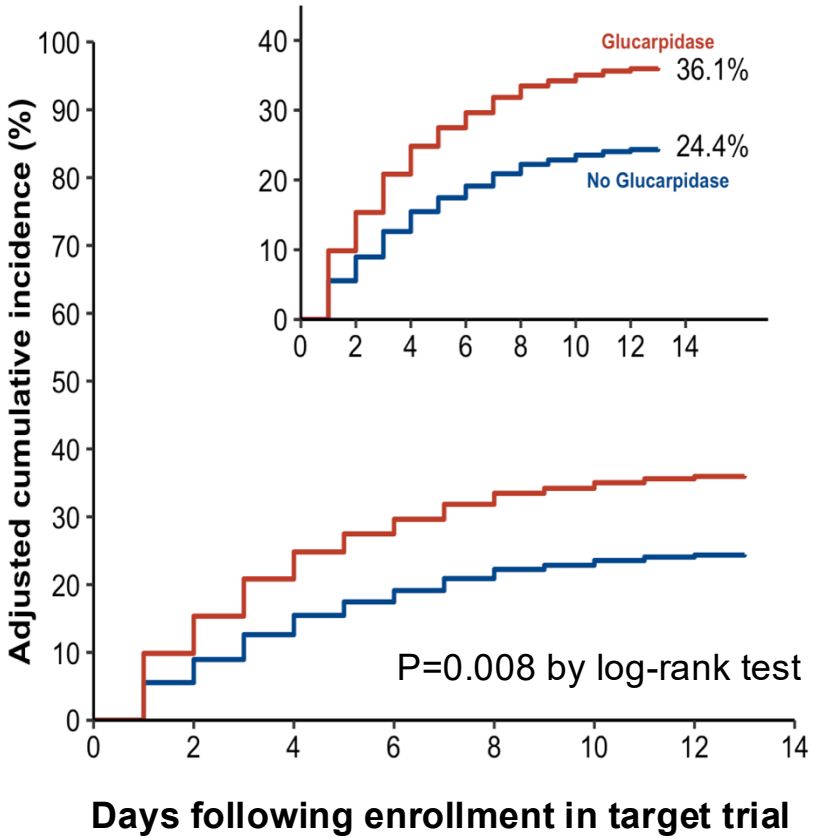
- Alive
- Hospitalized
- AKI (but not yet on KRT)
- Had not previously received glucarpidase

Glucarpidase-treated patients had ↑odds of kidney recovery

	No. Events/ No. Patients (%)	Adjusted OR (95% CI)
Primary analysis	384/1645 (23.3)	2.70 (1.69–4.31)
Sensitivity analyses		
1. Glucarpidase in the first 3 days	384/1645 (23.3)	2.74 (1.69–4.43)
2. Adjusted for site[a]	384/1645 (23.3)	2.64 (1.64–4.23)
3. Adjusted for site[b]	384/1645 (23.3)	2.71 (1.68–4.35)
4. Limited to 2012 or later	365/1509 (24.2)	3.11 (1.97–4.90)
5. Limited to MTX infusion <12h	343/1369 (25.1)	2.75 (1.61–4.70)
6. Limited to glucarpidase ≥50 U/kg	371/1572 (23.6)	3.00 (1.69–5.28)
Subgroup analyses		
Age (years)		
<65	194/858 (22.6)	3.79 (1.95–7.37)
≥65	190/787 (24.1)	2.13 (1.03–4.42)
Sex		
Male	278/1183 (23.5)	2.14 (1.13–4.05)
Female	106/462 (22.9)	3.96 (1.98–7.94)
Baseline eGFR (ml/min/1.73m2)		
<90	183/598 (30.6)	2.13 (0.94–4.81)
≥90	201/1047 (19.2)	3.61 (2.05–6.36)
AKI stage		
Stage 1 or 2	354/1240 (28.5)	2.95 (1.72–5.07)
Stage 3	30/405 (7.4)	4.83 (1.93–12.04)

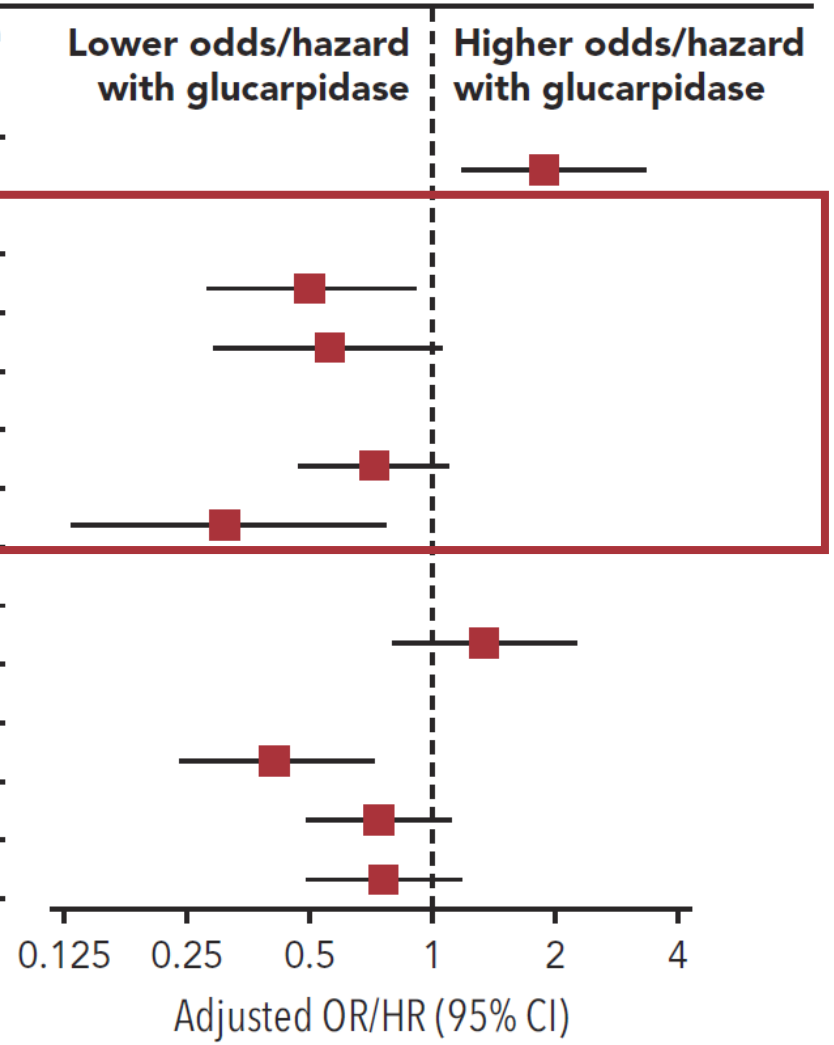


Time-to-kidney recovery: aHR 1.88 (95% CI, 1.18–3.33)



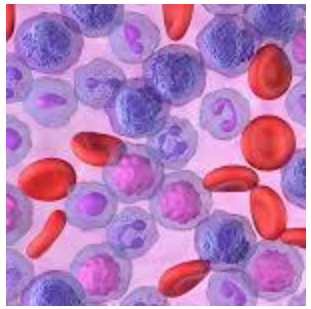
Glucarpidase-treated patients had ↓odds of neutropenia and transaminitis

Outcome	No. Events/ No. Patients (%)	Adjusted OR/HR[a] (95% CI)
Time-to-kidney recovery[a]	390/1645 (23.7)	1.88 (1.18–3.33)
Neutropenia on day 7		
Grade ≥2 (ANC <1500/mm^3)	266/1502 (17.7)	0.50 (0.28–0.91)
Grade ≥3 (ANC <1000/mm^3)	169/1573 (10.7)	0.56 (0.29–1.06)
Transaminitis on day 7		
Grade ≥1 (ALT ≥ULN)[b]	389/1167 (33.3)	0.72 (0.47–1.10)
Grade ≥2 (ALT ≥3x ULN)[c]	113/1167 (9.7)	0.31 (0.13–0.77)
Mucositis on day 7		
Any grade	177/1644 (10.8)	1.34 (0.80–2.26)
MTX Rechallenge		
Within 30 days following index MTX infusion	466/1645 (28.3)	0.41 (0.24–0.72)
Persistent kidney impairment or death at day 90	388/1349 (32.0)	0.74 (0.49–1.11)
Time-to-death[a]	232/1645 (14.1)	0.76 (0.49–1.18)



Rasburicase and TLS

Background on Tumor Lysis Syndrome (TLS) and Rasburicase



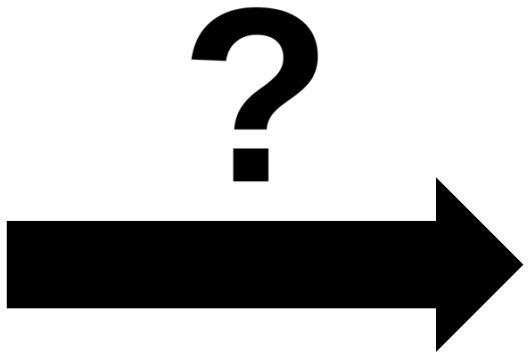
TLS is an oncologic emergency most often occurring in patients with hematologic malignancies with a high cancer burden

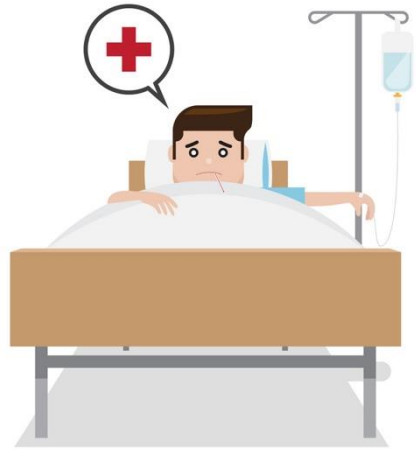
Rapid breakdown of tumor cells releases potassium, phosphate, and uric acid into the circulation, resulting in high rates of AKI

Rasburicase is a recombinant urate oxidase that is highly effective in lowering plasma uric acid

Despite rasburicase's potent biochemical effects, no study had rigorously examined its clinical efficacy in patients with TLS

Biochemical Effect





Improved Outcomes

Early treatment with rasburicase and risk of kidney replacement therapy and death in adults with tumour lysis syndrome: emulated target trial

Tushar Shenoy,[1] Daniel Sanchez-Almanzar,[1] Julie-Alexia Dias,[1,2] Robert Hayden,[1] Michael GS Shashaty,[3] Abinet M Aklilu,[4,5] Rushad Patell,[6,7] Shuchi Anand,[8] Amanda Renaghan,[9] Claude Bassil,[10,11] Javier A Neyra,[12] Anip Bansal,[13] Chintan V Shah,[14] Shruti Gupta,[1,7] Meghan E Sise,[7,15] Rituvanthikaa Seethapathy,[7,15] Sydney Chase,[16] Cyrilee Thompson,[1,7] Raghu Radhakrishnan,[17] Eesha Verma,[1] Jian Ni,[18] Steven T Hoge,[1] Victoria Lypka,[1] Rafia Ali,[1] Audrey E Monson,[1] Sarah Kaunfer,[1] Elizabeth Angus,[1] Stephen Griffiths,[3] Clara Walling,[19] Nadia Al Haddad,[19] Christina HW Brotman,[19] Todd Miano,[20] Anushree C Shirali,[4] David J Turco,[4] Saieda A Alleyne,[4] Kyra Shelton,[5] Shahzad Shaefi,[21] Daniela Garcia,[21] Atif Nasim,[21] Naveed Jan,[22] Phuong H Nguyen,[23] Susan Ziolkowski,[24] Nivetha Subramanian,[8] Vigneshwar Subramanian,[24] Neha Debnath,[8] Czarina T Faldu,[9] Kavindya Wickramasinghe,[25] Brian P Donahue,[25] Anish Shah,[26] Jessica Shostak,[27] Vaishnavi Jayakumar,[27] Jasmine Nadayil,[28] Rachid Baz,[29] Tomonori Takeuchi,[30,31] Stefania Renzi,[12,32] Aqeeb Ur Rehman,[12] Natalia Nombera-Aznaran,[12] Mariam Charkviani,[12] Megan Kotzin,[33] Jeff Kaiser,[34] Madison Edwards,[34] Akash Mathavan,[35] Akshay Mathavan,[35] Faith Obimdike,[35] Nikita Shah,[35] Ann S LaCasce,[7,36] Philippe Armand,[7,36] David E Leaf[1,7]

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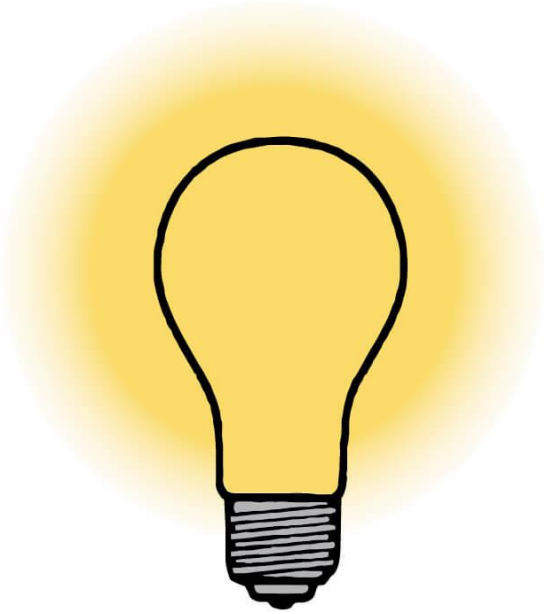
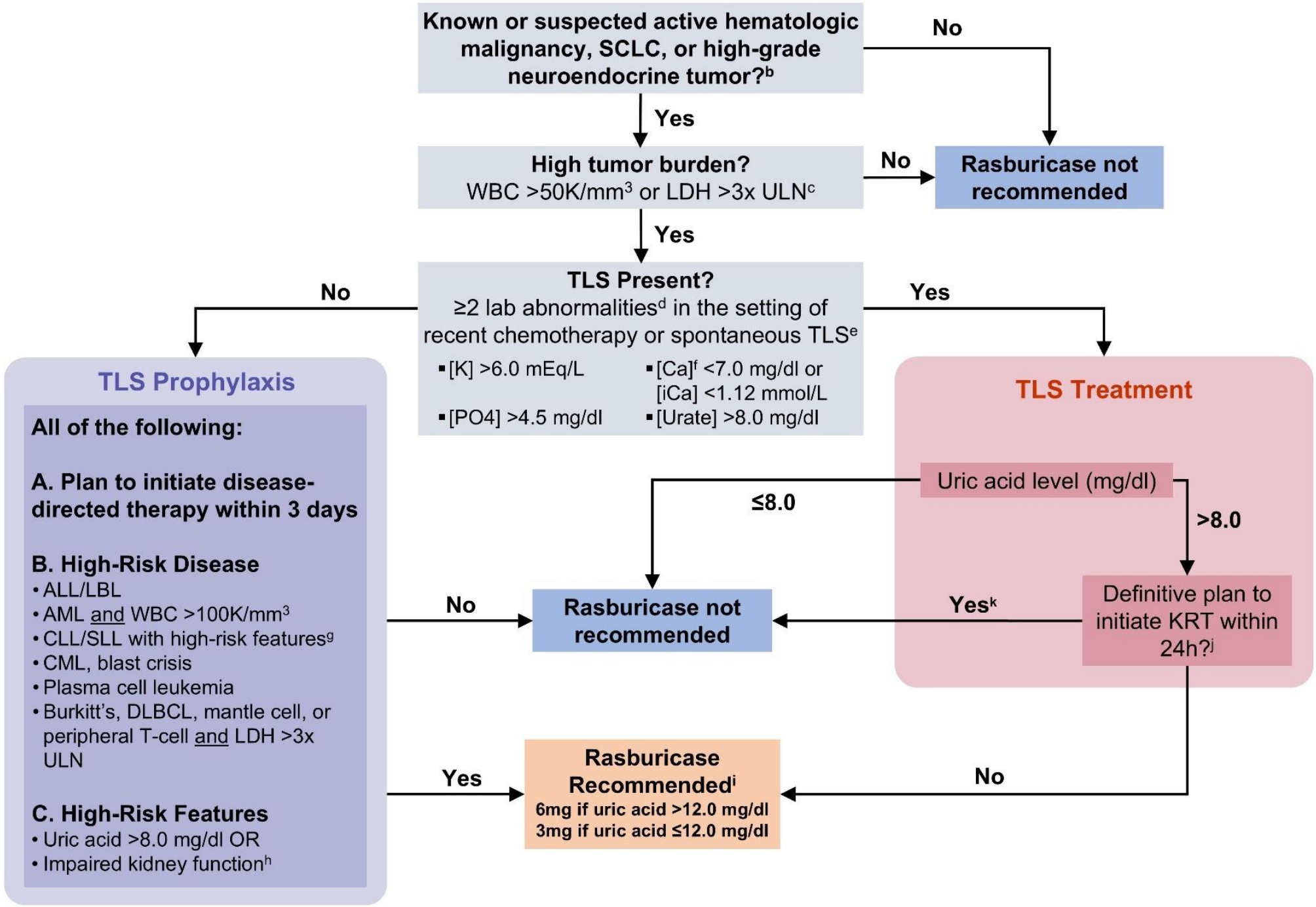
Preconceived Notions about Rasburicase



QI Project: Rasburicase Treatment Algorithm


Known or suspected active hematologic malignancy, SCLC, or high-grade neuroendocrine tumor?[b]
No
Yes
High tumor burden?
WBC >50K/mm3 or LDH >3x ULN[c]
No
Rasburicase not recommended
Yes
TLS Present?
≥2 lab abnormalities[d] in the setting of recent chemotherapy or spontaneous TLS[e]
▪ [K] >6.0 mEq/L
▪ [Ca][f] <7.0 mg/dl or [iCa] <1.12 mmol/L
▪ [PO4] >4.5 mg/dl
▪ [Urate] >8.0 mg/dl
No
Yes
TLS Prophylaxis
All of the following:
A. Plan to initiate disease-directed therapy within 3 days
B. High-Risk Disease
• ALL/LBL
• AML and WBC >100K/mm3
• CLL/SLL with high-risk features[g]
• CML, blast crisis
• Plasma cell leukemia
• Burkitt's, DLBCL, mantle cell, or peripheral T-cell and LDH >3x ULN
C. High-Risk Features
• Uric acid >8.0 mg/dl OR
• Impaired kidney function[h]
TLS Treatment
Uric acid level (mg/dl)
≤8.0
>8.0
Definitive plan to initiate KRT within 24h?[j]
Yes[k]
No
Rasburicase not recommended
Yes
Rasburicase Recommended[i]
6mg if uric acid >12.0 mg/dl
3mg if uric acid ≤12.0 mg/dl
No

TTE: Efficacy of Early Rasburicase vs No Early Rasburicase for TLS

Overview

Multicenter cohort study of >2,000 adults with TLS from **10 major cancer centers (36 sites)** across the U.S.

Data Collection

Manual chart review, >500 data elements/patient

Primary Exposure

Receipt vs. no receipt of rasburicase within 12h after TLS onset

Primary Outcome

AKI-KRT or death during the index admission

Statistical Analysis

- TTE framework
- MV adjustment for demographics, comorbidities, labs, and acute organ injury (including SOFA score)

Covariates

Demographics
- Age
- Sex
- Race

Comorbidities
- Diabetes mellitus
- Hypertension
- CHF
- CAD
- Atrial fibrillation
- COPD
- CKD
- Chronic liver disease
- Smoker
- PAD
- Stroke
- Body mass index

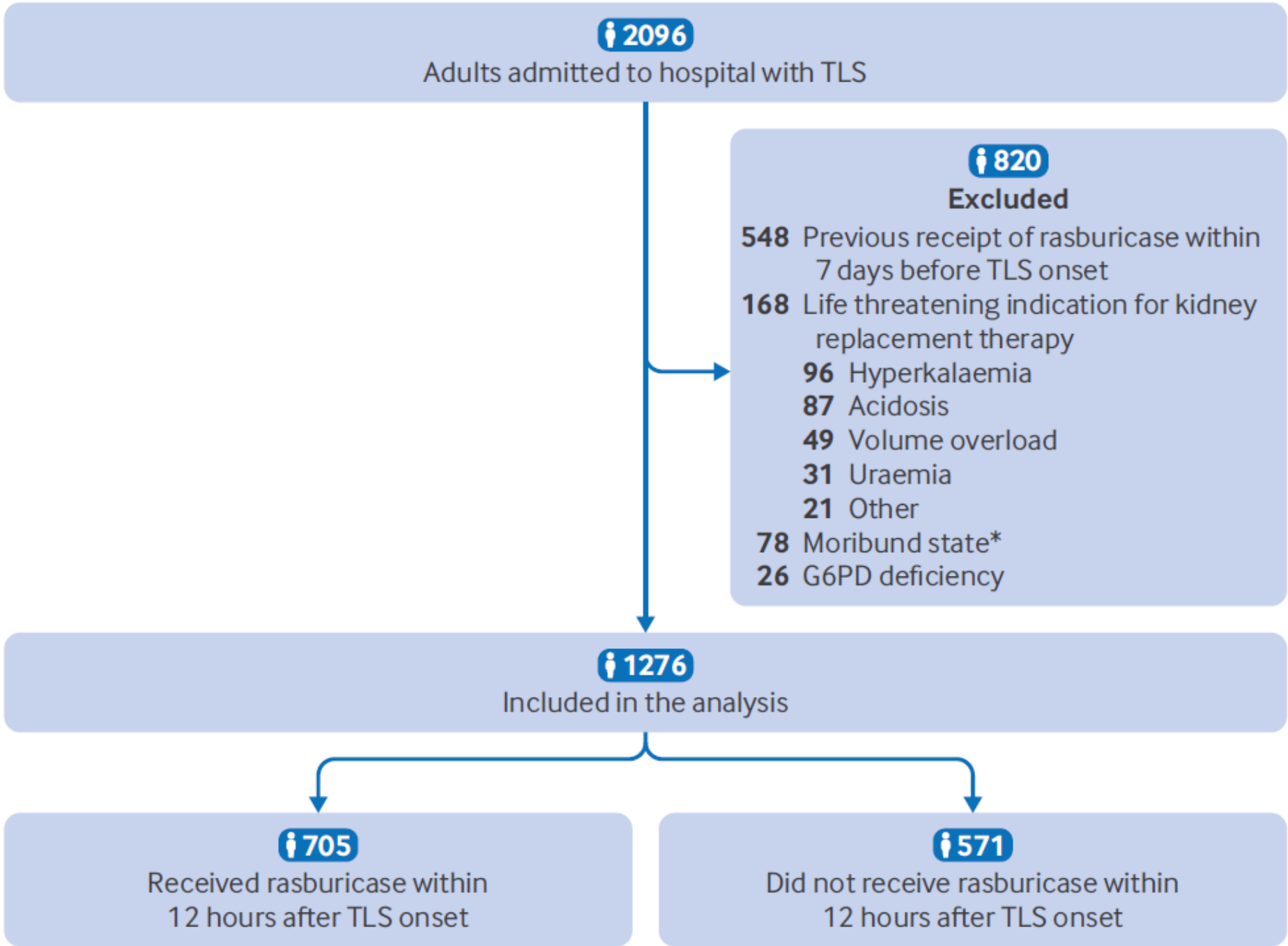
Malignancy Characteristics
- Hematologic vs solid
- Prior therapy
- Spontaneous TLS

Treatments at TLS Onset
- IV fluids
- Sodium bicarbonate
- Allopurinol

Severity of Illness
- Admitted to the ICU
- SOFA score
- AKI and its severity
- UOP
- Pressors
- IMV
- Bacterial infection
- DNR code status

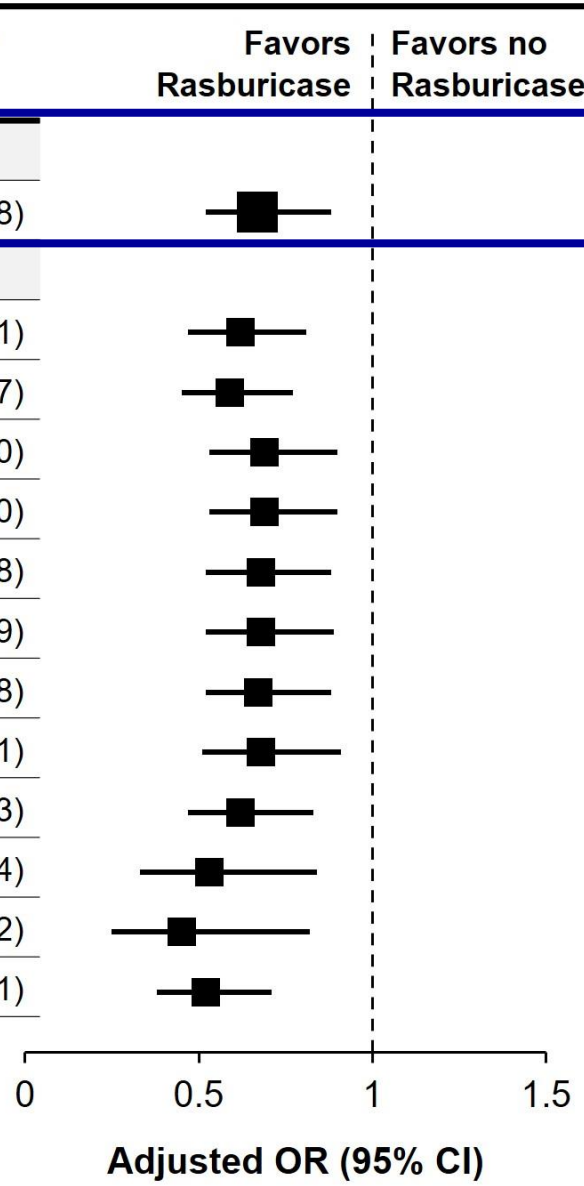
Labs
- Potassium
- Bicarbonate
- SCr
- Calcium
- Phosphate
- Uric acid
- LDH
- ALT
- Total bilirubin
- Albumin
- WBC count
- Hemoglobin
- Platelet count

Total = 43


2096
Adults admitted to hospital with TLS
820
Excluded
548 Previous receipt of rasburicase within 7 days before TLS onset
168 Life threatening indication for kidney replacement therapy
96 Hyperkalaemia
87 Acidosis
49 Volume overload
31 Uraemia
21 Other
78 Moribund state*
26 G6PD deficiency
1276
Included in the analysis
705
Received rasburicase within 12 hours after TLS onset
571
Did not receive rasburicase within 12 hours after TLS onset

Early Rasburicase associated with ↓Odds of AKI-KRT or Death

	No. Events / No. Patients (%)		Adjusted OR[a] (95% CI)
	Rasburicase	No Rasburicase	
Primary Outcome			
AKI-KRT or death	230/704 (32.7)	244/581 (42.0)	0.67 (0.52–0.88)
Sensitivity Analyses			
1. Adjusted using MV regression	228/705 (32.3)	238/571 (41.7)	0.62 (0.47–0.81)
2. Propensity score matching	106/487 (21.8)	140/487 (28.7)	0.59 (0.45–0.77)
3. Adjusted for uric acid level	230/704 (32.7)	244/581 (42.0)	0.69 (0.53–0.90)
4. Adjusted for malignancy type	230/704 (32.7)	244/581 (42.0)	0.69 (0.53–0.90)
5. Adjusted for nephrotoxic chemo/immunotherapy	230/704 (32.7)	244/581 (42.0)	0.68 (0.52–0.88)
6. Adjusted for site	230/704 (32.7)	244/581 (42.0)	0.68 (0.52–0.89)
7. Adjusted for year	230/704 (32.7)	244/581 (42.0)	0.67 (0.52–0.88)
8. Exclusion of severe acute organ injury	178/592 (30.1)	195/503 (38.8)	0.68 (0.51–0.91)
9. Exclusion of patients who died within 3 days	182/655 (27.8)	208/544 (38.2)	0.62 (0.47–0.83)
10. Rasburicase 6mg dose	60/169 (35.5)	91/178 (51.1)	0.53 (0.33–0.84)
11. Rasburicase 3mg dose	25/79 (31.6)	91/178 (51.1)	0.45 (0.25–0.82)
12. Early rasburicase vs. no rasburicase	230/704 (32.7)	193/399 (48.4)	0.52 (0.38–0.71)



Early Rasburicase associated with ↓Odds of AKI-KRT or Death

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	Rasburicase	No Rasburicase	
Primary Outcome			
AKI-KRT or death	230/704 (32.7)	244/581 (42.0)	0.67 (0.52–0.88)
	228/705 (32.3)	238/571 (41.7)	0.62 (0.47–0.81)
	106/487 (21.8)	140/487 (28.7)	0.59 (0.45–0.77)
	230/704 (32.7)	244/581 (42.0)	0.69 (0.53–0.90)
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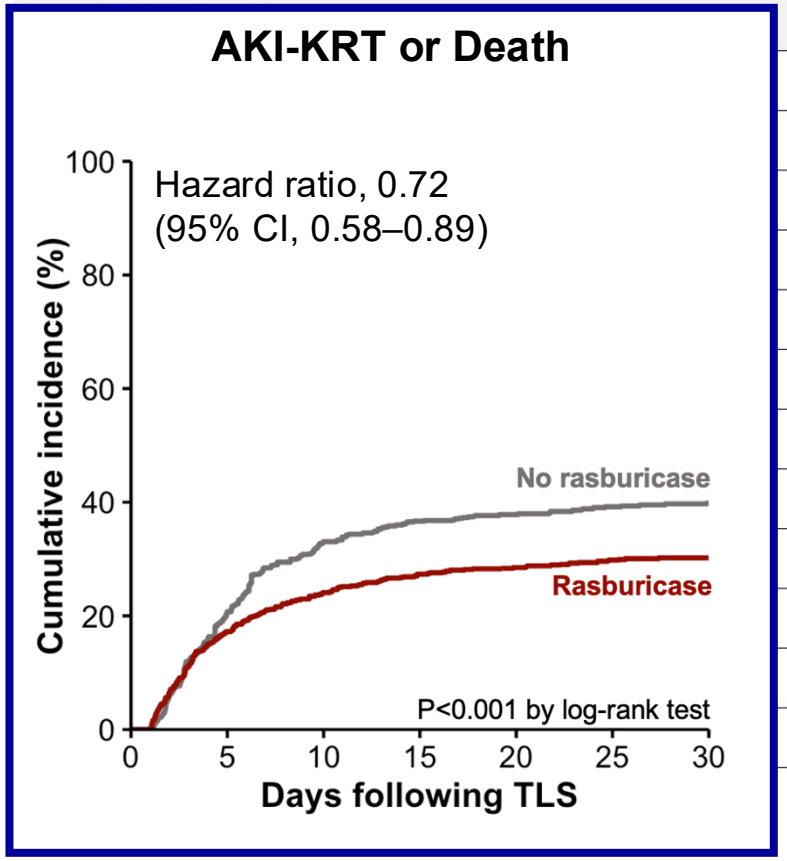
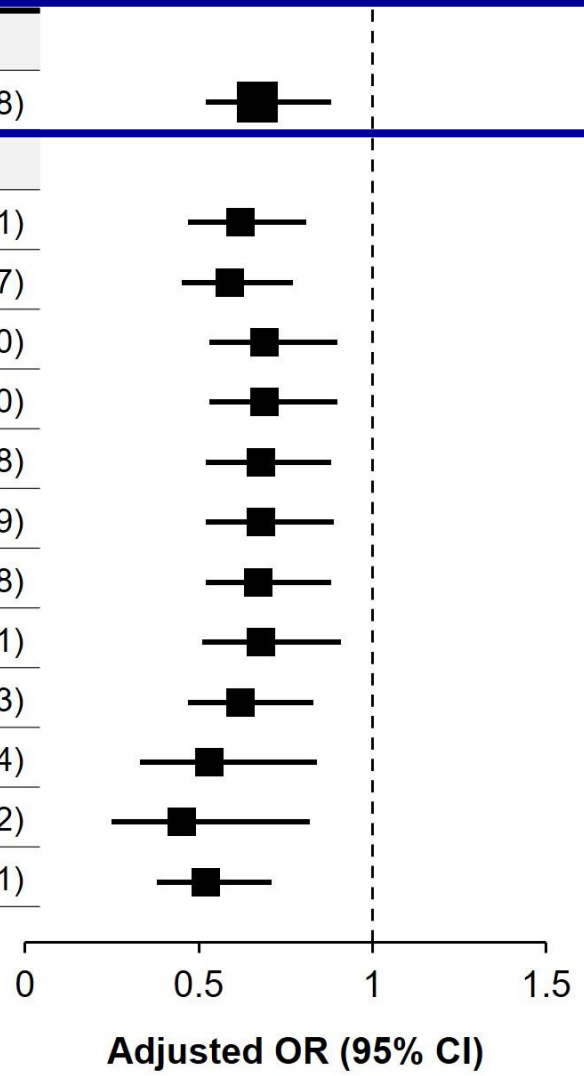
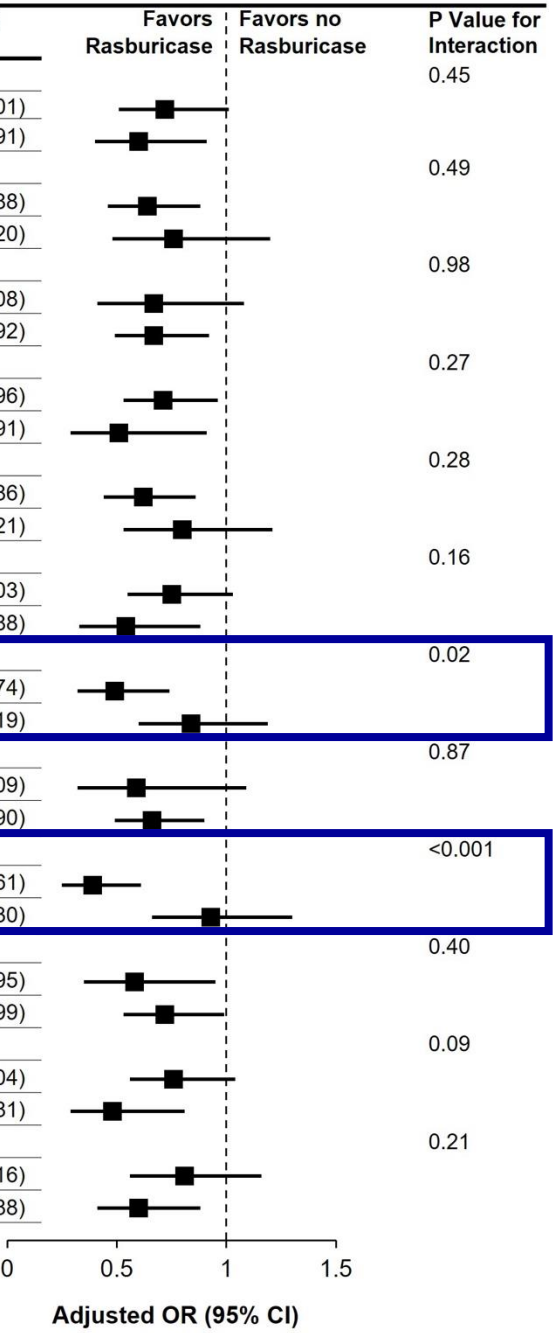




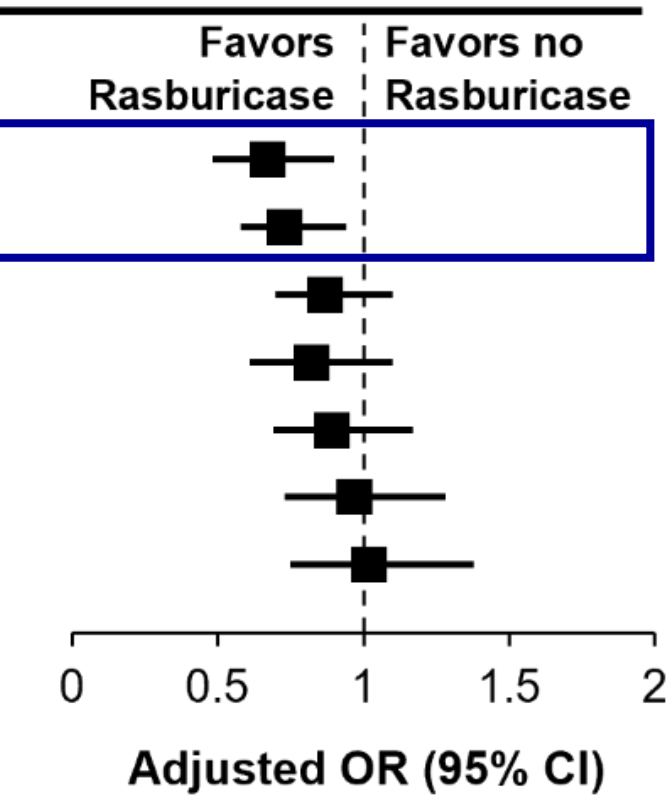
Subgroup Analyses

	No. Events / No. Patients (%)		Adjusted OR (95% CI)	P Value for Interaction
	Rasburicase	No Rasburicase		
Age (years)[a]				0.45
<70	138/429 (32.2)	146/366 (39.9)	0.72 (0.51–1.01)	
≥70	92/275 (33.5)	98/215 (45.6)	0.57 (0.40–0.91)	
Sex				0.49
Male	151/486 (31.1)	165/398 (41.5)	0.64 (0.46–0.88)	
Female	79/218 (36.2)	79/183 (43.2)	0.76 (0.48–1.20)	
Race				0.98
Non-White/other/unknown	66/174 (37.9)	65/135 (48.1)	0.67 (0.41–1.08)	
White	164/530 (30.9)	179/448 (40.0)	0.67 (0.49–0.92)	
Hematologic malignancy				0.27
Yes	174/578 (30.1)	181/478 (37.9)	0.71 (0.53–0.96)	
No	56/126 (44.4)	63/103 (61.2)	0.51 (0.29–0.91)	
Spontaneous TLS				0.28
Yes	148/449 (33.0)	168/377 (44.6)	0.62 (0.44–0.86)	
No	82/255 (32.2)	76/204 (37.2)	0.80 (0.53–1.21)	
Serum uric acid (mg/dL)[b]				0.16
<12	128/421 (30.4)	137/371 (36.9)	0.75 (0.55–1.03)	
≥12	102/283 (36.0)	107/210 (51.0)	0.54 (0.33–0.88)	
Serum bicarbonate (mEq/L)[c]				0.02
<20	114/278 (41.0)	136/231 (58.9)	0.49 (0.32–0.74)	
≥20	116/426 (27.2)	108/350 (30.9)	0.84 (0.60–1.19)	
ICU				0.87
Yes	67/119 (56.3)	65/94 (69.1)	0.59 (0.32–1.09)	
No	163/585 (27.9)	179/487 (36.8)	0.66 (0.49–0.90)	
Moderate-to-severe AKI				<0.001
Yes	80/242 (33.1)	117/209 (56.0)	0.39 (0.25–0.61)	
No	150/462 (32.5)	127/372 (34.1)	0.93 (0.66–1.30)	
Oliguria				0.40
Yes	66/162 (40.7)	85/155 (54.8)	0.58 (0.35–0.95)	
No	164/542 (30.3)	159/426 (37.3)	0.72 (0.53–0.99)	
No. Cairo-Bishop lab abnormalities				0.09
2	171/549 (31.2)	164/439 (37.4)	0.76 (0.56–1.04)	
3–4	59/155 (38.1)	80/142 (56.3)	0.48 (0.29–0.81)	
Allopurinol on day of TLS onset[d]				0.21
Yes	112/387 (28.9)	89/265 (33.6)	0.81 (0.56–1.16)	
No	115/308 (37.3)	153/308 (49.7)	0.60 (0.41–0.88)	



Sensitivity Analysis: Timing of Rasburicase Exposure

Timing of rasburicase receipt following TLS onset	No. Events / No. Patients (%)		Adjusted OR (95% CI)
	Rasburicase	No Rasburicase	
12 hours[a]	230/704 (32.7)	244/581 (42.0)	0.67 (0.52–0.88)
18 hours	290/845 (34.4)	184/440 (41.8)	0.73 (0.56–0.96)
24 hours	327/911 (35.9)	147/375 (39.2)	0.87 (0.66–1.15)
30 hours	347/970 (35.8)	127/316 (40.3)	0.82 (0.62–1.10)
36 hours	363/1003 (36.2)	111/283 (39.2)	0.89 (0.65–1.20)
42 hours	373/1016 (36.7)	101/270 (37.4)	0.97 (0.70–1.33)
48 hours	380/1028 (37.0)	94/257 (36.5)	1.02 (0.74–1.41)



IV Mg and Cisplatin-AKI

Cisplatin-associated AKI (CP-AKI)

Cisplatin remains a first-line treatment for numerous malignancies

- **AKI is one of the most common toxicities (~35%)**
- **It increases susceptibility to extrarenal cisplatin toxicities**
- **Jeopardizes eligibility for other anticancer treatments**

No therapy reliably prevents CP-AKI in humans

In animal models, prophylactic administration of Mg attenuates AKI

Research

JAMA Oncology | Original Investigation

Intravenous Magnesium and Cisplatin-Associated Acute Kidney Injury

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Methods: TTE of IV Mg vs. no IV Mg and CP-AKI

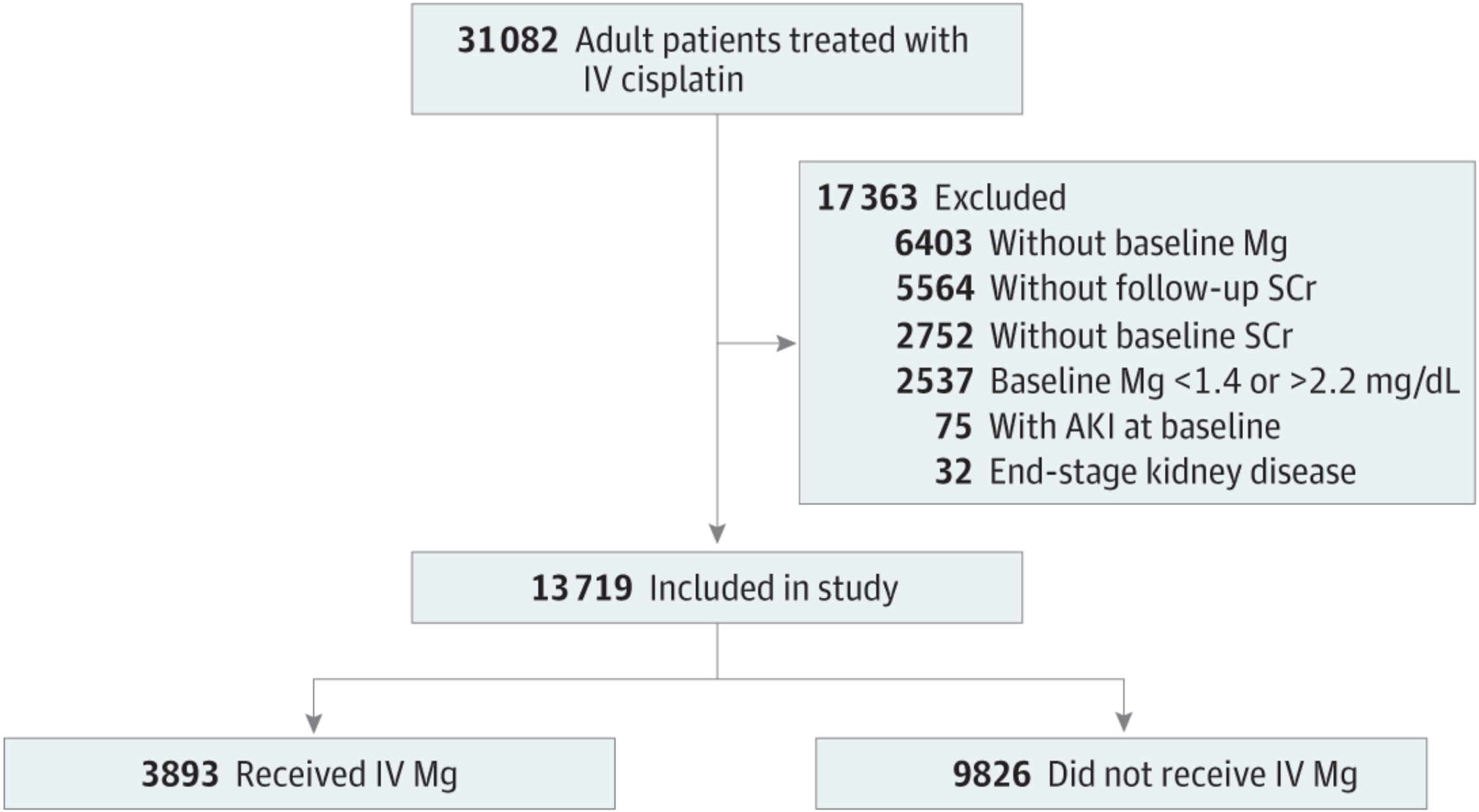
Overview
Multicenter cohort study of 13,719 adults treated with a first dose of IV cisplatin at 5 major cancer centers across the US

Primary Exposure
IV Mg vs. no IV Mg on the first day of cisplatin treatment

Primary Outcome
Moderate-to-severe CP-AKI
(≥2-fold increase in SCr or KRT within 14 days)

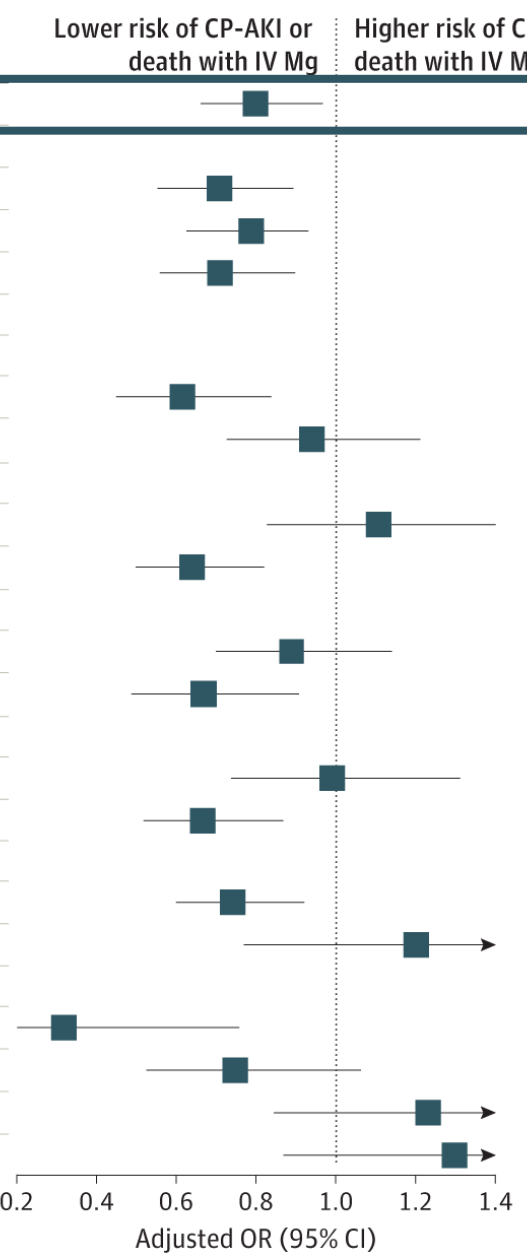
Statistical Analysis
- TTE framework
- IPTW to adjust for confounders

Memorial Sloan Kettering Cancer Center
DANA-FARBER CANCER INSTITUTE
MASSACHUSETTS GENERAL HOSPITAL
MD Anderson Cancer Center
Northwell Health®


31 082 Adult patients treated with IV cisplatin
17 363 Excluded
6403 Without baseline Mg
5564 Without follow-up SCr
2752 Without baseline SCr
2537 Baseline Mg <1.4 or >2.2 mg/dL
75 With AKI at baseline
32 End-stage kidney disease
13 719 Included in study
3893 Received IV Mg
9826 Did not receive IV Mg

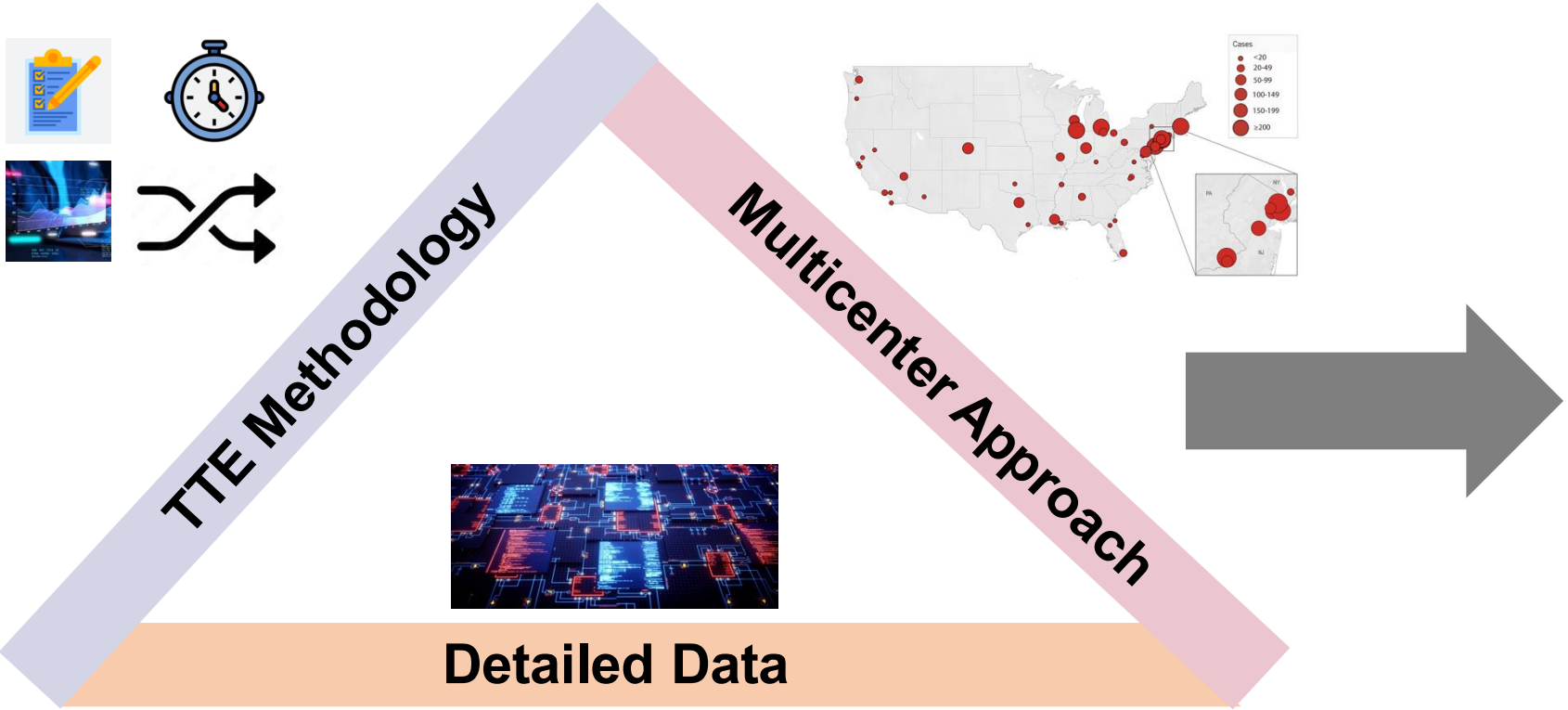
IV Mg-Treated Patients had ↓Odds of Cisplatin-associated AKI

Overall	No. of patients with CP-AKI/total No. (%)		Adjusted OR (95% CI)	*P* value
	IV Mg	No IV Mg		
Primary outcome	104/3893 (2.7)	520/9826 (5.3)	0.80 (0.66-0.97)	NA
Sensitivity analyses				
Adjusted with multivariable regression	104/3893 (2.7)	520/9826 (5.3)	0.71 (0.56-0.89)	NA
IV Mg within 3 d before CP-AKI	109/4198 (2.6)	462/9521 (4.9)	0.79 (0.63-0.98)	NA
≥2 g IV Mg	48/2334 (2.1)	477/9826 (4.9)	0.71 (0.56-0.90)	NA
Subgroups				
Age, y				.04
<65	60/2763 (2.2)	261/6325 (4.1)	0.62 (0.45-0.84)	
≥65	34/1130 (3.0)	216/3240 (6.7)	0.94 (0.73-1.21)	
Sex				<.01
Male	48/2091 (2.3)	302/5726 (5.3)	1.11 (0.83-1.43)	
Female	46/1802 (2.6)	175/4100 (4.3)	0.64 (0.50-0.82)	
Baseline eGFR, mL/min/1.73m^2				.05
<90	37/1678 (2.2)	201/4446 (4.5)	0.89 (0.70-1.14)	
≥90	57/2215 (2.6)	276/5380 (5.1)	0.67 (0.49-0.91)	
Baseline serum Mg, mg/dL				.04
1.4-1.9	63/1857 (3.4)	245/3924 (6.2)	0.99 (0.74-1.31)	
2.0-2.2	31/2036 (1.5)	232/5902 (3.9)	0.67 (0.52-0.87)	
Diabetes				.61
Diabetes	19/580 (3.3)	78/1250 (6.2)	0.74 (0.60-0.92)	
No diabetes	75/3313 (2.3)	399/8576 (4.7)	1.20 (0.77-1.85)	
Cisplatin dose, mg				.07
<50	12/1259 (1.0)	38/1703 (2.2)	0.32 (0.13-0.76)	
50-74	15/1263 (1.2)	79/3078 (2.6)	0.75 (0.53-1.06)	
75-99	16/623 (2.6)	66/1556 (4.2)	1.23 (0.85-1.79)	
≥100	51/748 (6.8)	294/3489 (8.4)	1.30 (0.87-1.95)	



Conclusions

Combining TTE methodology, detailed data, and a multicenter approach is a powerful combination for answering key questions in onconephrology and across a range of fields



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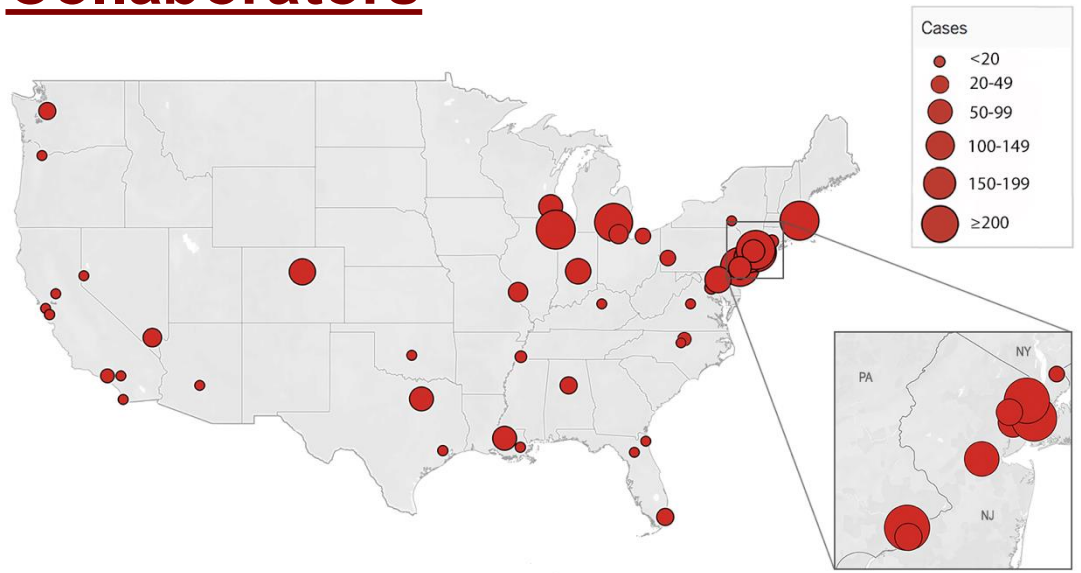

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