LONG-TERM KIDNEY OUTCOMES FOLLOWING CHILDHOOD ACUTE KIDNEY INJURY RECEIVING DIALYSIS

Cal Robinson, Nivethika Jeyakumar, Bin Luo, Ron Wald, Amit Garg, Danielle Nash, Eric McArthur, Jason Greenberg, David Askenazi, Cherry Mammen, Lehana Thabane, Stuart Goldstein, Rulan Parekh, Michael Zappitelli, Rahul Chanchlani

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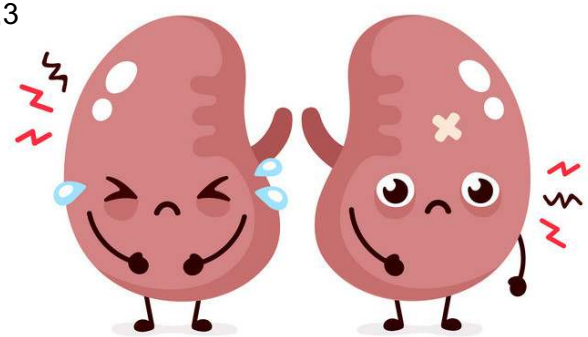
Background

- Pediatric AKI is **common**
  - >5% all admissions [1], ~30% NICU/PICU admissions [2,3]
  - Dialysis receipt in 6-9% of AKI episodes [3,4]

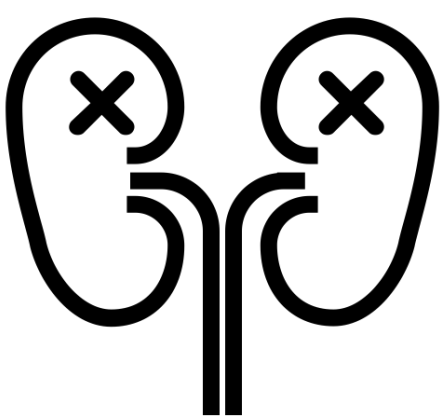


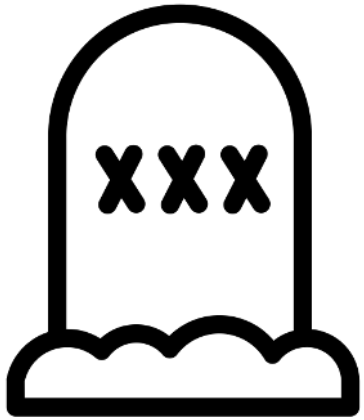
- Pediatric AKI is **harmful** and **costly**
  - Short-term mortality – 14-30% (all AKI) [4,5]
  - Prolonged mechanical ventilation, hospital length of stay [3,4,7]
  - Healthcare costs (adult + children) – 5-24 billion USD/year [6]

- Adult AKI → increased risks of **long-term mortality, CKD, hypertension** [5,8,9]
- **Limited pediatric data** on long-term kidney outcomes after severe AKI
  - **Conflicting results** from recent prospective studies [10-13]

Objectives

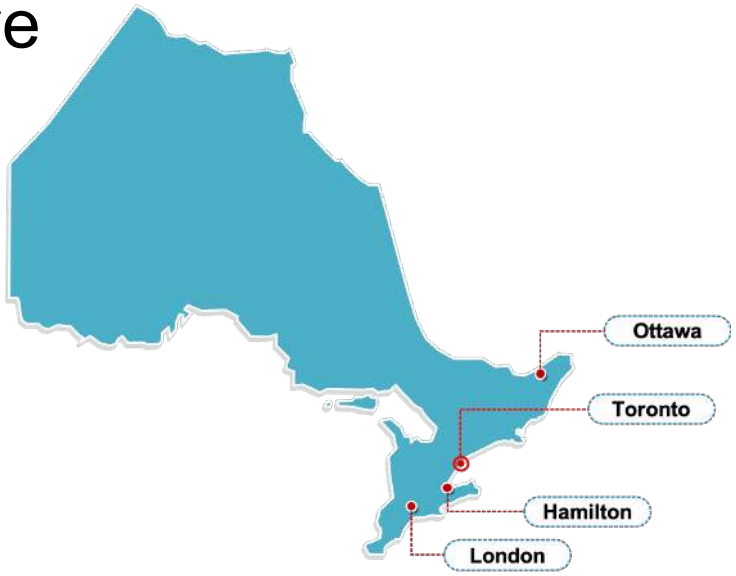
- To determine the risk of **kidney failure** (chronic dialysis or kidney transplant) or **death** in pediatric dialysis-receiving AKI survivors





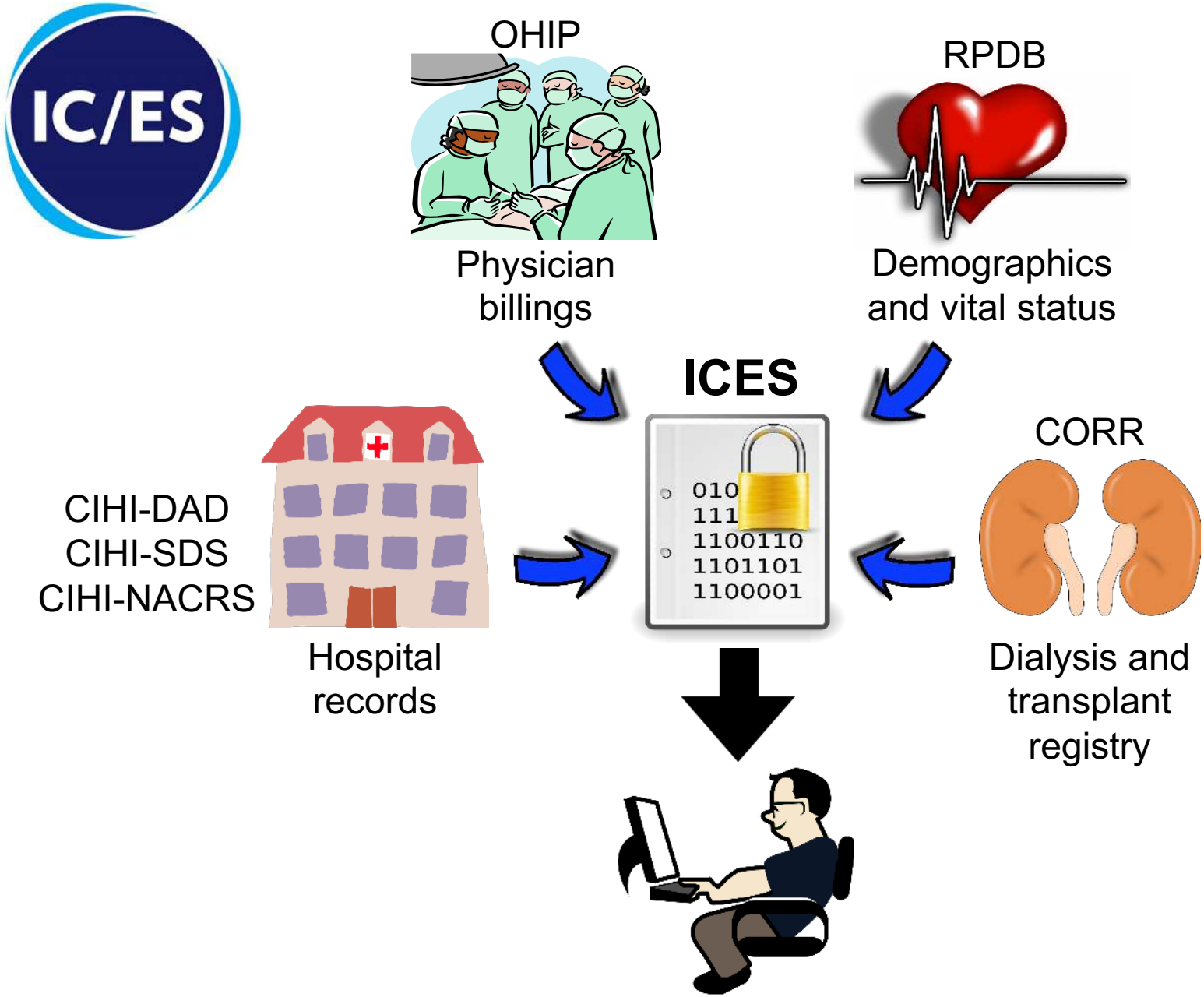
Study Design

- Population-based, retrospective matched-cohort study in Ontario, Canada
  - ~ 3 million children
  - Universal healthcare system
  - < 1% annual emigration



- ICES provincial health administrative databases
  - DAD – inpatient
  - OHIP – outpatient, physician billing
  - RPDB – demographics, vital status
  - Linked using unique encoded identifiers

IC/ES

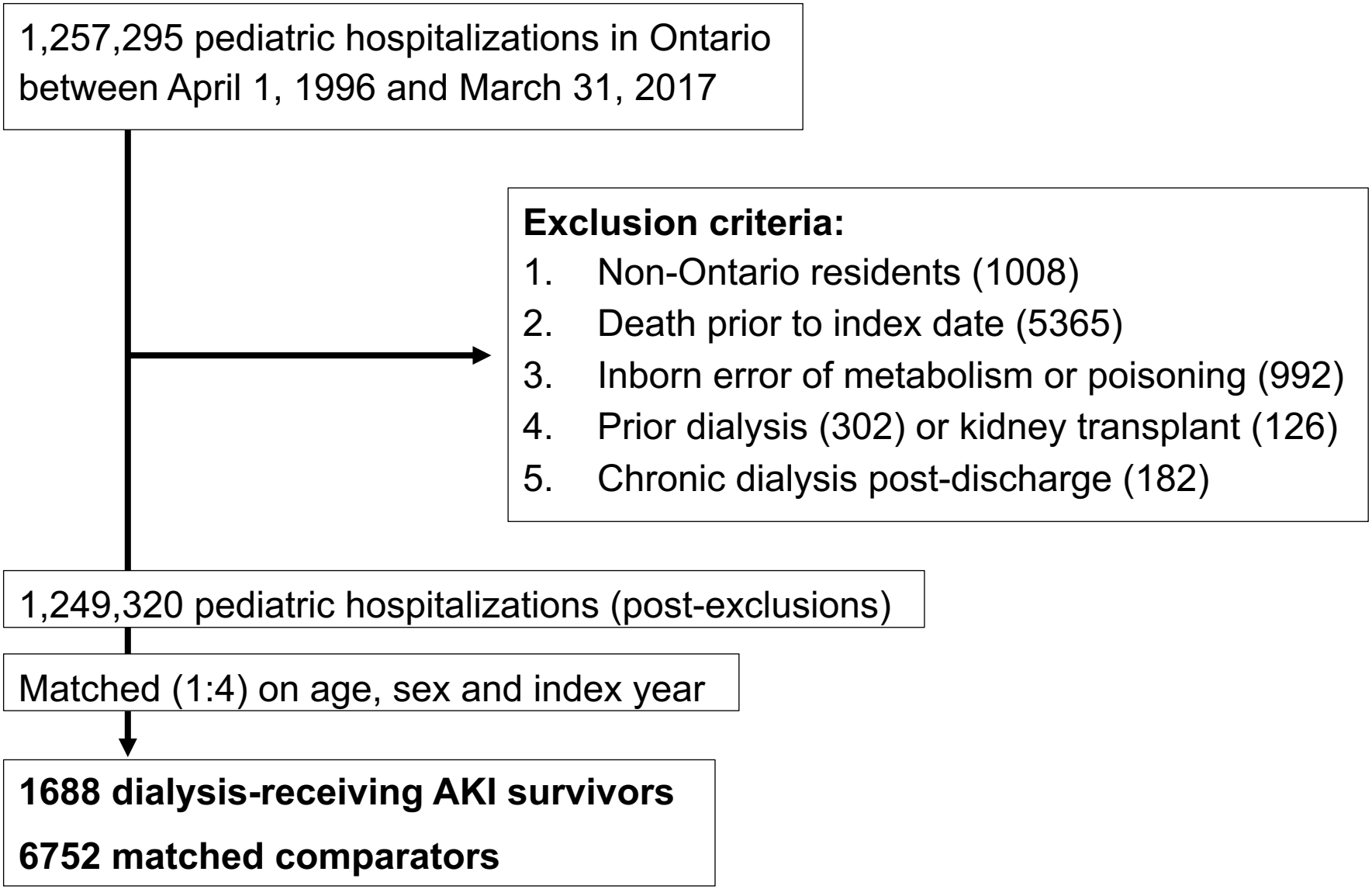


Slide courtesy: ICES

Study population

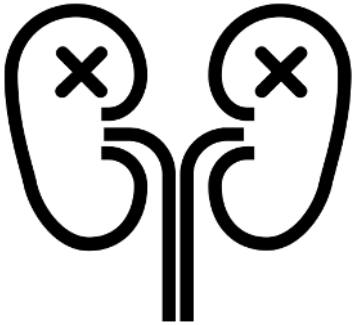
- All pediatric hospitalizations (0-18yr) in Ontario
- Inclusion: between April 1, 1996 – March 31, 2017
- Dialysis-receiving AKI
  - Administrative coding for acute dialysis (intermittent hemodialysis, peritoneal dialysis or CRRT) or dialysis access
  - For neonates (0-29 days) – dialysis access codes not used
- Comparator cohort
  - All episodes of care without dialysis-receiving AKI
  - Matched (1:4) by age, sex and index year

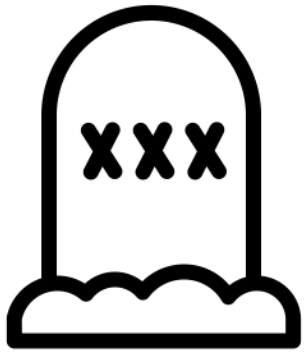
Cohort Development



Outcomes

- Primary outcome
  - Composite of all-cause mortality or kidney failure (chronic dialysis or kidney transplant)
- Secondary outcomes
  - *De novo* CKD
  - *De novo* hypertension
  - MAKE (death, kidney failure or CKD)
  - Subsequent AKI
- All outcomes defined by administrative codes
- From 90 ± 14 days post-discharge to death, 2 years after last healthcare contact or March 31, 2018





Statistical Analysis

- Incidence rates calculated per 1,000 person-years
- Multivariable Cox proportional hazards models
  - Unadjusted and adjusted models
  - Time-stratified Cox models
- Subgroup analysis
  - Cardiac surgery during index admission
  - Prior cardiac surgery, prior malignancy
  - Neonates vs. children
- Time to event analysis by Kaplan-Meier method

Baseline characteristics

Variable	Dialysis-receiving AKI N (%)	Comparators N (%)	Standardized Difference (%)
Total Patients	**1,688**	**6,752**	-
Median age at index date, years (IQR)	5 (0-15)	5 (1-15)	3
Sex (male)	913 (54.1%)	3,652 (54.1%)	0
Pre-existing comorbidities			
Hypertension	96 (6.1%)	178 (2.8%)	16
Chronic kidney disease	41 (2.6%)	25 (0.4%)	18
Malignancy	137 (8.7%)	414 (6.6%)	8
Cardiac surgery	111 (7.1%)	76 (1.2%)	30
PMCA – Complex chronic disease	464 (29.5%)	794 (12.6%)	42
Index hospitalization characteristics			
Mechanical ventilation	906 (53.7%)	364 (5.4%)	125
ECMO	561 (33.2%)	44 (0.7%)	96
Cardiac surgery	568 (33.6%)	60 (0.9%)	96
Median hospital length of stay, days (IQR)	16 (7-36)	2 (1-4)	165
ICU admission (neonatal and pediatric)	1111 (65.8%)	596 (8.8%)	146

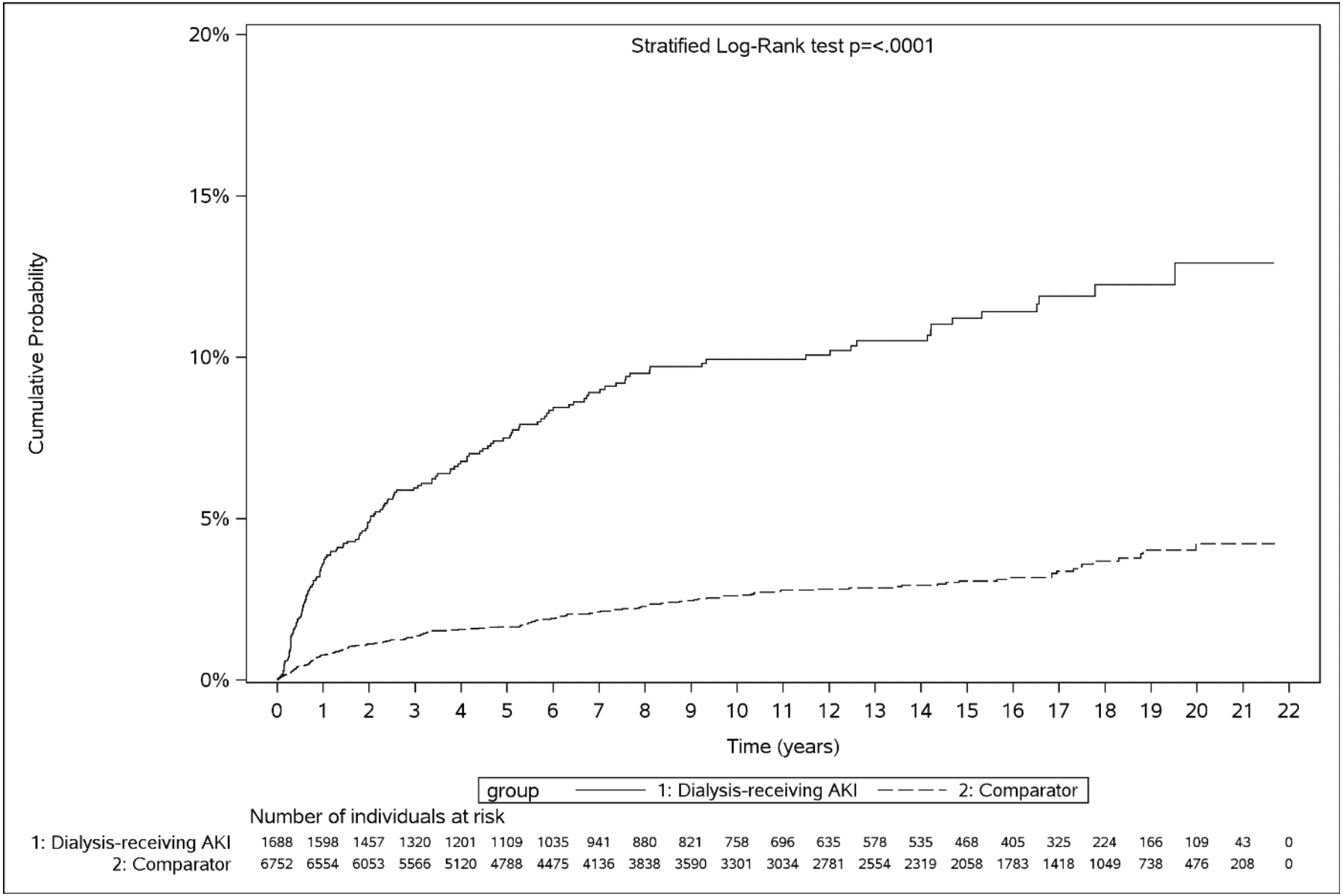
Outcomes (median 9.6yr follow-up)

	Dialysis-receiving AKI (N=1,688) n (%)	Comparators (N=6,752) n (%)	Unadjusted HR (95% CI)	Adjusted HR † (95% CI)
Kidney failure and death composite	**156 (9.2%)**	**170 (2.5%)**	**3.86 (3.10 - 4.80)**	**2.96 (2.20 - 3.97)**
Kidney failure	44 (2.6%)	10 (0.1%)	18.52* (9.33 - 36.75)	17.88* (8.61 - 37.13)
All-cause mortality	113 (6.7%)	161 (2.4%)	2.90 (2.28 - 3.69)	1.95 (1.38 - 2.76)
MAKE	297/1622 (18.3%)	253/6488 (3.9%)	5.24* (4.42 - 6.20)	4.97* (4.04 - 6.10)
De novo CKD	213/1622 (13.1%)	113/6488 (1.7%)	8.35* (6.62 - 10.54)	8.70* (6.68 - 11.34)
De novo hypertension	174/1436 (12.1%)	169/5744 (2.9%)	4.57* (3.69 - 5.65)	3.35* (2.59 - 4.33)

* Violation of the assumption of proportionality in the associated Cox model

† Adjusted for: pre-existing CKD, hypertension, diabetes and malignancy; PMCA classification; receipt of mechanical ventilation, cardiac surgery, ECMO, sepsis and stem cell transplantation

Cumulative probability of kidney failure or death



Time-stratified Cox models

Outcomes	aHR*	95% CI	p-value	aHR*	95% CI	p-value	aHR*	95% CI	p-value
Kidney failure	0 - 4 years post-discharge			> 4 - 16 years post-discharge			> 16 years post-discharge		
	39.75	11.75 - 134.45	<0.001	11.32	4.00 - 32.04	<0.001	2.20	0.19 - 25.37	0.53
MAKE	0 - 0.5 years post-discharge			> 0.5 - 5 years post-discharge			> 5 years post-discharge		
	12.72	8.45 - 19.14	<0.001	5.15	3.87 - 6.87	<0.001	1.84	1.26 - 2.70	0.002
De novo CKD	0 – 1 year post-discharge			> 1 – 5 years post-discharge			> 5 years post-discharge		
	34.53	20.39 - 58.48	<0.001	7.15	4.77 - 10.71	<0.001	2.02	1.23 - 3.32	0.006
De novo hypertension	0 – 5 years post-discharge			> 5 years post-discharge			-		
	6.13	4.26 - 8.82	<0.001	1.96	1.40 – 2.74	<0.001	-		

*Adjusted for: pre-existing CKD, hypertension, diabetes and malignancy; PMCA classification; receipt of mechanical ventilation, cardiac surgery, ECMO, sepsis and stem cell transplantation

Subgroup analysis

- Incidence (per 1000py) of kidney failure or death
- Among AKI-D survivors
  - Cardiac surgery during index admission
    - No – 9.82 *vs.* Yes – 9.2
  - Prior cardiac surgery
    - No – 8.6 *vs.* Yes – 22.8
  - Prior malignancy
    - No – 7.3 *vs.* Yes – 45.7
  - Neonates and children
    - Neonates – 13.8 *vs.* Children – 9.4

Discussion

- Large cohort of neonates and children with dialysis-receiving AKI
- Long duration of follow-up (median 9.6 years, up to 22 years)
- Minimal loss to follow-up, multiple data sources
- Wide generalizability of population-based cohort
- Dialysis-receiving AKI survivors were at significantly higher risk of kidney failure or death, MAKE, CKD and hypertension

Limitations

- Healthcare administrative data
  - Potential miscoding of exposure, outcomes
  - Lab and medication data were unavailable during the study period
- Potential ascertainment bias (increased healthcare utilization of AKI survivors)
- Unable to match for additional variables due to small event numbers in comparator cohort

Conclusions

- Pediatric dialysis-receiving AKI survivors are at higher risk of adverse long-term kidney outcomes and death
- Justifies close CKD and BP surveillance among severe AKI survivors
  - Particularly during the first 5yr after the episode
- Future research should evaluate methods of risk-stratifying AKI survivors and study tertiary prevention methods, including post-AKI clinic follow-up

Acknowledgements

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  - Parts of this material are based on data and information compiled and provided by MOHLTC and CIHI. The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

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Dialysis Outcomes in Children with Lupus Nephritis

HEATHER WASIK, MD MHS, ASSISTANT PROFESSOR OF PEDIATRICS, SUNY UPSTATE MEDICAL UNIVERSITY

VIMAL CHADHA, MD

SHIRLEY GALBIATI, MS

BRADLEY WARADY, MD

MEREDITH ATKINSON, MD, MHS

NAPRTCS
North American Pediatric Renal Trials and Collaborative Studies

Disclosures

Nothing to disclose

Background

- In the US, 20% of new cases of systemic lupus erythematosus (SLE) are diagnosed in patients under age 18[1]
- Lupus nephritis (LN) occurs in up to 80% of children with SLE[2]
- Only slightly more than half of patients with childhood-onset LN and proliferative glomerular lesions enter a renal remission[3-4]
  - Children with LN at high risk of developing ESRD

1. Wenderfer SE et al. *Pediatr Res.* 81.3 (2017): 406-414
2. Sule S et al. *Clin Kidney J.* 7.1 (2014): 406-414
3. Rianthavorn P et al. *Pediatr Nephrol.* 30.11(2015): 1969-1976
4. Askenazi D et al. *Pediatr Nephrol.* 22.7(2007): 981-986.

Background

- Data from the United States Renal Data System has shown[1,2]:
  - Children with ESRD secondary to LN have increased risk of death compared to those with ESRD from all other causes
  - African American (AA) children with LN on hemodialysis have twice the risk of death compared to AA children with ESRD from all other causes
- Less is known about the specific risk factors for mortality and other adverse outcome in children with LN, and whether dialysis modality modifies risks

1. Sule S et al. *Clin Kidney J.* 7.1 (2014): 406-414.
2. Sule S et al. *Pediatri Nephrol.* 26.1(2011): 93-98

Objective

- To characterize outcomes in children with LN on dialysis with regard to
  - Hospitalization
  - Mortality
  - Time to transplant

Study Design and Population

- Retrospective analysis of NAPRTCS registry data of patients <21 years of age initiating dialysis 1991-2018

- Inclusion Criteria
  - Exposed group: All patients with LN listed as cause of kidney disease
  - Comparison group: All patients with non-lupus glomerular disease listed as cause of kidney disease
- Exclusion Criteria
  - All patients with “other” or “unknown autoimmune disease” listed as cause of kidney disease

Study Design and Population

Retrospective analysis of NAPRTCS registry data of patients <21 years of age initiating dialysis 1991-2018

- 238 dialysis patients with LN
- 2,006 dialysis patients with non-lupus glomerular disease

Inclusion

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Primary Outcome Measures

- Hospitalization following dialysis initiation
- Patient survival on dialysis
- Time to renal transplantation

Analytic Approach

- Descriptive analyses
  - Chi Square testing used to compare categorical variables
  - Student t or Wilcoxon rank sum tests used to compare continuous variables

Analytic Approach

- Hospitalization: Contingency tables with Chi Square testing to compare risk of hospitalization within 6 and 12 months
- Time to Mortality/Transplant: Kaplan-Meier analysis with log-rank tests
- Risk for Mortality/Transplant: Multivariable Cox regression to compare time to death and transplant adjusting for patient demographic and clinical characteristics

Analytic Approach

- Risk factor analysis
  - Analyses restricted to children with LN
  - Multivariable logistic regression used to evaluate risk factors for hospitalization
  - Multivariable Cox Regression used to evaluate factors associated with receipt of kidney transplant

Demographic Characteristics

	Lupus nephritis n=238	Other glomerular disease n = 2,005	p-value
Age category (%)			
<1 year	1 (0.4%)	27 (1.3%)	
2-5 years	1 (0.4%)	191 (9.5%)	<0.001
6-12 years	45 (18.9%)	616 (30.7%)	
≥13 years	191 (80.3%)	1172 (58.4%)	
Sex (%)			
Male	52 (21.8%)	1047 (52.2%)	<0.001
Female	186 (78.2%)	957 (47.8%)	
Race (%)			
Black	123 (51.7%)	640 (31.9%)	
White	39 (16.4%)	821 (41.0%)	<0.001
Multiple	0 (0%)	1 (0%)	
Unknown	76 (31.9%)	543 (27.1%)	

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Dialysis Characteristics

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Dialysis initiation era (%)			
1991-1995	67 (28.3%)	563 (28.1%)	0.9
1996-2000	71 (30.0%)	590 (29.6%)	
2001-2018	100 (41.8%)	852 (42.2%)	
Dialysis index modality (%)			
Peritoneal dialysis	90 (37.8%)	1151 (57.4%)	<0.001
Hemodialysis	148 (62.2%)	854 (42.5%)	

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Baseline Clinical Characteristics

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Mean hematocrit (SD)	29.7 (6.3)	31.0 (6.3)	0.01
Hypertension (%)	204 (94.9%)	1845 (92.0%)	0.1
Number of medications			
1-3	23 (9.7%)	286 (14.3%)	
4-5	91 (38.2%)	1040 (51.8%)	<0.001
≥6	102 (42.9%)	486 (24.2%)	
Missing	22 (9.2%)	193 (9.6%)	
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Anemia (%)	178 (85.7%)	1685 (84.0%)	0.5
Mean hematocrit (SD)	29.7 (6.3)	31.0 (6.3)	0.01
Hypertension (%)	204 (94.9%)	1845 (92.0%)	0.1
Number of medications			
1-3	23 (9.7%)	286 (14.3%)	
4-5	91 (38.2%)	1040 (51.8%)	<0.001
≥6	102 (42.9%)	486 (24.2%)	
Missing	22 (9.2%)	193 (9.6%)	
Mean height z-score (SD)	-0.9 (1.5)	-0.9 (1.5)	0.9
Mean weight z-score (SD)	-0.5 (1.7)	-0.5 (1.7)	0.7
Mean BMI z-score (SD)	-0.01 (1.4)	0.08 (1.4)	0.4

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Hospitalization

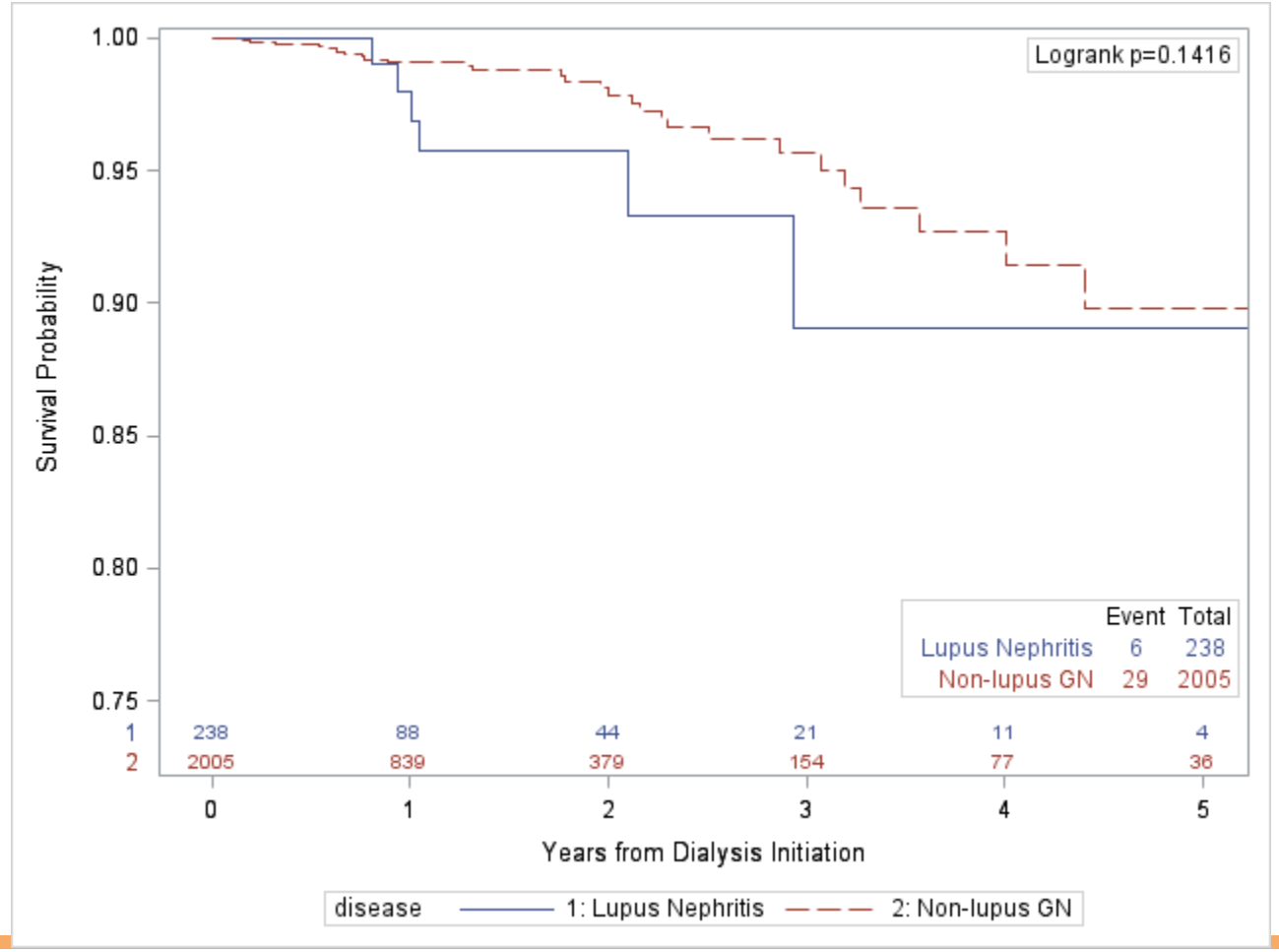
Within 6 months of dialysis initiation

	Hospitalization		
	No	**Yes**	**Total**
Lupus Nephritis	98 50.8%	95 49.2%	193
Non-lupus GN	1,032 63.3%	598 36.7%	1,630
Total	1,130	693	1,823
	Frequency Missing = 421		
	Chi-square p-value: <0.001		

Within 12 months of dialysis initiation

	Hospitalization		
	No	**Yes**	**Total**
Lupus Nephritis	60 36.6%	104 63.4%	193
Non-lupus GN	612 49.6%	621 50.4%	1,233
Total	672	725	1,397
	Frequency Missing = 847		
	Chi-square p-value: <0.001		

Patient Survival



Multivariable Cox Regression

Risk of Death in Patients with Lupus Nephritis			
Model	**Adjusted Hazard Ratio**	**95% Confidence interval**	**P-value**
1	1.49	0.54 - 3.59	0.4
2	1.43	0.51 - 3.46	0.5
3	1.26	0.45 - 3.07	0.6
4	1.22	0.43 - 2.97	0.7

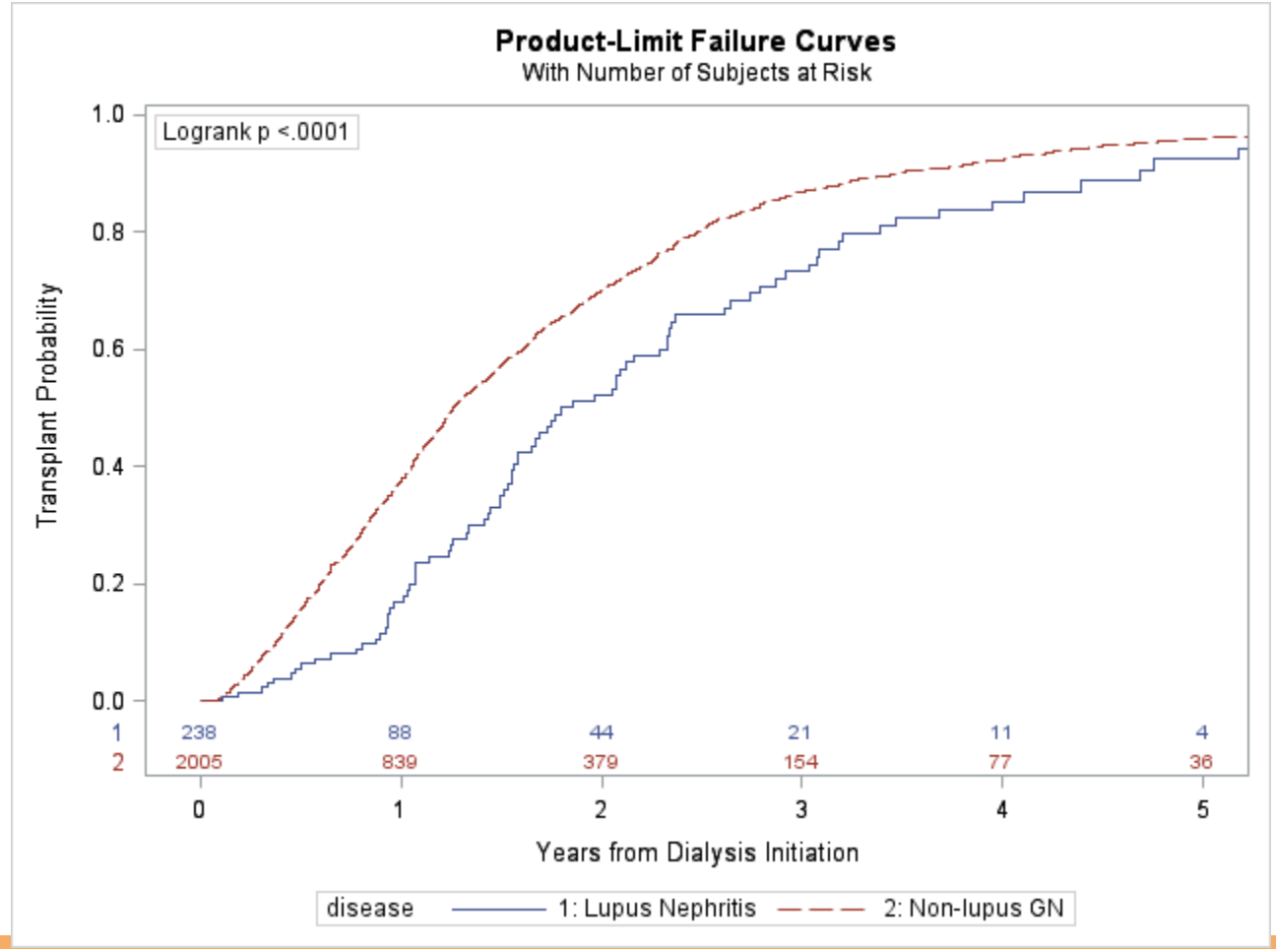
Model 1: age, race, sex

Model 2: age, race, sex, index dialysis modality

Model 3: age, race, sex, index dialysis modality, hypertension, anemia

Model 4: age, race, sex, index dialysis modality, hypertension, anemia, dialysis initiation era

Cumulative Incidence of Kidney Transplantation



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Multivariable Cox Regression

Likelihood of Kidney Transplantation in Patients with Lupus Nephritis			
Model	**Adjusted Hazard Ratio**	**95% Confidence interval**	**P-value**
1	0.70	0.56 - 0.87	0.002
2	0.70	0.56 - 0.87	0.002
3	0.68	0.54 - 0.85	0.001
4	0.68	0.54 - 0.85	0.001

Model 1: age, race, sex

Model 2: age, race, sex, index dialysis modality, age-sex interaction term

Model 3: age, race, sex, index dialysis modality, hypertension, anemia, age-sex interaction term

Model 4: age, race, sex, index dialysis modality, hypertension, anemia, dialysis initiation era, age-sex interaction term

Risk Factor Analysis

- Among children with LN:
  - Anemia was a risk factor for hospitalization following dialysis initiation:
    - aOR = 4.1, 95% CI 1.37-12.52, p=0.01
  - Older age (years) associated with increased likelihood of kidney transplantation:
    - aHR = 1.14, 95% CI 1.04-1.26, p=0.01

Study Strengths

- Large cohort of patients with LN
- Includes patients from multiple centers
- NAPRTCS registry collects granular clinical data

Study Limitations

- Observational study
- Voluntary registry: selection bias
- Missing data
- NAPRTCS registry does not collect data on lupus disease activity

Conclusions

- Compared to patients with non-lupus glomerular disease, those with LN are:
  - More likely to be hospitalized in the year following dialysis initiation
  - Less likely to receive a transplant during follow-up
    - After adjusting for demographic and clinical characteristics and index dialysis modality
- No survival difference following dialysis initiation in patients with LN and those with non-lupus glomerular disease
  - Analysis limited by low number of deaths in study population

Questions?

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