



GLOBAL BURDEN OF AKI

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DISCLOSURES

- Ravindra L Mehta MD
- Speaker
- I had a personal financial relationship with commercial entities during the last two years :
 - Baxter, AM Pharma, CSL- Behring, Astute Medical Inc. Regulus, Akebia, Intercept, Mallinckrodt, Ferring
 - Grants: Relypsa, Fresenius-Kabi; Fresenius, Grifols

Global Burden of AKI

What is known

What we are learning

What we don't know

KDIGO

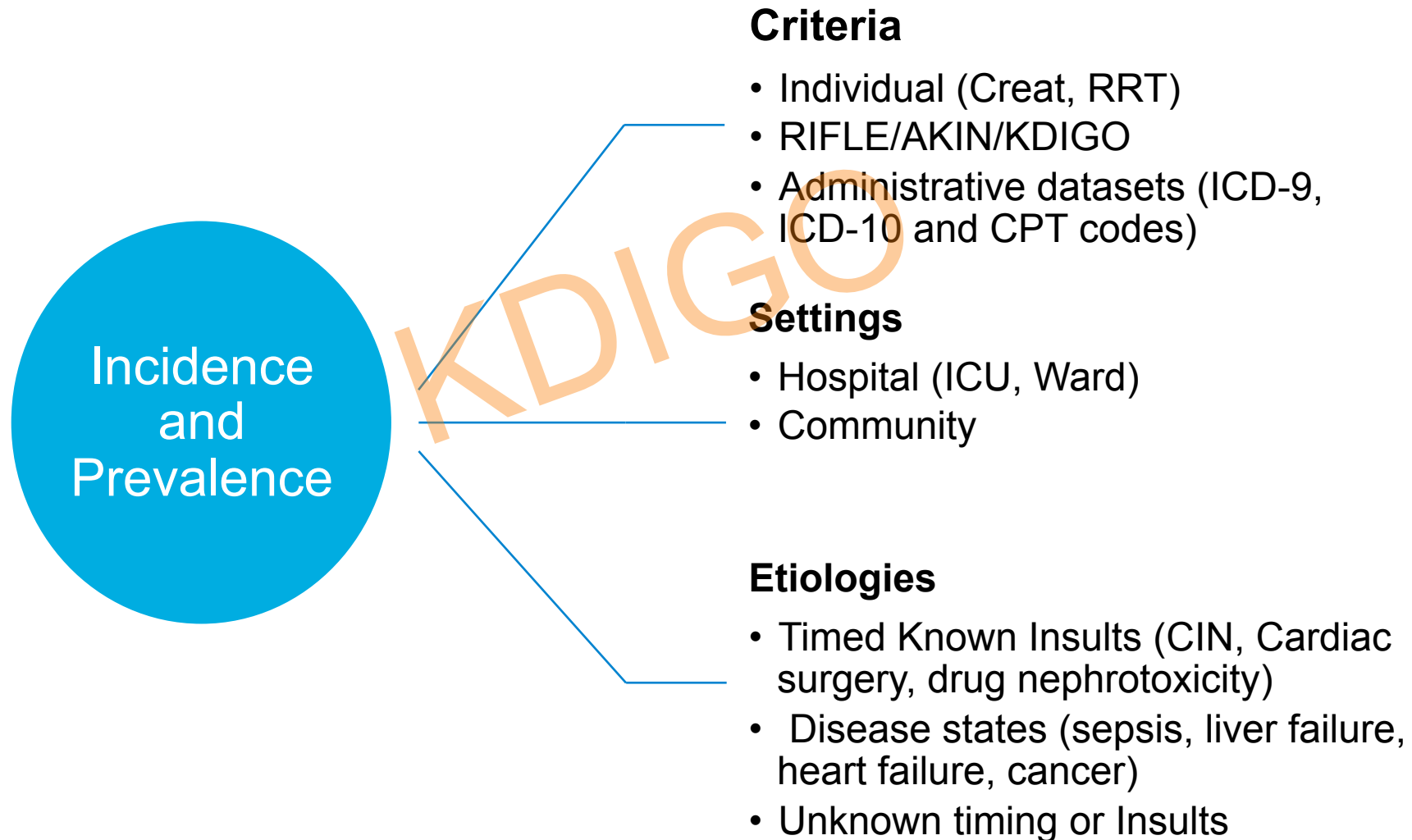
Global Burden of AKI

- *AKI has a global presence*

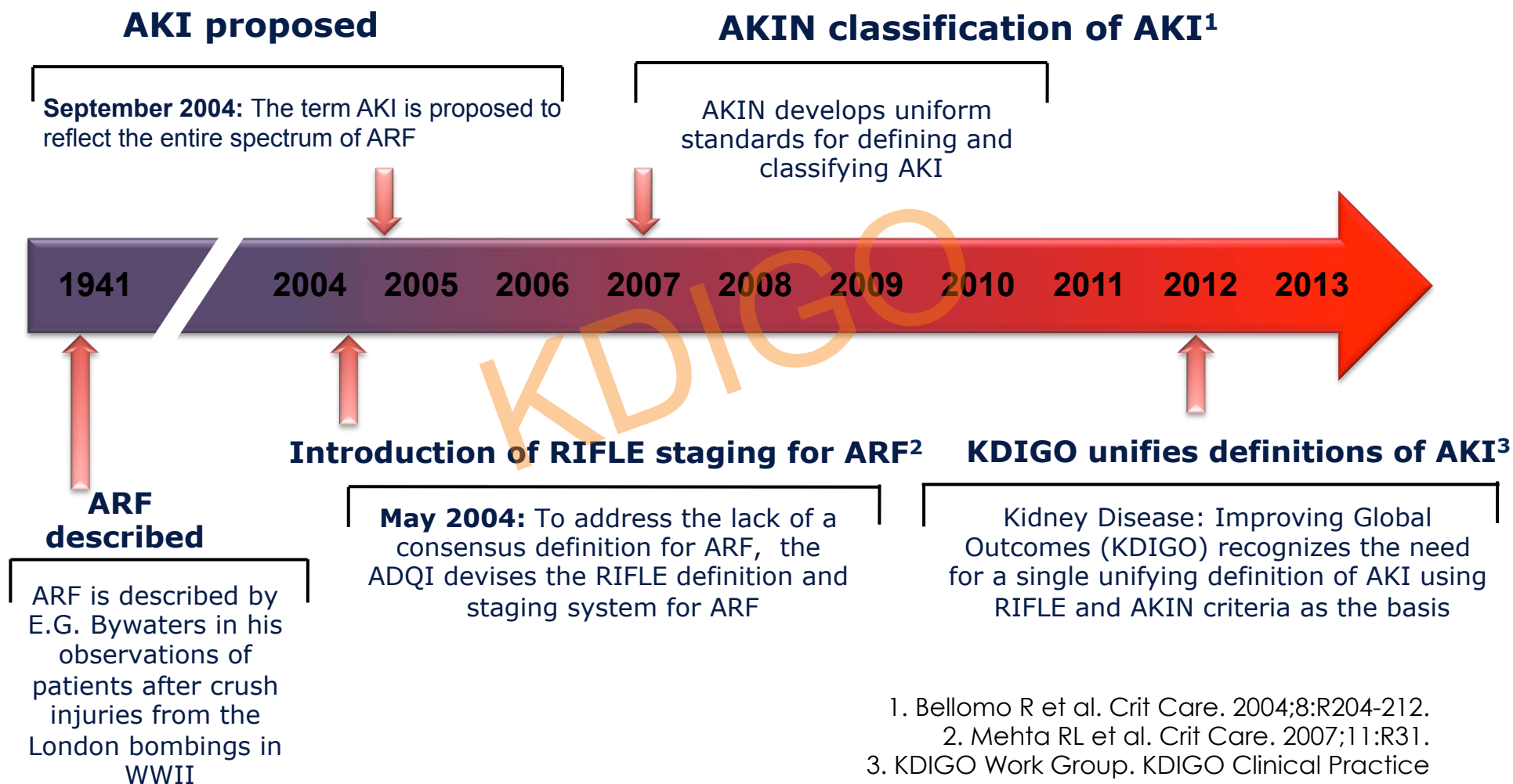


Global Burden of AKI

- *AKI Epidemiology has evolved*

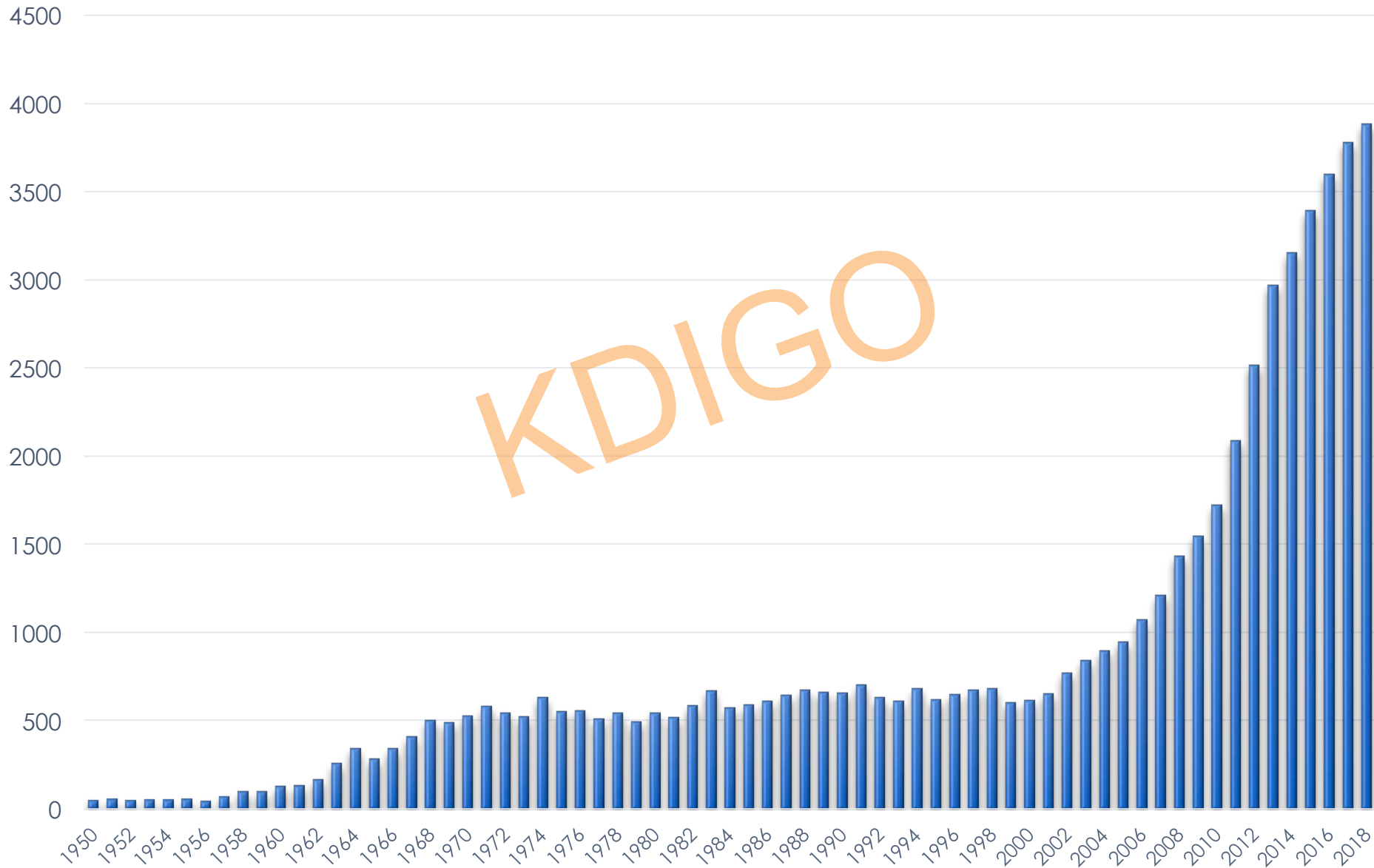


Evolving Definition and Classification of AKI



1. Bellomo R et al. Crit Care. 2004;8:R204-212.
2. Mehta RL et al. Crit Care. 2007;11:R31.
3. KDIGO Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012;2:1-138. www.KDIGO.org.

Number of Papers with ARF/AKI in Pub Med

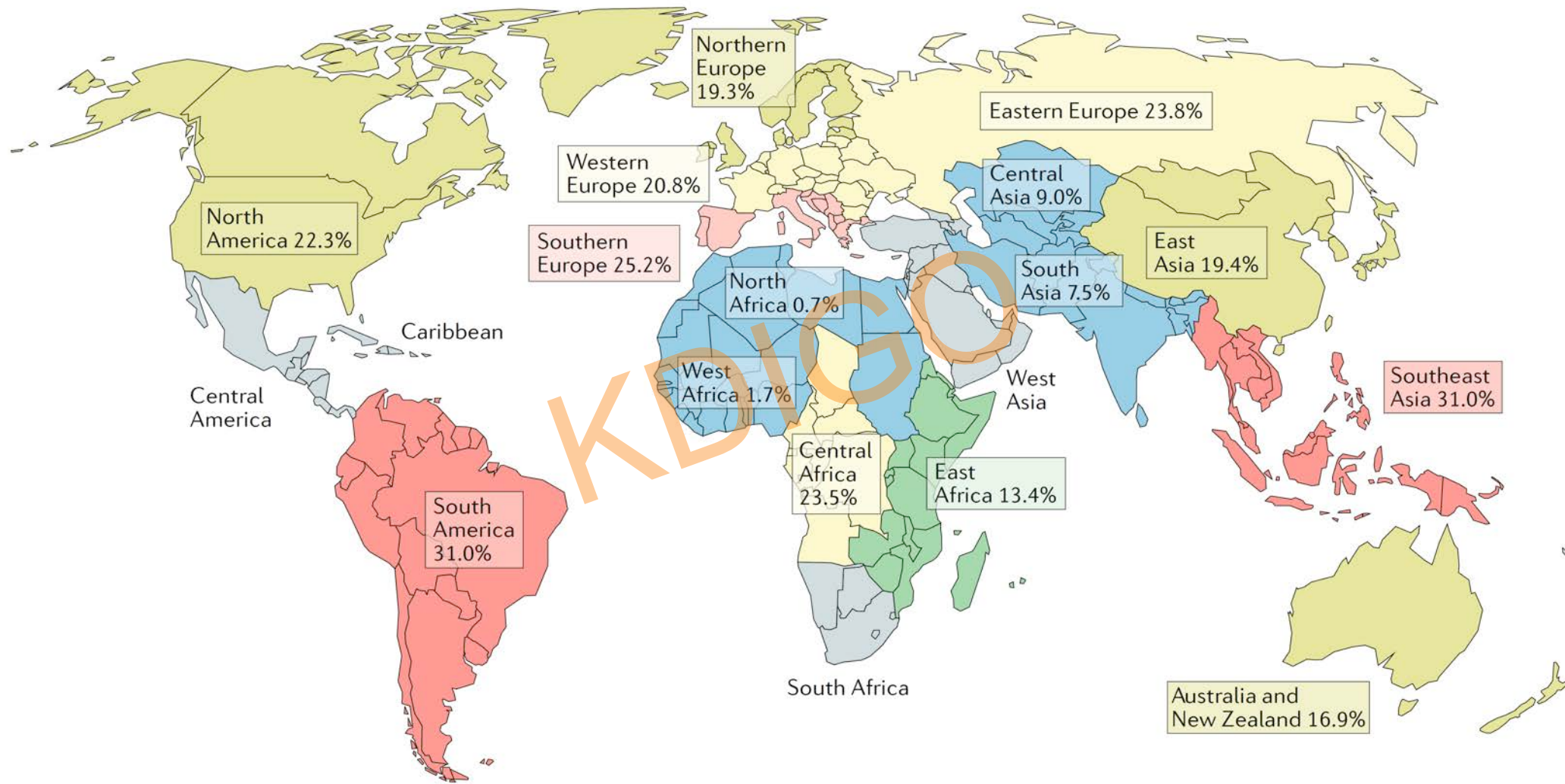


KDIGO Criteria for AKI

Stage ^a	Serum creatinine level	Urine output
Diagnosis	• Increase of ≥ 0.3 mg/dl ($26.5 \mu\text{mol/l}$) within 48 h, or • Increase of ≥ 1.5-fold above baseline, known or assumed to have occurred within 7 days	• < 0.5 ml/kg/h for 6 h
1	• ≥ 1.5–1.9 times baseline, or • > 0.3 mg/dl ($26.5 \mu\text{mol/l}$) increase from baseline	• < 0.5 ml/kg/h for 6–12 h
2	• ≥ 2.0–2.9 times baseline	• < 0.5 ml/kg/h for ≥ 12 h
3	• ≥ 3.0 times baseline, or • Increase of serum creatinine to ≥ 4.0 mg/dl ($353.6 \mu\text{mol/l}$), or • RRT or • In patients aged < 18 years, a decrease in eGFR to < 35 ml/min/1.73 m^2	• < 0.3 ml/kg/h for ≥ 24 h or • Anuria for ≥ 12 h

Population	Age	Incidence (range)	RRT requirement (%)	Mortality (%)
Non-ICU hospitalized patients	Adult	< 1 in 5 patients	< 10	10–20
Critically ill patients	Adult	1 in 3 to 2 in 3 patients	5–11	NR
	Paediatric	1 in 4 patients (10–82%)	1–2	11
Patients undergoing cardiac surgery	Adult	1 in 5 patients (2–50%)	< 5	10
	Paediatric	1 in 3 to 1 in 2 patients	NR	6
Patients with sepsis	Adult	1 in 20 to 1 in 2 patients	15	30–60

Global variation in incidence of AKI

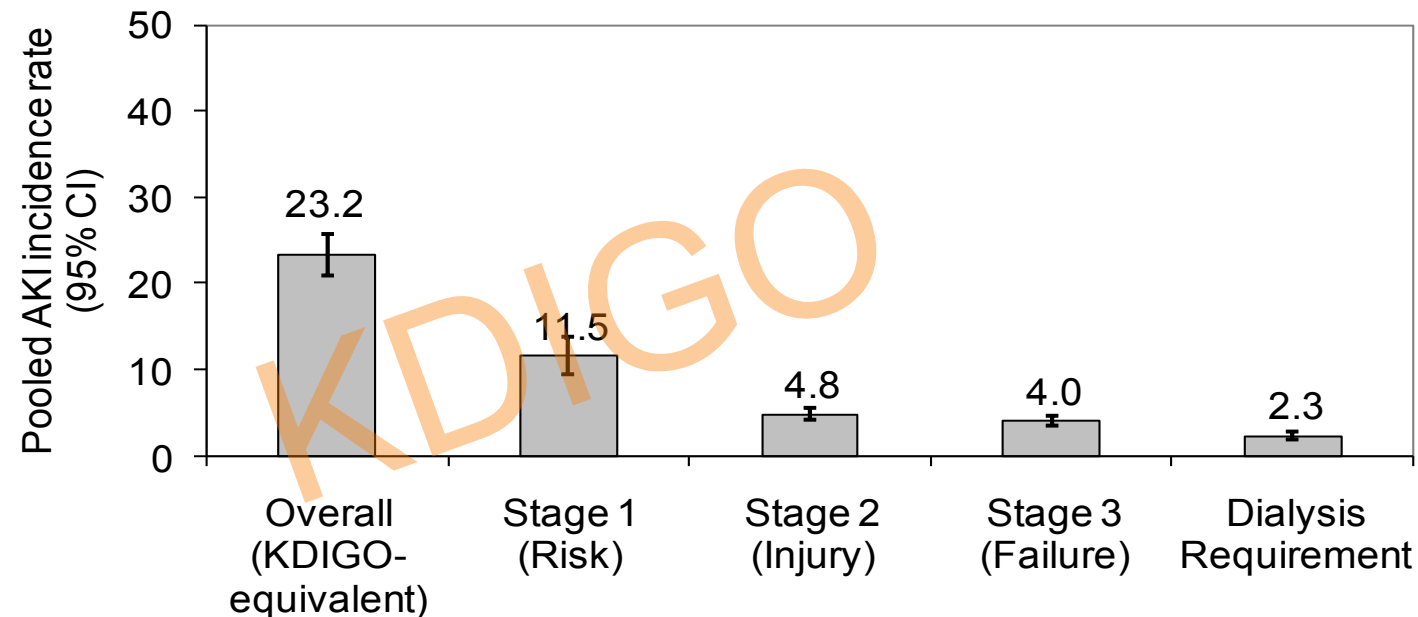


www.thelancet.com Published online March 13, 2015 [http://dx.doi.org/10.1016/S0140-6736\(15\)60126-X](http://dx.doi.org/10.1016/S0140-6736(15)60126-X)

Hoste et al: Nature Reviews in Nephrology 2018 <https://doi.org/10.1038/s41581-018-0052-0>

World Incidence of AKI: A Meta-Analysis

Among the 154 studies (n=3,585,911) that adopted a KDIGO-equivalent AKI definition, the pooled incidence rates of AKI were 21.6% in adults (95% confidence interval [95% CI], 19.3 to 24.1) and 33.7% in children (95% CI, 26.9 to 41.3).



No. studies	154	112	108	108	189
No. patients	3,585,911	3,303,992	3,281,715	3,281,715	29,400,495

Using the KDIGO definition, 1 in 5 adults and 1 in 3 children worldwide experience AKI during a hospital episode of care.

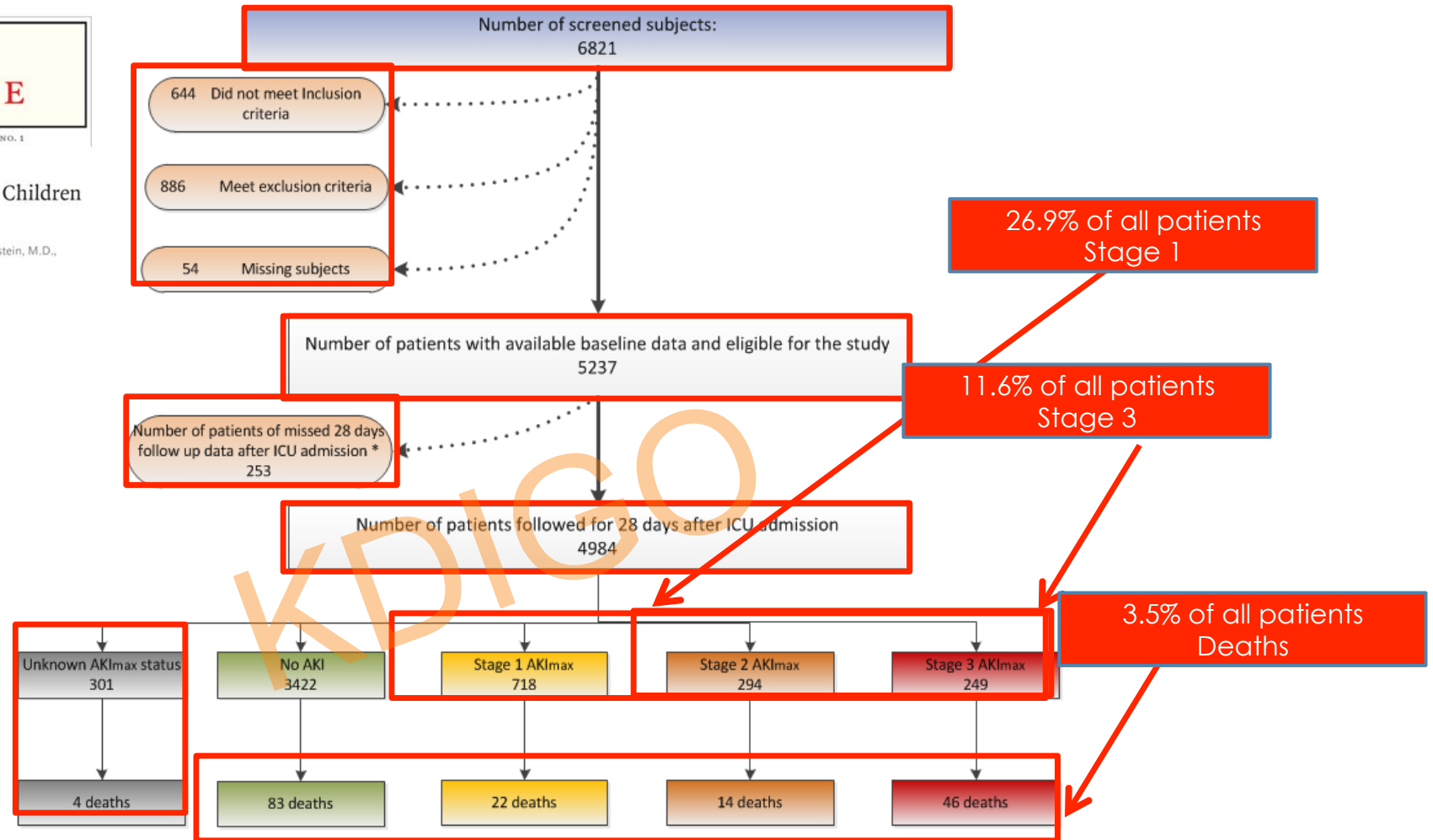
AKI Global Snapshot

Epidemiology and Outcomes by Region

	Number of centres	Number of patients (N=4018)	Median age (years)	ICU patients	Hospital-acquired acute kidney injury
Paediatric	89	354 (9%)	2 (0.2-11)	136 (38%)	187 (53%)
Adult	262	3661 (91%)	62 (48-75)	1102 (30%)	1429 (39%)
Region					
Africa	44	539 (13%)	53 (34.0-65.0)	103 (19%)	82 (15%)
Eastern and central Europe	11	88 (2%)	68 (56.0-78.0)	10 (11%)	17 (19%)
Latin America and the Caribbean	45	556 (14%)	60 (44.0-75.0)	178 (32%)	250 (45%)
Middle East	14	135 (3%)	60 (34.0-72.0)	31 (23%)	45 (33%)
North and east Asia	32	1105 (28%)	68 (57.0-79.0)	365 (33%)	694 (63%)
North America	31	280 (7%)	22.5 (0.3-63.0)	115 (41%)	180 (64%)
Oceania and south-east Asia	16	169 (4%)	65 (52.0-77.0)	40 (24%)	54 (32%)
Russia and CIS	17	154 (4%)	53 (34.0-66.0)	79 (51%)	65 (42%)
South Asia	45	748 (19%)	50 (34.0-63.0)	261 (35%)	134 (18%)
Western Europe	34	244 (6%)	74 (61.0-81.5)	56 (23%)	95 (39%)

Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults

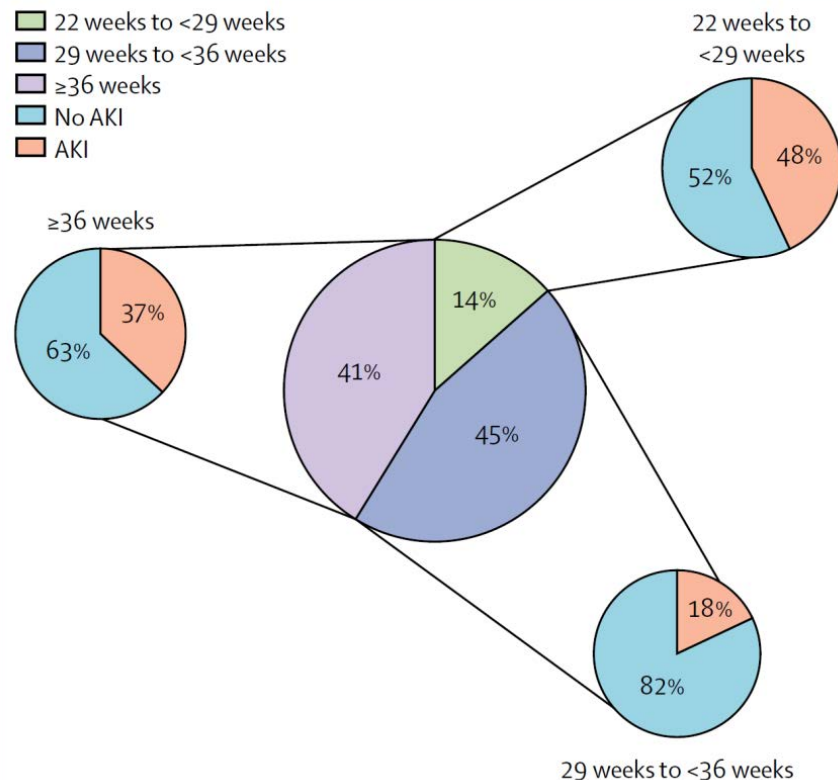
Ahmad Kaddourah, M.D., Rajit K. Basu, M.D., Sean M. Bagshaw, M.D., and Stuart L. Goldstein, M.D.,
for the AWARE Investigators*



* 28-day outcome data are missed by participating centers, outcome-associated analysis excluded these patients.

32 Centers
4 Continents
Jan-December 2014
NCT01987921

■ 22 weeks to <29 weeks
 ■ 29 weeks to <36 weeks
 ■ ≥36 weeks
 ■ No AKI
 ■ AKI



Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study

Jennifer G Jetton, Louis J Boohaker, Sidharth K Sethi, Sanjay Wazir, Smriti Rohatgi, Danielle E Soranno, Aftab S Chisht, Robert Woroniecki, Cherru Mammen, Jonathan R Swanson, Shanthi Sridhar, Craig S Wong, Juan C Kupferman, Russell L Griffin, David J Askenazi, on behalf of the AWAKEN Study Group*

Enrolled 2162 infants, of whom 2022 (94%) had data to ascertain AKI status. 605 (30%) infants had AKI.

Infants with AKI had higher mortality than those without AKI (59 [10%] of 605 vs 20 [1%] of 1417 infants; $p < 0.0001$), and longer length of hospital stay (median 23 days [IQR 10–61] vs 19 days [9–36]; $p < 0.0001$).

24 participating neonatal intensive care units (NICUs) in four countries (Australia, Canada, India, USA) between Jan 1 and March 31, 2014.

	Any AKI			Maximum AKI stage				p value
	No (n=1417)	Yes (n=605)	p value	0 (n=1417)	1 (n=281)	2 (n=143)	3 (n=181)	
Survived	..	..	<0.0001	..	..	..	..	<0.0001
Yes	1397 (99%)	546 (90%)	..	1397 (99%)	255 (91%)	133 (93%)	158 (87%)	
No	20 (1%)	59 (10%)	..	20 (1%)	26 (9%)	10 (7%)	23 (13%)	
Length of stay (days)	19 (9–36)	23 (10–61)	<0.0001	19 (9–36)	18 (9–55)	30 (11–79)	27 (13–59)	<0.0001

Data are n (%) or median (IQR). 140 enrolled patients had less than two serum creatinine measurements and no urinary output data. Among patients who did not die, 306 were transferred for convalescence or escalation of care. AKI=acute kidney injury.

Table 2: Clinical outcomes by AKI status

Global Burden of AKI

- *AKI has a Global presence*
- **AKI is heterogeneous**



Inherent and Aetiological Risk Factors for AKI by GNI per person

	N	Total (n=4015)	HICs (n=1260)	UMICs (n=1605)	LLMICs (n=1153)
Aetiological risk factors					
Dehydration	1536	38.2	492 (39%)*	518 (32%)‡	526 (46%)†
Hypotension or shock	1615	40.2	564 (45%)*	611 (38%)	440 (38%)†
Cardiac	905	22.5	306 (24%)*	448 (28%)‡	151 (13%)†
Liver	331	8.2	97 (8%)	148 (9%)	86 (7%)
Acute kidney disease	488	12.2	140 (11%)*	150 (9%)‡	198 (17%)†
Urinary obstruction	320	8.0	99 (8%)	11 (1%)‡	110 (10%)
Infection					
Preeclampsia					
Systemic					
Nephrotoxic agents	980	24.4	365 (29%)*	349 (22%)	266 (23%)†
Poisoning	73	1.8	27 (2%)	23 (1%)	23 (2%)
Envenomation	35	0.9	4 (<1%)	11 (1%)‡	20 (2%)†
Post-surgery	269	6.7	116 (9%)*	109 (7%)‡	44 (4%)†
Sepsis	1123	28.47	341 (27%)*	331 (21%)‡	451 (39%)†

Most common causes of AKI across the different settings were hypotension and shock, dehydration and infections

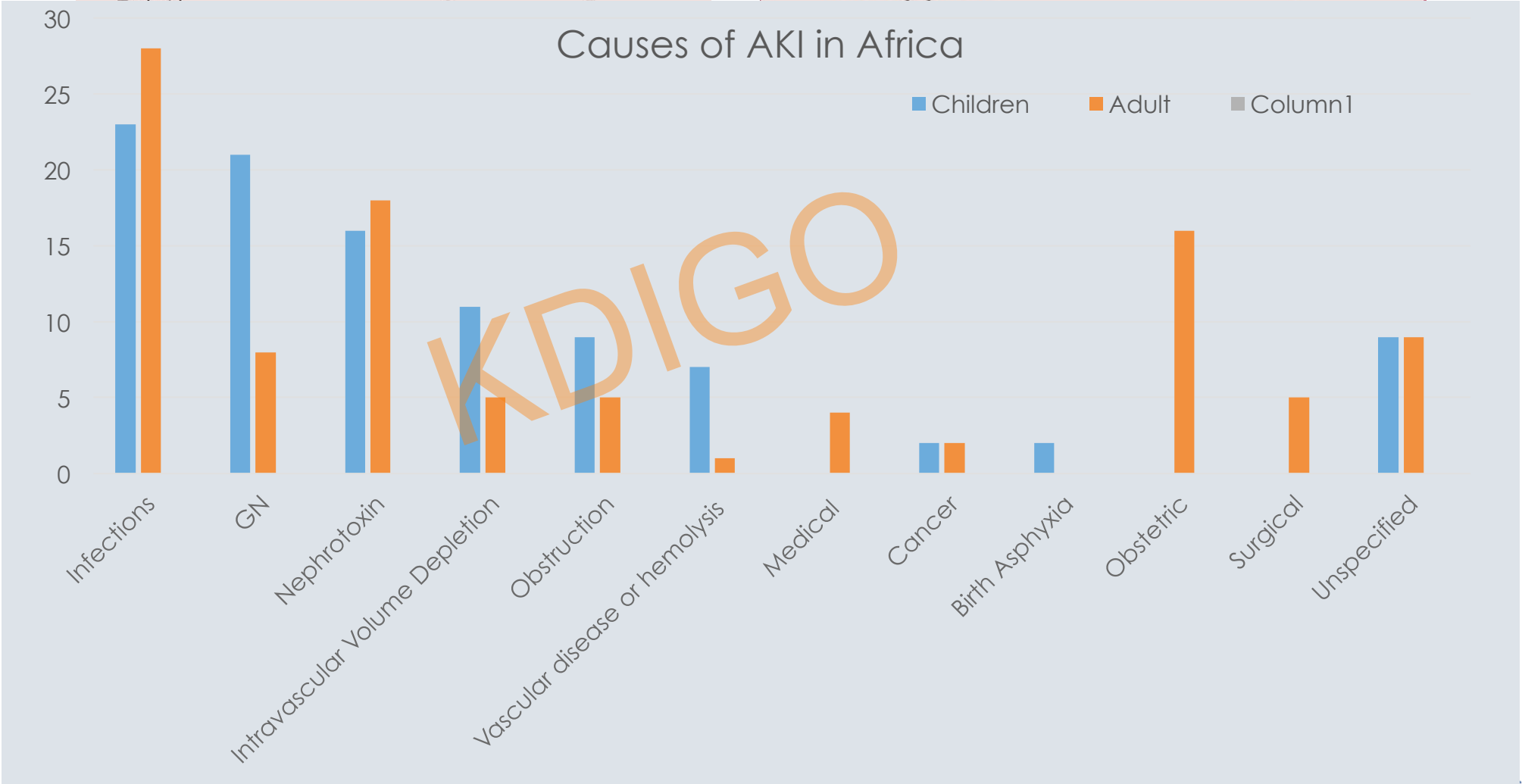
Yang L, Xing G, Wang L, Wu Y, Li S, Xu G, et al. Acute kidney injury in China: a cross-sectional survey.

	Total (N=7604)	Academic hospitals (N=5662)	Local hospitals (N=1942)	p value
AKI classification				
Pre-renal	3936 (51.8%)	2866 (50.6%)	1070 (55.1%)	0.0007
Intrinsic-renal	2100 (27.6%)	1632 (28.8%)	468 (24.1%)	<0.0001
Post-renal	670 (8.8%)	472 (8.3%)	198 (10.2%)	0.0126
Unclassified	898 (11.8%)	692 (12.2%)	206 (10.6%)	0.06
Injury factors				
Renal hypoperfusion	5914 (77.8%)	4400 (77.7%)	1514 (78.0%)	0.82
Nephrotoxic drugs	5444 (71.6%)	4087 (72.2%)	1357 (69.9%)	0.05
Environmental toxins	191 (2.5%)	129 (2.3%)	62 (3.2%)	0.0263
Sepsis	483 (6.4%)	328 (5.8%)	155 (8.0%)	0.0006
Other critical illness	3224 (42.4%)	2484 (43.9%)	740 (38.1%)	<0.0001
Surgery	1629 (21.4%)	1406 (24.8%)	223 (11.5%)	<0.0001

AKI Study in Africa

	Children (n=1643)*	Adults (n=993)†
Infection	380 (23%)	274 (28%)
Septicaemia	370	232
HIV	6	0
Tetanus	4	1
Pyelonephritis	0	12

	Children (n=1643)*	Adults (n=993)†
(Continued from previous column)		
Congenital anomaly of the kidney and the urinary tract		
Posterior urethral valves	32	0
Renal agenesis	4	0
Prune belly syndrome	1	0



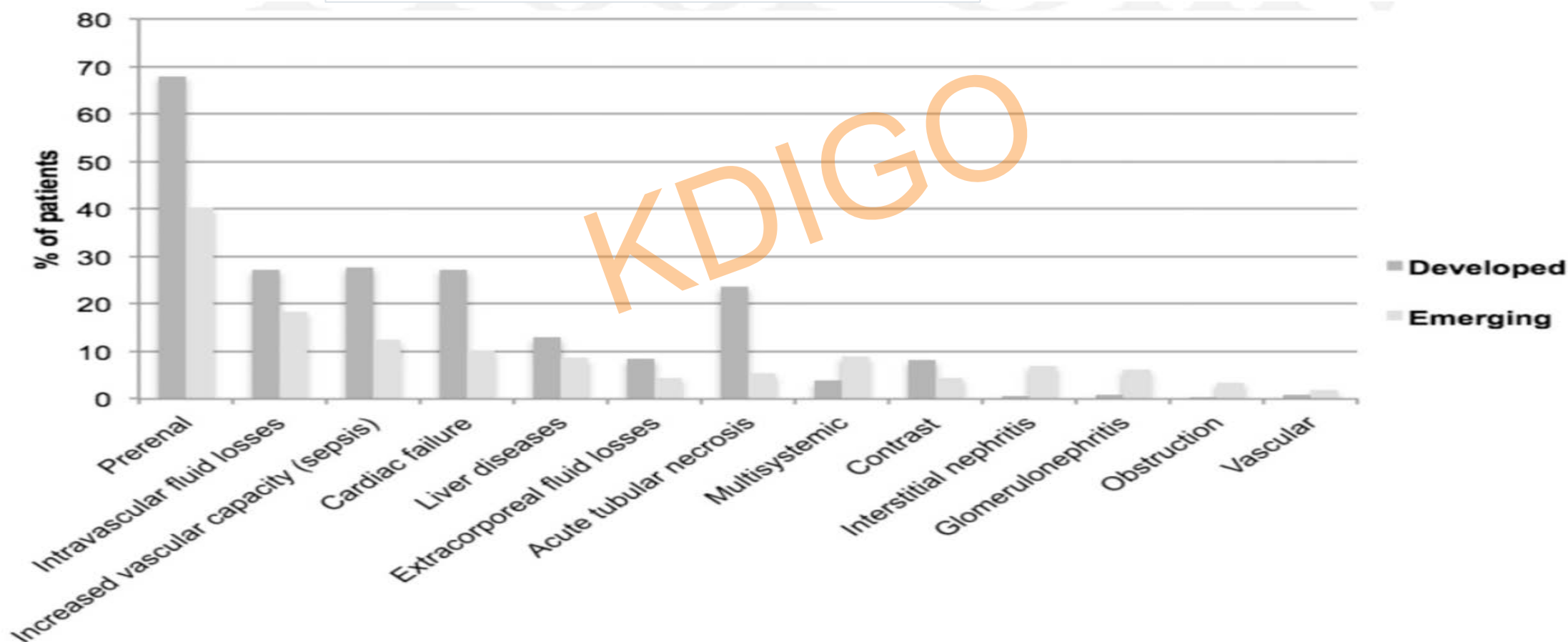
Renal stone	60	16
(Table 2 continues in next column)		

*17 paediatric studies. †14 adult studies.		
Table 2: Causes of acute kidney injury in children and adults		

A Prospective International Multicenter Study of AKI in the Intensive Care Unit

Josée Bouchard,^{*} Anjali Acharya,[†] Jorge Cerda,[‡] Elizabeth R. Maccariello,[§] Rajasekara Chakravarthi Madarasu,^{||} Ashita J. Tolwani,[¶] Xinling Liang,^{**} Ping Fu,^{††} Zhi-Hong Liu,^{‡‡} and Ravindra L. Mehta^{§§}

Causes of AKI



Recognition and management of acute kidney injury in children: The ISN 0by25 Global Snapshot study

Variables	N	All	HIC	UMIC	LLMIC	P
			(n = 174)	(n = 72)	(n = 108)	
Age, years	354	2.0 (0.17, 11.0)	0.4 (0.03, 6.0)	8.0 (2, 16.5)	4.0 (0.3, 13.5)	<0.001
Boys	353	193 (54)	80 (46)	41 (57)	72 (67)	0.005
Community AKI	350	163 (46.0)	33 (19.0)	44 (61.1)	86 (79.6)	<0.001
Location at diagnosis						<0.001
Emergency		61(17.4)	10(5.8)	27(37.5)	24(22.6)	
Intensive care unit		136(38.9)	75(43.6)	25(34.7)	36(34.0)	
Outpatient		11(3.1)	2(1.2)	4(5.6)	5(4.7)	
Inpatient wards		142(40.6)	85(49.4)	16(22.2)	41(38.7)	
BMI, kg/m ²	188	17.0 (14.3, 21.3)	17.8 (15.3, 21.3)	18.1 (15.8, 22.2)	15.0 (12.5, 18.3)	0.001
Chronic kidney impairment	354	26 (7.3)	11 (6.3)	6 (8.3)	9 (8.3)	0.77
Known baseline sCr		215	141 (80)	34 (47)	40 (37)	<0.001
Baseline sCr (micromol/l)		35.4(17.7, 69)	26.5(17.7, 44.2)	70.7(53.0, 94.0)	67.8(38.2, 114.9)	<0.001
eGFR ml/min/1.73 m ² (Schwartz equation)						
Adolescent (13–18 yr)	87	88.6 (68.4, 111.8)	112 (88.3, 125.1)	79.6 (68.1, 91.5)	84.2 (54.3, 87.5)	0.013

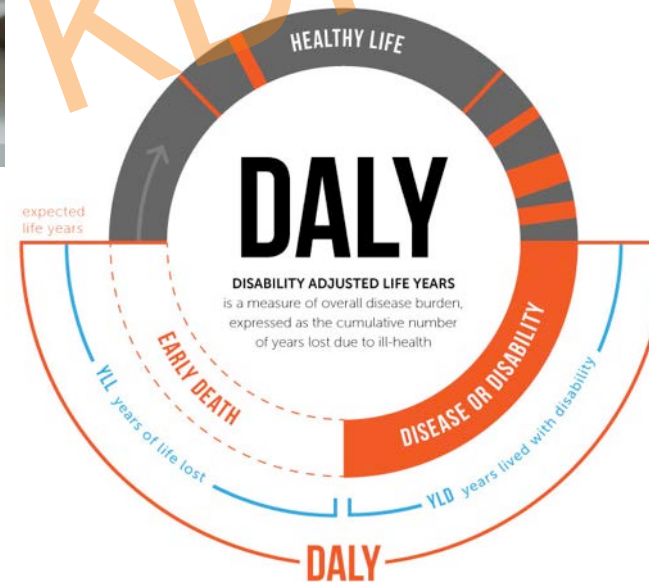
Chief factors associated with AKI in HIC were hypotension (30%), post-surgical complications (27%) and dehydration (26%). In contrast, dehydration was the most common etiologic factor in LLMIC (43.5%) and UMIC (30.6%). Infection, nephrotoxic medications and primary kidney diseases were more common AKI etiologies in LLMIC than in UMIC or HIC countries.

Infection	104	29.38	33 (18.97)	23 (31.94)	48 (44.44)	<0.001
Nephrotoxic agents	71	20.06	23 (14)	14 (19)	33 (30)	0.3642
Primary kidney diseases	62	17.51	14 (8.05)	19 (26.39)	29 (26.85)	<0.001
Post-surgical	56	15.82	47 (27.01)	3 (4.17)	6 (5.56)	0.0218
Systemic diseases	48	13.56	23 (13.22)	16 (22.22)	9 (8.33)	<0.001
Cardiac diseases	41	11.58	34(19.54)	2(2.78)	5(4.63)	0.1334
Urinary obstruction	16	4.52	3(1.72)	4(5.56)	9(8.33)	0.0281

P value refers to difference among country categories (HIC, UMIC and LLMIC); HIC: high income country; UMIC: upper middle income country; LLMIC: low and lower middle income country. Values represent median (interquartile range) or number (proportion).

Global Burden of AKI

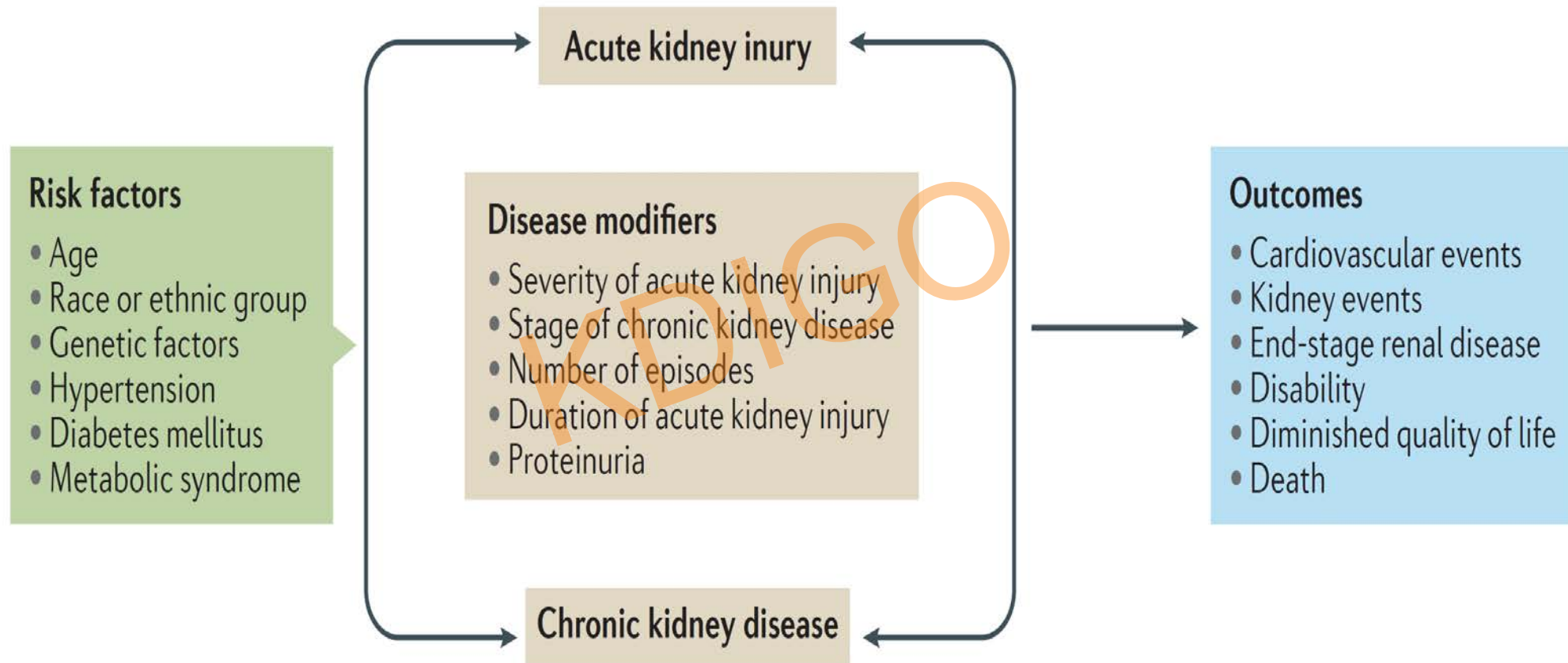
- *AKI has a global presence*
- *Aki is heterogeneous*
- **AKI has a high disease burden**



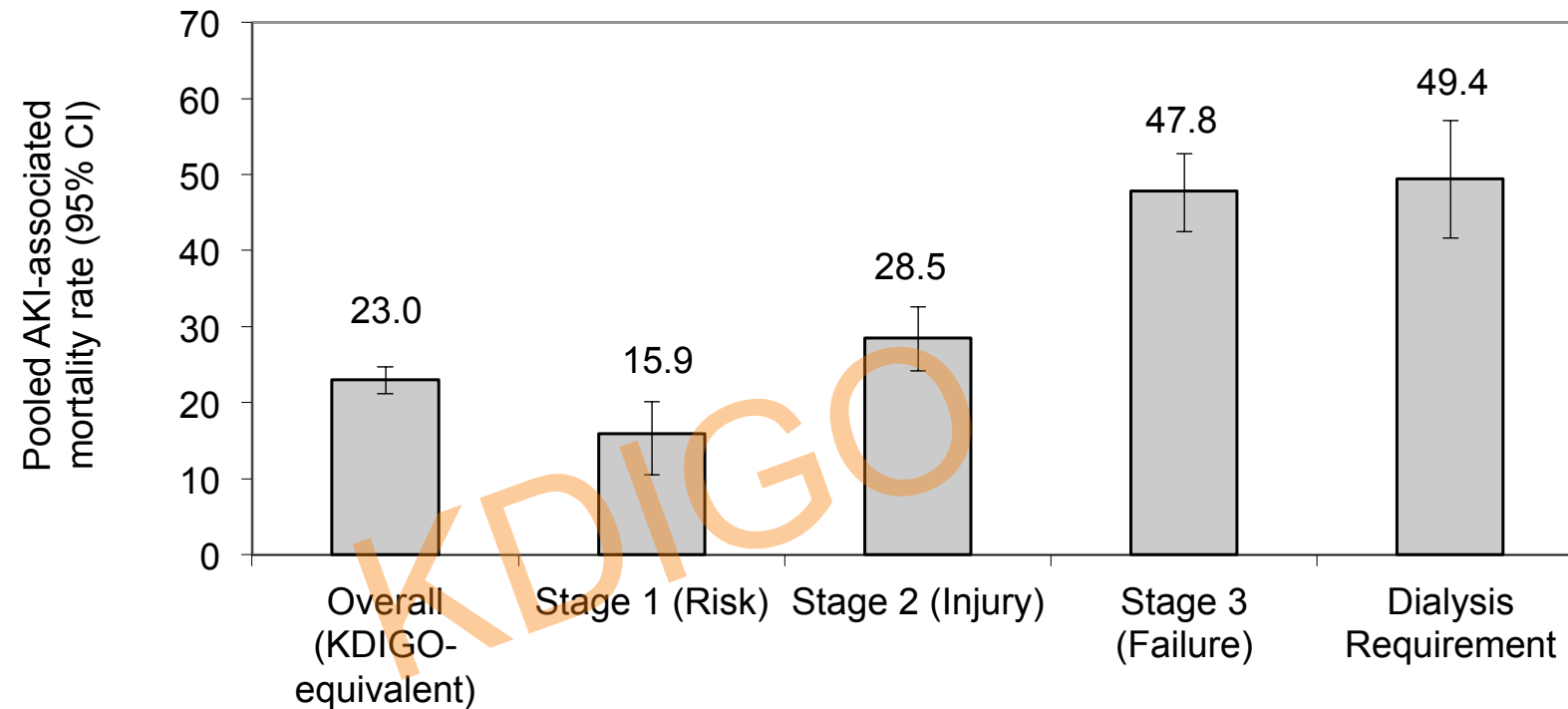
Outcomes of Patients with UO vs sCr Criteria

Characteristic	No AKI (n=8179)	Maximum AKI Severity			P Value ^c
		UO (n=14,177)	SC (n=4694)	Both (n=4995)	
Duration of stage 3 AKI (d), mean (SD)	N/A	1.3 (0.6)	3.5 (4)	5.6 (6.9)	<0.001
RRT during hospital stay	4 (0)	304 (2.1)	232 (4.9)	1251 (25)	<0.001
Length of stay (d), median (Q1, Q3) ^a					
ICU	3 (2–4)	5 (3–9)	4 (2–6)	7 (4–15)	<0.001
Hospital	7 (5–11)	13 (8–22)	14 (8–24)	22 (12–38)	<0.001
Mortality					
Hospital	350 (4.3)	1761 (12.4)	788 (16.8)	1597 (32)	<0.001
30 days ^b	425 (5.2)	1822 (12.9)	808 (17.2)	1375 (27.5)	<0.001
90 days ^b	596 (7.3)	2710 (19.1)	1074 (22.9)	1890 (37.8)	<0.001
1 year ^b	1064 (13)	3966 (28)	1498 (31.9)	2395 (47.9)	<0.001

AKI Outcomes



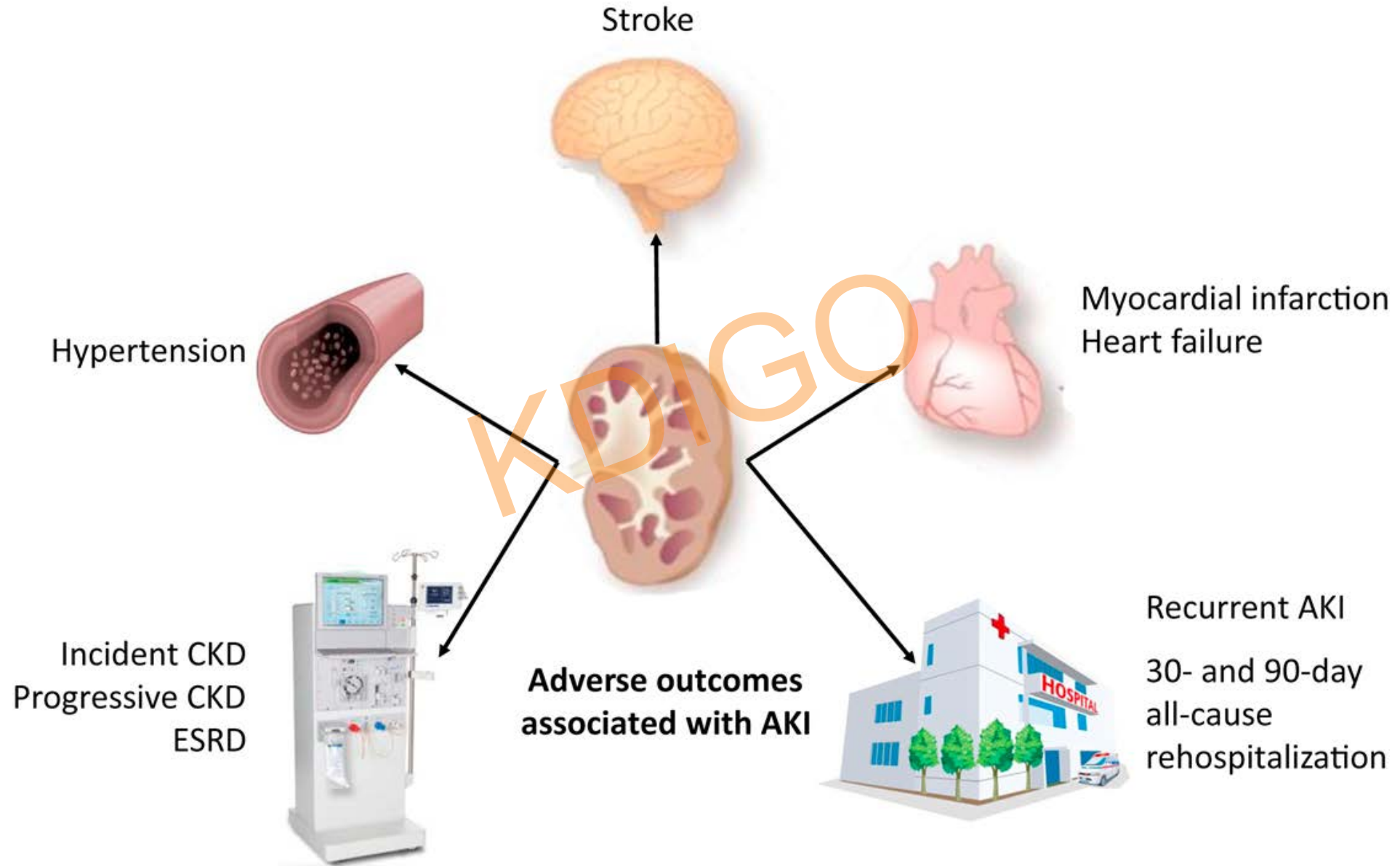
World Incidence of AKI: A Meta-Analysis



No. studies	110	26	25	25	31
No. patients with AKI	429,535	8,226	42,354	42,354	6,534

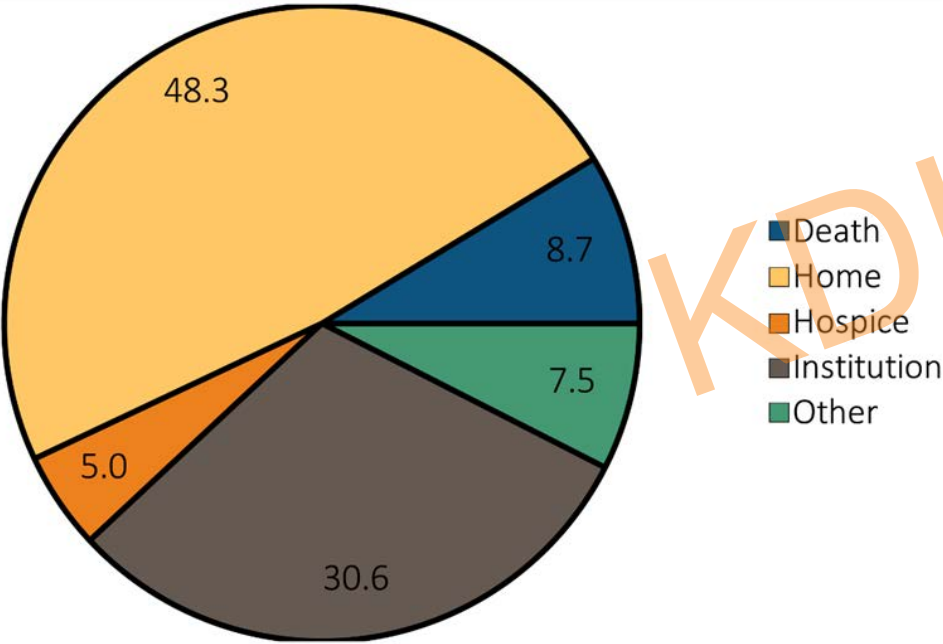
The pooled AKI-associated mortality rates were **23.9% in adults** (95% CI, 22.1 to 25.7) and **13.8% in children** (95% CI, 8.8 to 21.0). The AKI associated mortality rate declined over time, and was inversely related to income of countries and percentage of gross domestic product spent on total health expenditure.

Long Term Consequences

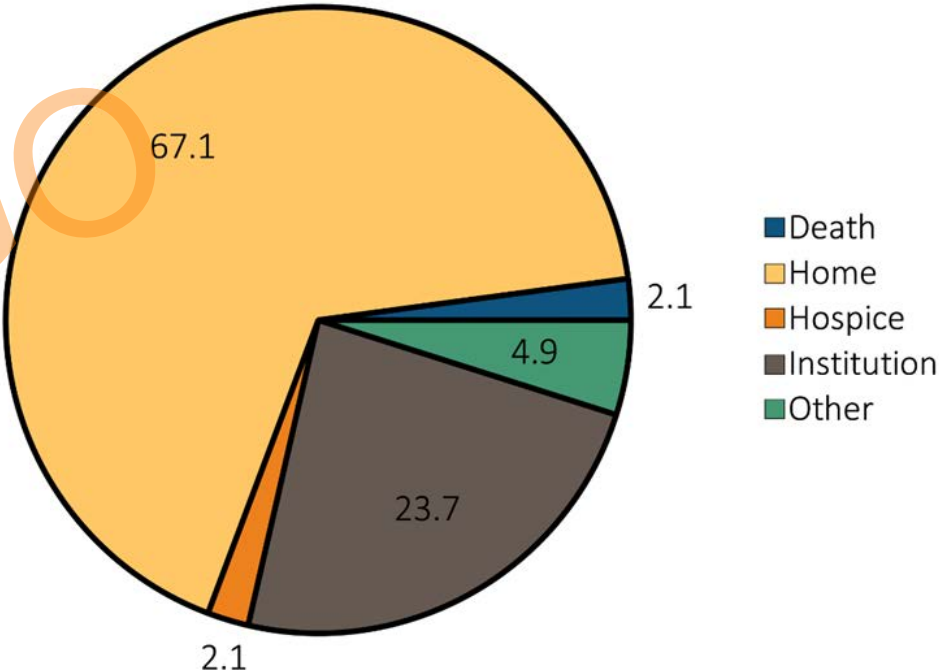


Hospital discharge status of first hospitalization for Medicare patients aged 66+ with and without AKI diagnosis in 2015

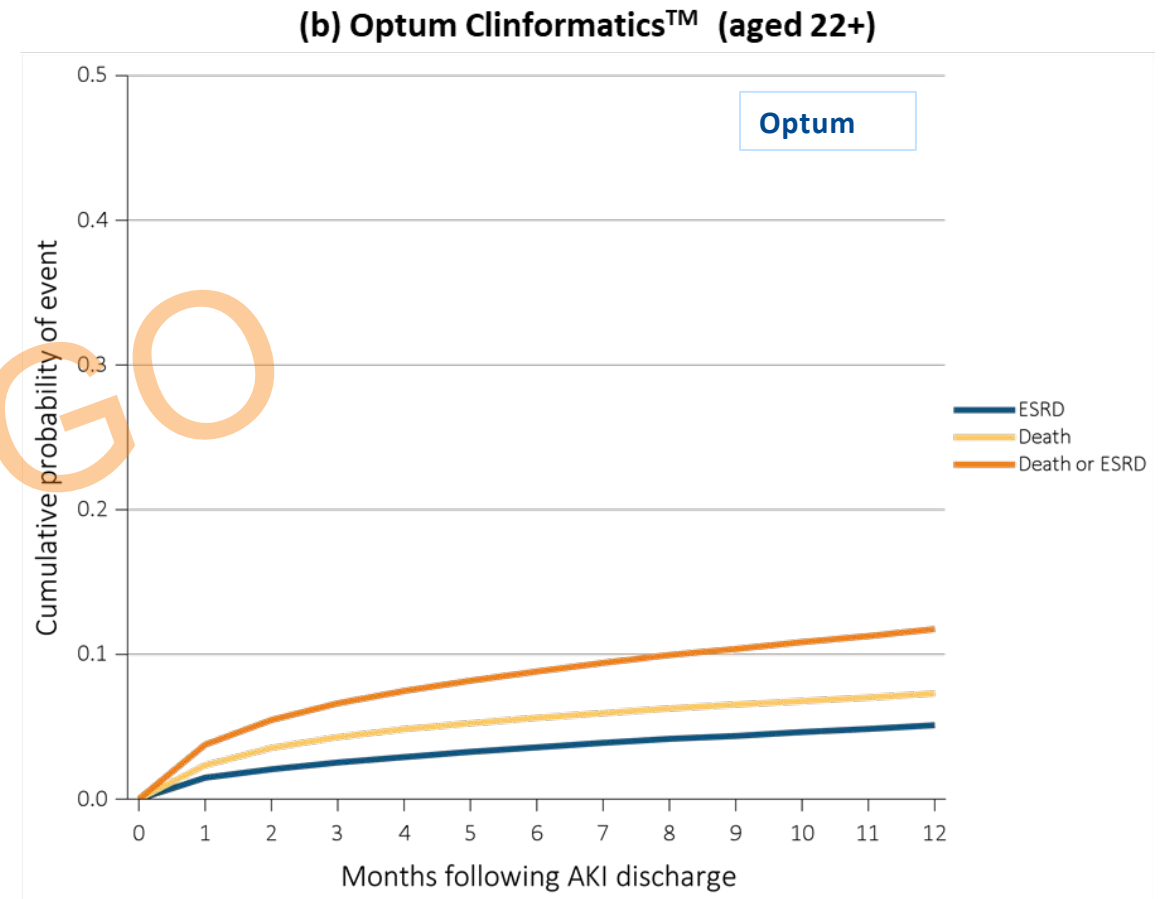
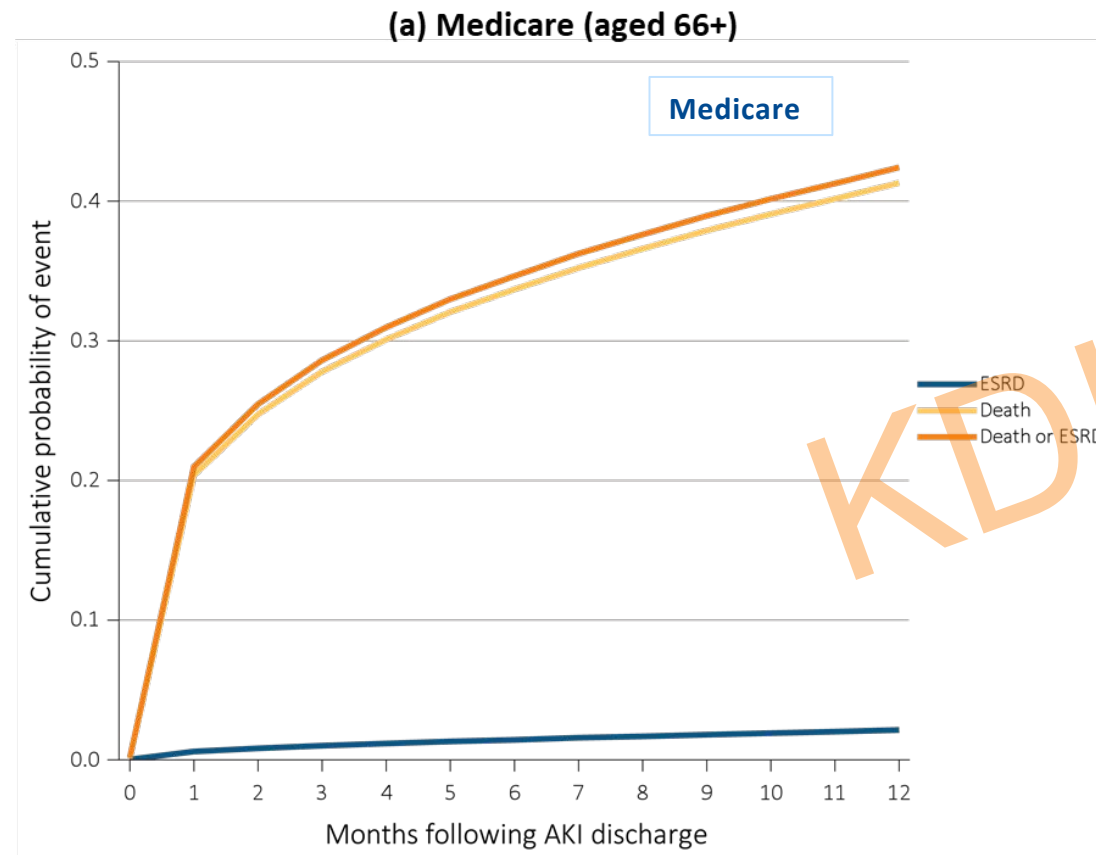
(a) With diagnosis of AKI during stay



(b) Without diagnosis of AKI during stay

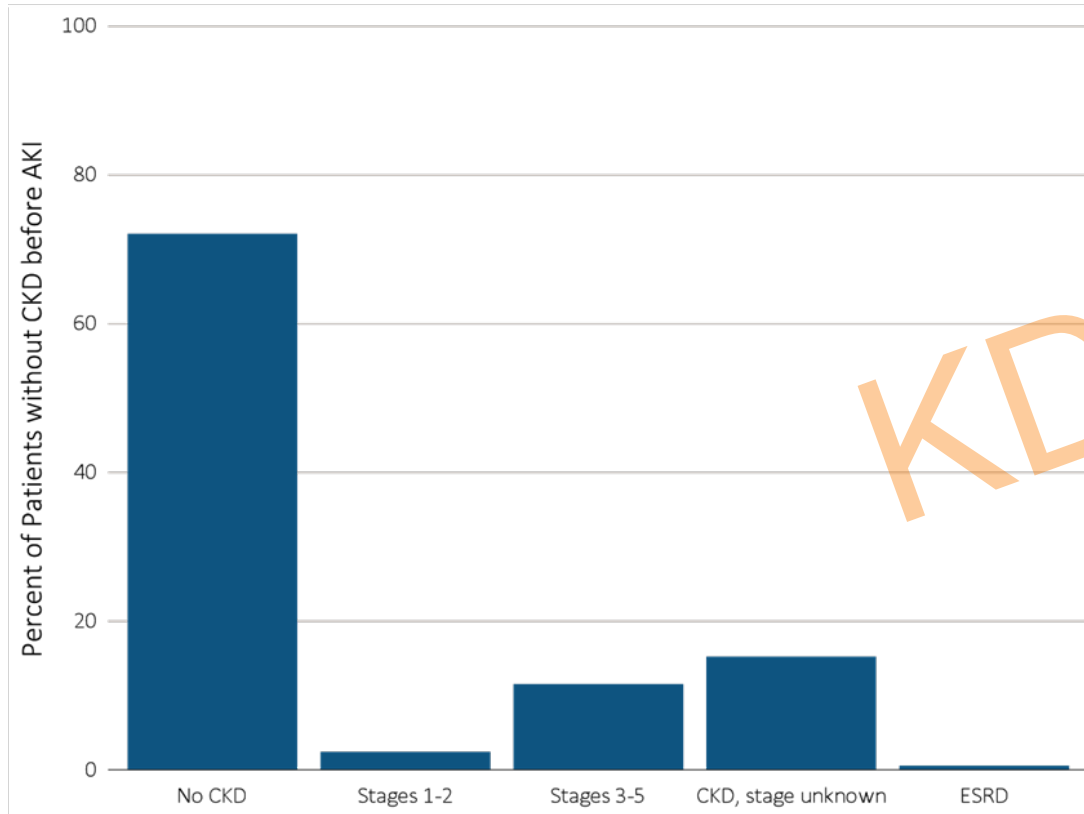


Cumulative probability of death-censored ESRD, death, and the composite of death or ESRD within one year of live discharge from first AKI hospitalization occurring in 2013-2014

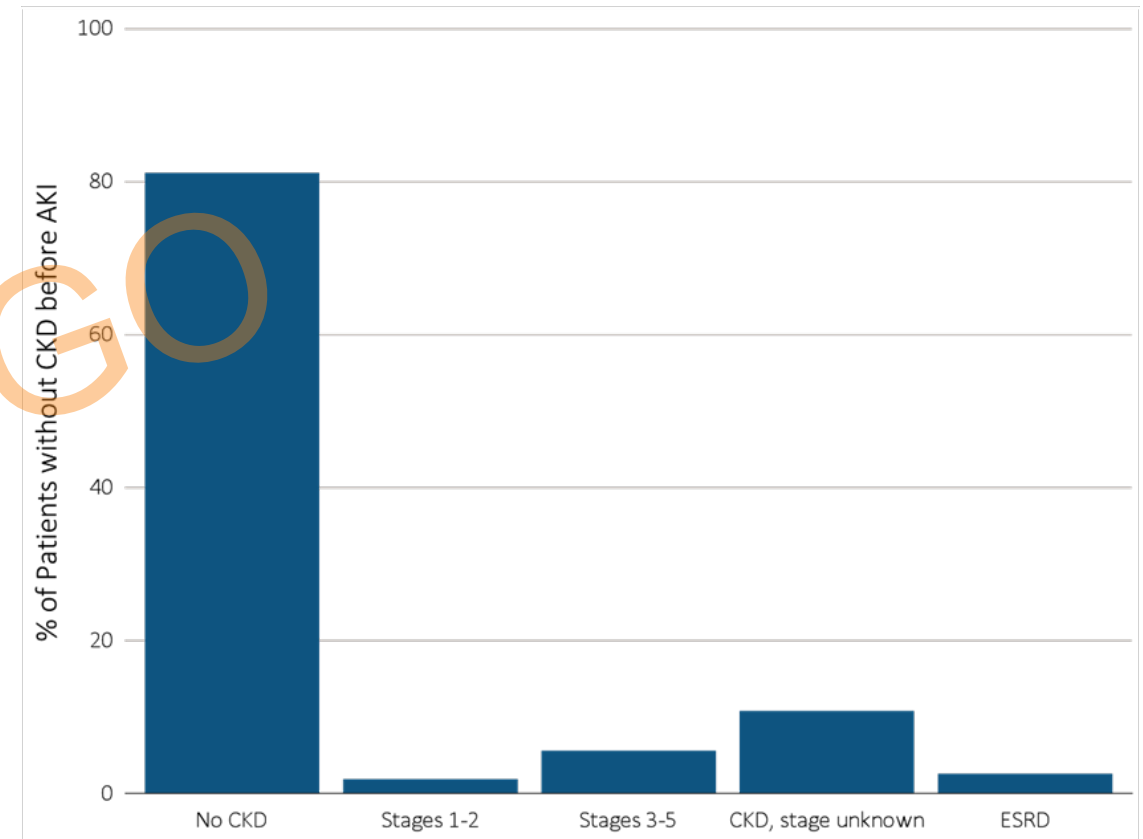


Renal status one year following discharge from AKI hospitalization in 2013-2014, among surviving patients without kidney disease prior to AKI hospitalization, by CKD stage and ESRD status

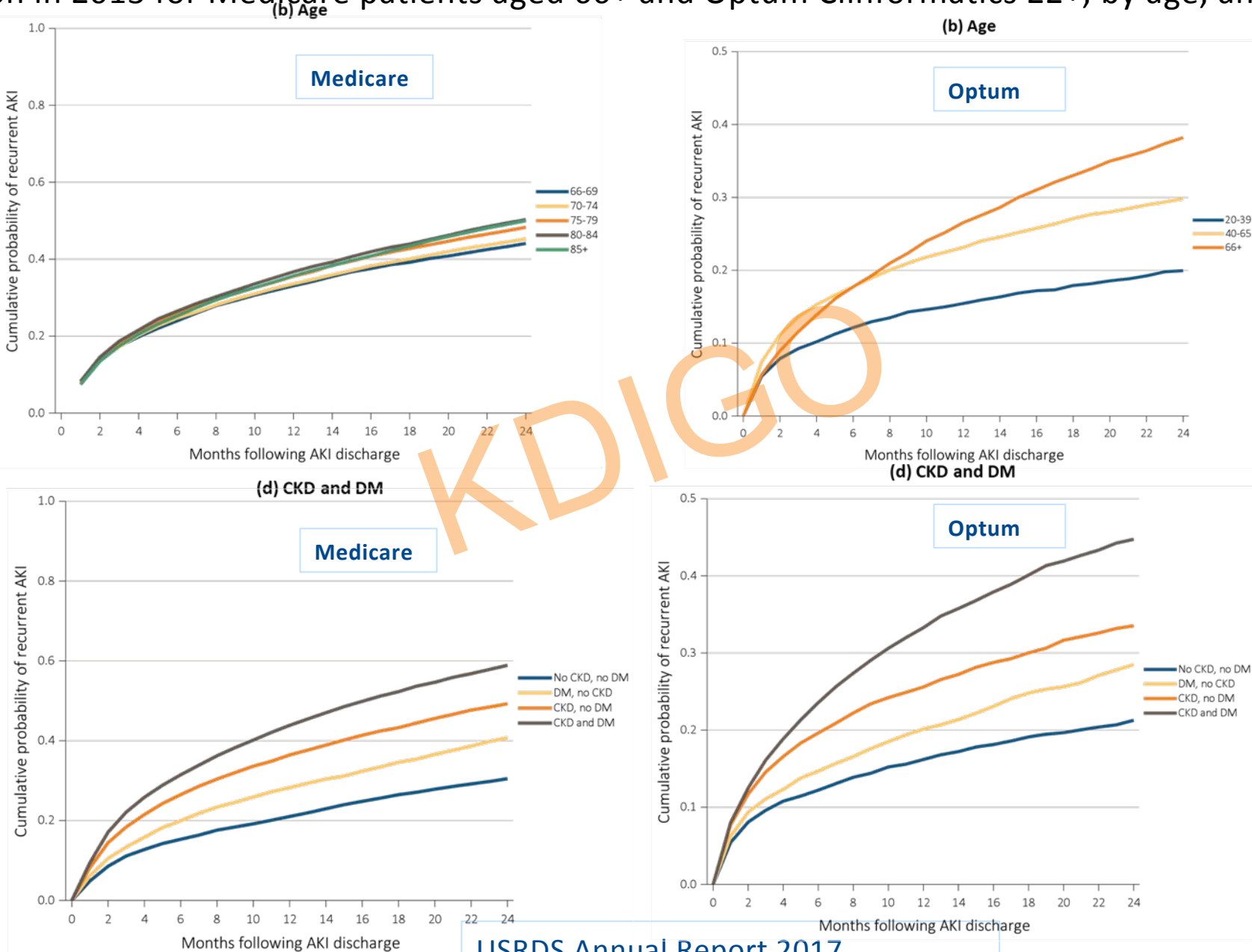
(a) Medicare (aged 66+)



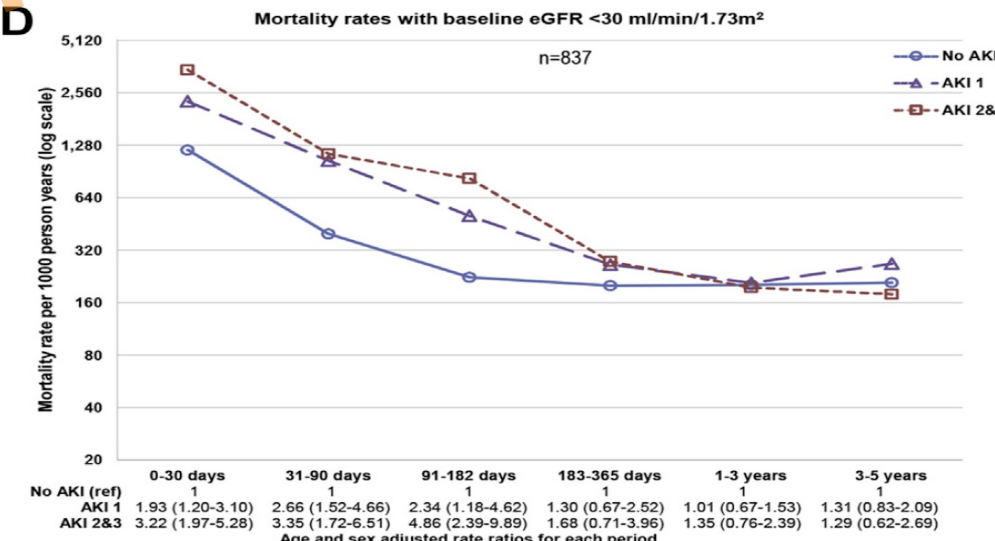
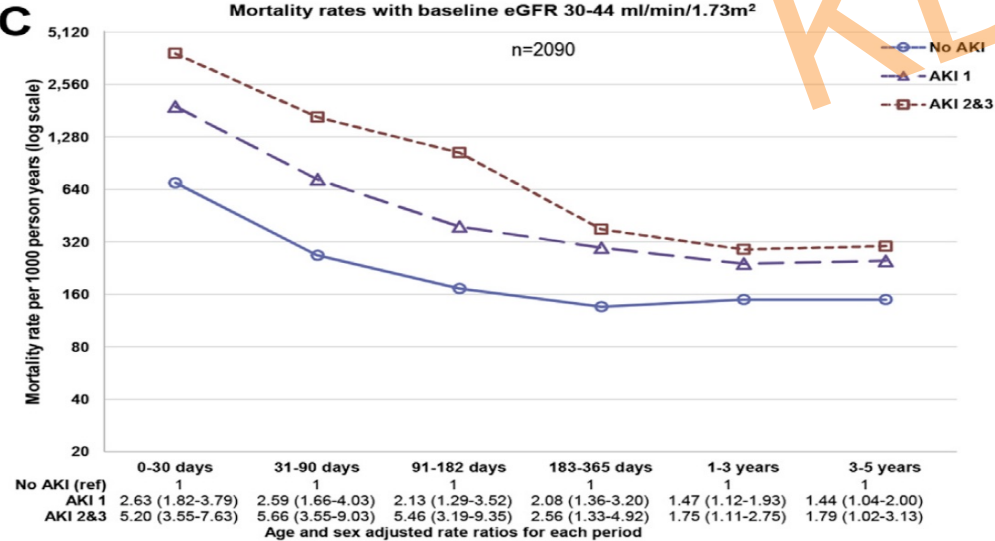
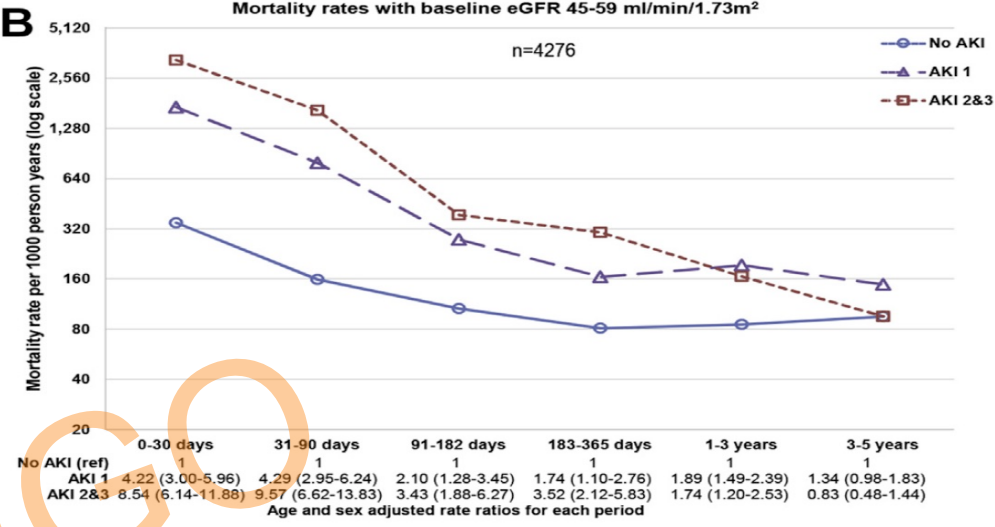
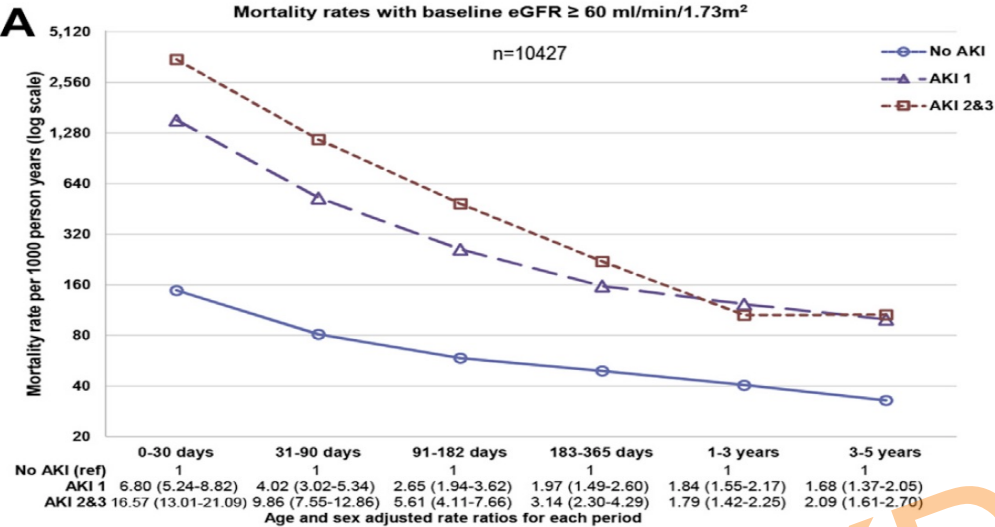
(b) Optum Clinformatics™ (aged 22+)



Cumulative probability of a recurrent AKI hospitalization within two years of live discharge from first AKI hospitalization in 2013 for Medicare patients aged 66+ and Optum Clinformatics 22+, by age, and by CKD and DM



Mortality rates and age- and sex-adjusted rate ratios by baseline eGFR group and acute kidney injury

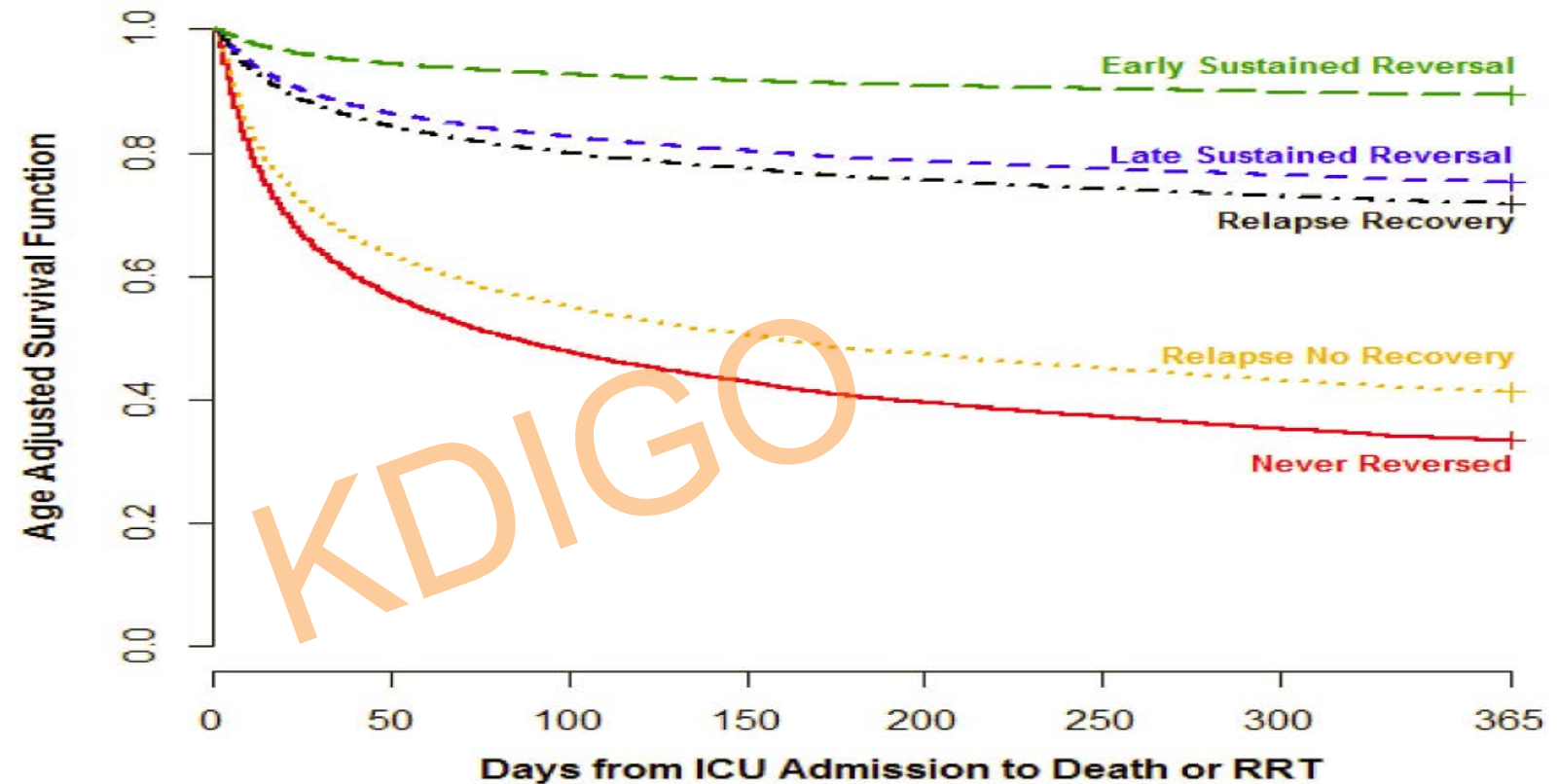


Kellum et al: Recovery After Acute Kidney Injury AJRCCM 2016 as 10.1164/rccm.201604-0799OC

16,968 critically ill patients with KDIGO stage 2-3 AKI using an electronic database.

Reversal of AKI was defined as alive and no longer meeting criteria for even stage 1.

Recovery was defined as reversal at hospital discharge.



No. at risk

Early Sustained Reversal	4507	4404	4317	4235	4176	4122	4070	4026
Late Sustained Reversal	1642	1529	1424	1357	1310	1272	1242	1203
Relapse Recovery	3823	3535	3245	3061	2910	2818	2719	2625
Relapse No Recovery	2496	1386	1190	1114	1075	1052	1027	1008
Never Reversed	4496	2127	1922	1826	1757	1709	1678	1648

Prognostic Significance of AKI Natural History

Element of Natural History	Short-term outcome	Long term outcome
Timing of onset in ICU	Mortality	NA
Severity of injury	Mortality	CKD/Mortality/Readmit
Duration of injury	Mortality	Mortality
Recovery/Transient injury	Survival	Survival
Recurrent Episodes	NA	CKD
Fluid Status	Mortality	CKD/Mortality
Baseline GFR	Survival	ESRD

(Hsu et al, CJASN 09; Wald et al, JAMA, 09; Thakar et al, CCM, 2009; Ishani et al, Archives, 2011; Parikh and Coca et al, KI, 2010; Uchino et al, NDT, 2009; , Bouchard CJASN 2010, Macedo KI 2011, Thakar et al, CJASN, 2011; Susanthipong CJASN 2013, Hueng CJASN 2014, Warnock et al 2016, Goldstein et al NEJM 2017)

Global Burden of AKI

What is known

- **AKI is common in both adults and children**
- **It is encountered in multiple settings**
- **Associated with high mortality and increased resource utilization**
- **Non-renal recovery is common and associated with development of CKD and dialysis need**
- **Hypertension and CV events are common long term outcomes**
- **Prior CKD, Duration, Severity, Frequency are associated with poor outcomes**

Global Burden of AKI

What is known

What we are learning

What we don't know

KDIGO

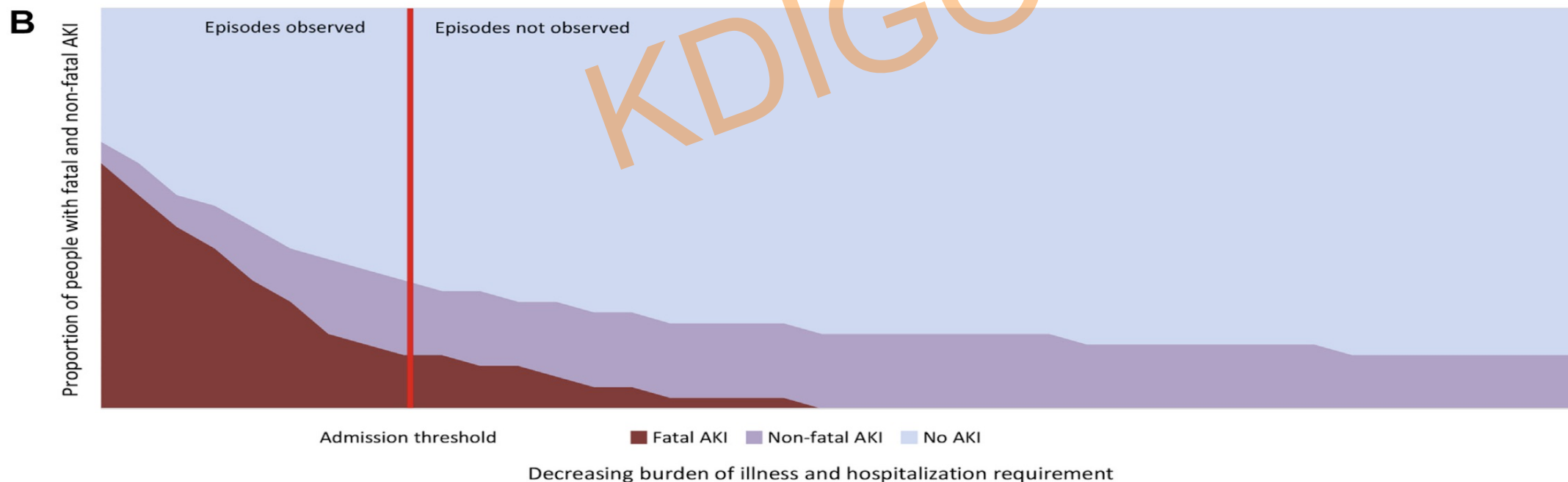
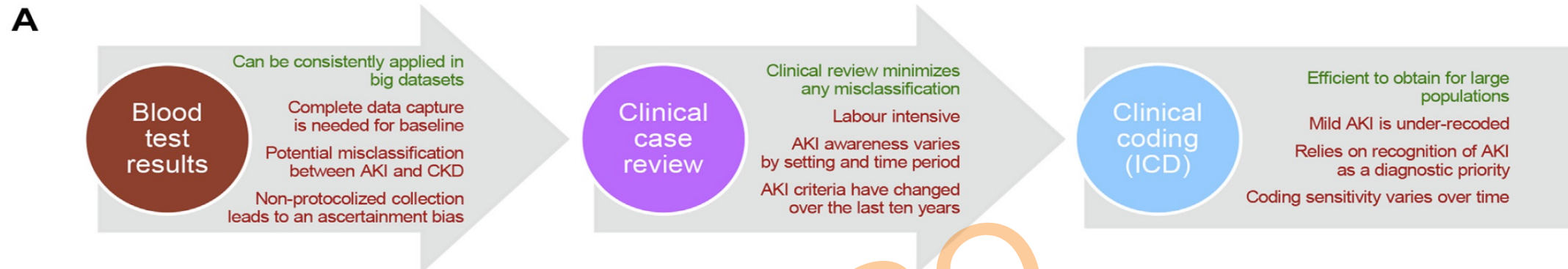
Global Burden of AKI

What we are Learning

- *Gaps in our diagnostic and staging criteria*



Methodologic challenges in AKI epidemiology



AKI Guidelines: Current Status of Criteria for Diagnosis and Staging

Criteria	RIFLE ²⁵	AKIN ²⁶	KDIGO ^{27,92}
Date of release	2004	2007	2012
Baseline	Not specifically defined. If not available, back-calculate a serum creatinine using an eGFR of 75 ml/min/1.73 m ² using the MDRD equation	48-h window	Not specifically defined. If not available, use lowest serum creatinine during hospitalization, or calculate SCr using MDRD assuming baseline eGFR 75 ml/min/1.73 m ² when there is no evidence of CKD
Time interval	Diagnosis and staging: within 1–7 days and sustained more than 24 h	Diagnosis: within 48 h Staging: 1 week	Diagnosis: 50% increase in SCr within 7 days or 0.3 mg/dl (26.5 µmol/l) within 48 h

Use lowest during hospitalization



Retrospective diagnosis

Calculate sCr using MDRD eGFR 75ml/min when no evidence of CKD



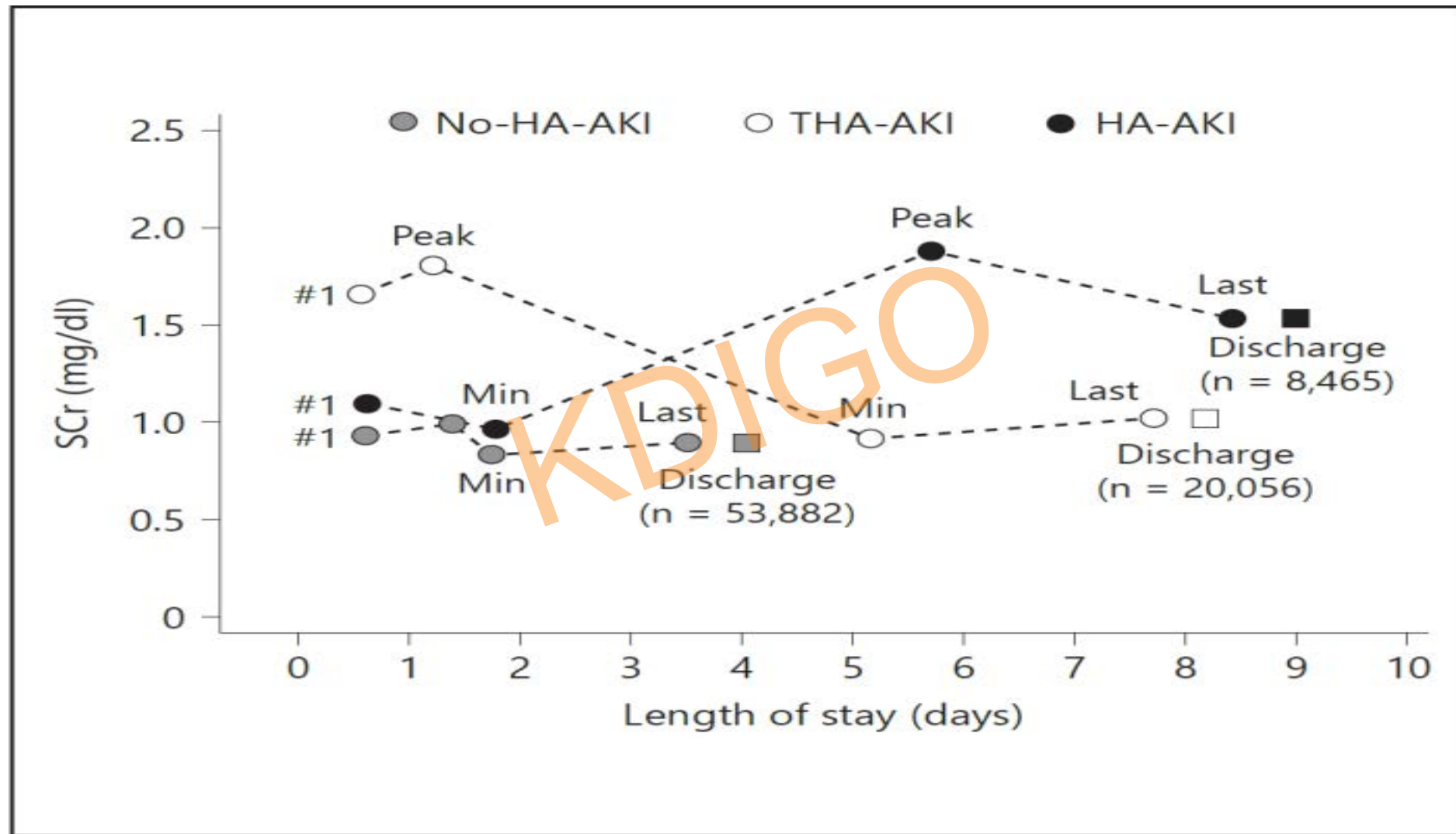
CKD status is often unknown

No mention on decline sCr



Will not classify patients that recovered from AKI

Creatinine trajectories by AKI types, combined cohort (82,402 patients) UAB and UCSD.



Creatinine trajectories by AKI types, combined cohort (82,402 patients)..

Table 1. Characteristics and mortality rates for inpatients without, or with AKI (82,403 patients; 2,611 inpatient deaths (3.2%))

	No-HA-AKI: 53,683 (65%) ^a	THA-AKI: 20,255 (25%) ^a	HA-AKI: 8,465 (10%) ^a
Demographic characteristics, time course and changes in sCr			
Age, years ^b	56 (42–68)	58 (44–69)	59 (48–70) ^c
Male sex, n (%)	27,287 (51)	12,077 (60)	4,521 (53) ^c
Whites, other patients, n (%)	37,574 (70)	13,564 (67)	5,690 (67)
Black patients ^d , n (%)	12,772 (24)	5,924 (29)	2,440 (29)
Hispanic patients, n (%)	3,337 (6.2)	767 (3.8)	335 (4.0)
Length of stay, days	3.1 (2.0–5.1)	6.2 (4.0–11.0)	7.1 (4.1–12.0) ^c
Intensive care unit stay, n (%)	9,278 (17)	7,969 (39)	3,691 (44) ^c
Max-eGFR, ml/min/1.73 m ²	99 (80–116)	98 (73–117)	93 (69–111) ^c
Max-eGFR <60 ml/min/1.73 m ² (60), n (%)	5,998 (11)	3,529 (17)	1,666 (20) ^c
Inpatient mortality, 30 day length of stay			
Inpatient deaths, n (%)	673 (1.3)	817 (4.0)	1,121 (13) ^c
Incident rate for deaths (per 30-patient days)	0.093 (0.086–0.100)	0.149 (0.139–0.159)	0.442 ^c (0.417–0.469)
Incident rate ratios for deaths	1.00 (reference)	1.60 (1.44–1.77)	4.75 (4.32–5.23) ^c

	Total	North	Northwest	Southeast	Southwest
Population (million) ¹⁶	1355.13	471.67	98.42	589.26	195.78
Hospital admissions (million) ¹⁷	140.07	46.76	11.76	60.24	21.31
Screened cases*	2 223 230 (1.59%)	704 271 (1.51%)	270 575 (2.30%)	974 848 (1.62%)	273 536 (1.28%)
Number of screened cases in January and July					
Total	374 286	119 284	46 099	162 973	45 930
Academic hospital	257 498	86 721	42 372	101 313	27 092
Local hospital	116 788	32 563	3 727	61 660	18 838
AKI detection rate (KDIGO criteria), n (%; 95% CI)					
Total	3687 (0.99%; 0.95-1.02)	974 (0.82%; 0.77-0.87)	404 (0.88%; 0.79-0.96)	1759 (1.08%; 1.03-1.13)	550 (1.20%; 1.10-1.30)
Academic hospital	2897 (1.13%; 1.08-1.17)	802 (0.92%; 0.86-0.99)	397 (0.94%; 0.85-1.03)	1268 (1.25%; 1.18-1.32)	430 (1.59%; 1.44-1.74)
Local hospital	790 (0.68%; 0.63-0.72)	172 (0.53%; 0.45-0.61)	7 (0.19%; 0.05-0.33)	491 (0.80%; 0.73-0.87)	120 (0.64%; 0.52-0.75)
AKI detection rate (expanded criteria), n (%; 95% CI)					
Total	7604 (2.03%; 1.99-2.08)	2097 (1.76%; 1.68-1.83)	851 (1.85%; 1.72-1.97)	3406 (2.09%; 2.02-2.16)	1250 (2.72%; 2.57-2.87)
Academic hospital	5662 (2.20%; 2.14-2.26)	1692 (1.95%; 1.86-2.04)	827 (1.95%; 1.82-2.08)	2272 (2.24%; 2.15-2.33)	871 (3.21%; 3.00-3.43)
Local hospital	1942 (1.66%; 1.59-1.74)	405 (1.24%; 1.12-1.36)	24 (0.64%; 0.39-0.90)	1134 (1.84%; 1.73-1.95)	379 (2.01%; 1.81-2.21)

AKI=acute kidney injury. KDIGO=Kidney Disease: Improving Global Outcomes. *Percentage is screened cases per total hospital admissions.

	Non-recognised AKI	Delayed recognition of AKI	Timely recognition of AKI	p value*
Total (N=7555)†	5608 (74.2%)	343 (4.6%)	1604 (21.2%)	NA
Hospital level				0.0431
Academic hospitals (n=5616)	4199 (74.8%)	237 (4.2%)	1180 (21.0%)	
Local hospitals (n=1939)	1409 (72.7%)	106 (5.5%)	424 (21.9%)	
GDP per head				<0.0001
Tertile 1 (n=2245)	1712 (76.3%)	125 (5.6%)	408 (18.2%)	
Tertile 2 (n=2729)	2061 (75.5%)	90 (3.3%)	578 (21.2%)	
Tertile 3 (n=2581)	1835 (71.1%)	128 (5.0%)	618 (23.9%)	
Age (years)				<0.0001
18–39 (n=874)	594 (68.0%)	29 (3.3%)	251 (28.7%)	
40–59 (n=2321)	1715 (73.9%)	93 (4.0%)	513 (22.1%)	
60–79 (n=3101)	2354 (75.9%)	132 (4.3%)	615 (19.8%)	
≥80 (n=1259)	945 (75.1%)	89 (7.1%)	225 (17.9%)	
Disease factors				<0.0001
CKD basis (n=5718)	1150 (62.6%)	121 (6.6%)	566 (30.8%)	
Non-CKD (n=1837)	4458 (78.0%)	222 (3.9%)	1038 (18.2%)	

We defined recognition as timely if AKI was recognized by the physicians in charge within 3 days of the point from which AKI could be diagnosed and before the disorder progressed to higher stages, otherwise we defined recognition as delayed.

	Expanded criteria*		KDIGO AKI criteria†	
	OR (95% CI)	p value	OR (95% CI)	p value
Age (per 10 years increase)	1.35 (1.27–1.42)	<0.0001	1.33 (1.25–1.42)	<0.0001
Sex (male vs female‡)	1.21 (1.02–1.43)	0.0307	1.21 (0.99–1.49)	0.06
History of cardiovascular disease (yes vs no‡)	1.20 (1.02–1.42)	0.0302	1.25 (1.03–1.53)	0.0263
Diabetes (yes vs no‡)	1.13 (0.95–1.37)	0.23	1.11 (0.88–1.39)	0.39
Chronic kidney disease (yes vs no‡)	0.85 (0.70–1.05)	0.13	0.81 (0.63–1.03)	0.09
Delayed vs timely‡ recognition of AKI	1.45 (1.04–2.03)	0.0298	1.29 (0.89–1.89)	0.18
Severe comorbidity (yes vs no‡)	5.25 (4.36–6.31)	<0.0001	4.84 (3.86–6.06)	<0.0001
AKI stage at peak				
1	1‡	..	1‡	..
2	1.36 (1.04–1.78)	0.023	1.36 (1.04–1.78)	0.023
3	2.15 (1.61–2.87)	<0.0001	2.15 (1.61–2.87)	<0.0001
Renal referral (yes vs no‡)	0.66 (0.53–0.82)	0.0003	0.61 (0.47–0.80)	0.0002
Academic vs local‡ hospital	1.17 (0.97–1.41)	0.09	1.14 (0.91–1.43)	0.26

Delayed recognition of AKI was associated with a 30% increased risk for mortality whereas nephrology referral improved chances of survival by 36%

All variables listed in the table were included in the logistic regression model and adjusted for hospital-acquired or community-acquired patients. AKI=acute kidney injury. KDIGO=Kidney Disease: Improving Global Outcomes. OR=odds ratio. RRT=renal replacement therapy. *7431 cases were included in the analysis after excluding 129 cases, which were missing the information for all-cause in-hospital mortality, one for history of cardiovascular disease, and 49 for delayed or timely recognition of AKI. †3591 cases were included in the analysis after excluding 73 cases missing the information for all-cause in-hospital mortality and 26 for delayed or timely recognition of AKI. ‡Reference value.

Table 4: Multivariate logistic regression analysis for factors associated with all-cause in-hospital mortality in AKI

Global Burden of AKI

What we are Learning

- *Gaps in our diagnostic and staging criteria*
- *Community Acquired AKI is underreported*



DEVELOPED WORLD



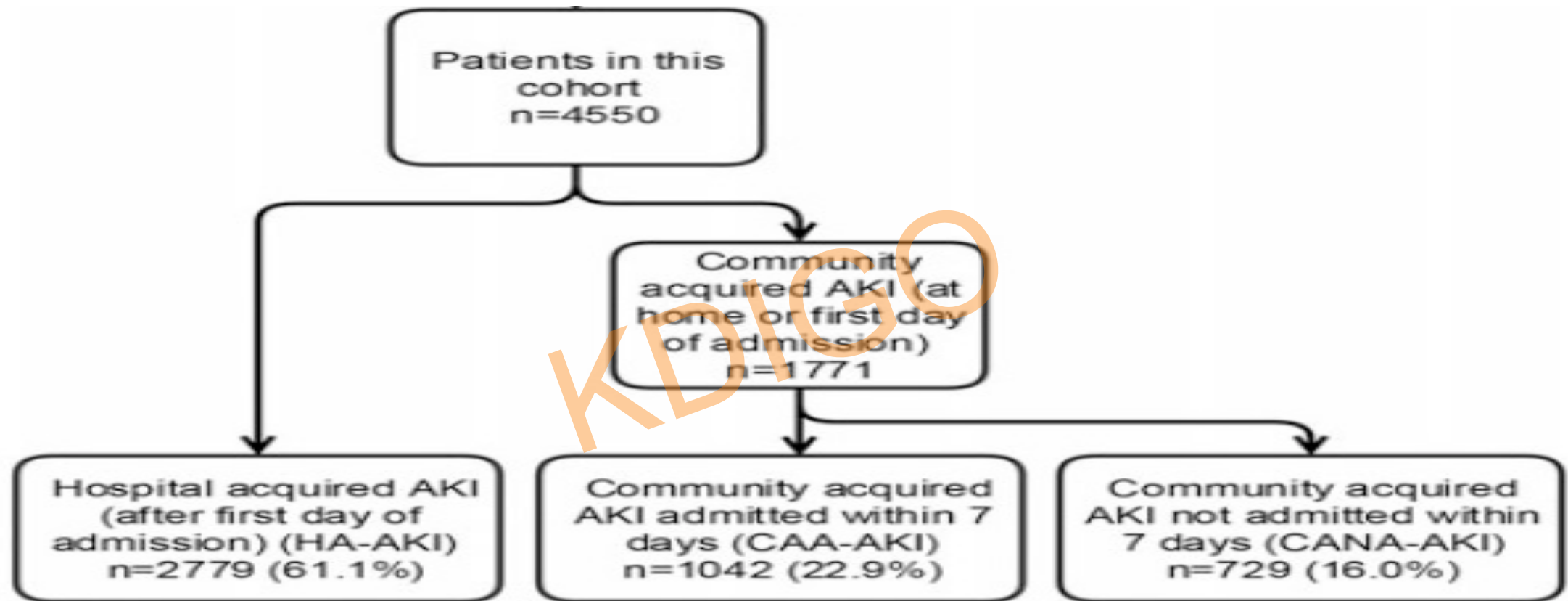
DEVELOPING WORLD

Community Acquired – AKI Studies Hospitalized Patients

Definition	Studies
On admission, AKIN/RIFLE/KDIGO criteria	Selby 2012 (UK) Der Mesropian (US) Challiner 2014 (UK) Hsu 2016 (Taiwan) Holmes 2016 (UK) Soto 2016 (Portugal) Wang 2017 (China)
Within 24 hours, AKIN/RIFLE/KDIGO criteria	Schissler 2013 (US) Sawheny 2016 (UK)
Within 48 hours, AKIN/RIFLE/KDIGO criteria	Wonnacott 2014 (UK) Mehta 2016 (multinational)

KDIGO-based AKI criteria operate differently in hospitals and the community—
findings from a large population cohort

Grampian Laboratory Outcomes Morbidity and Mortality Study-II (GLOMMS-II)



HA-AKI

CAA - AKI

CANA - AKI

61 %

23%

16%

Sawhney et al. Nephrol Dial Transplant (2016) 31: 922–929

Mortality by AKI Group

	HA -AKI	CAA-AKI	CANA-AKI
N	2779	1042	729
30 day mortality	24%	20%	2.6%
1 year mortality	42%	42%	17%

In CANA- AKI - the short-term mortality was low, but long-term mortality was high.

AKI Recovery by Group

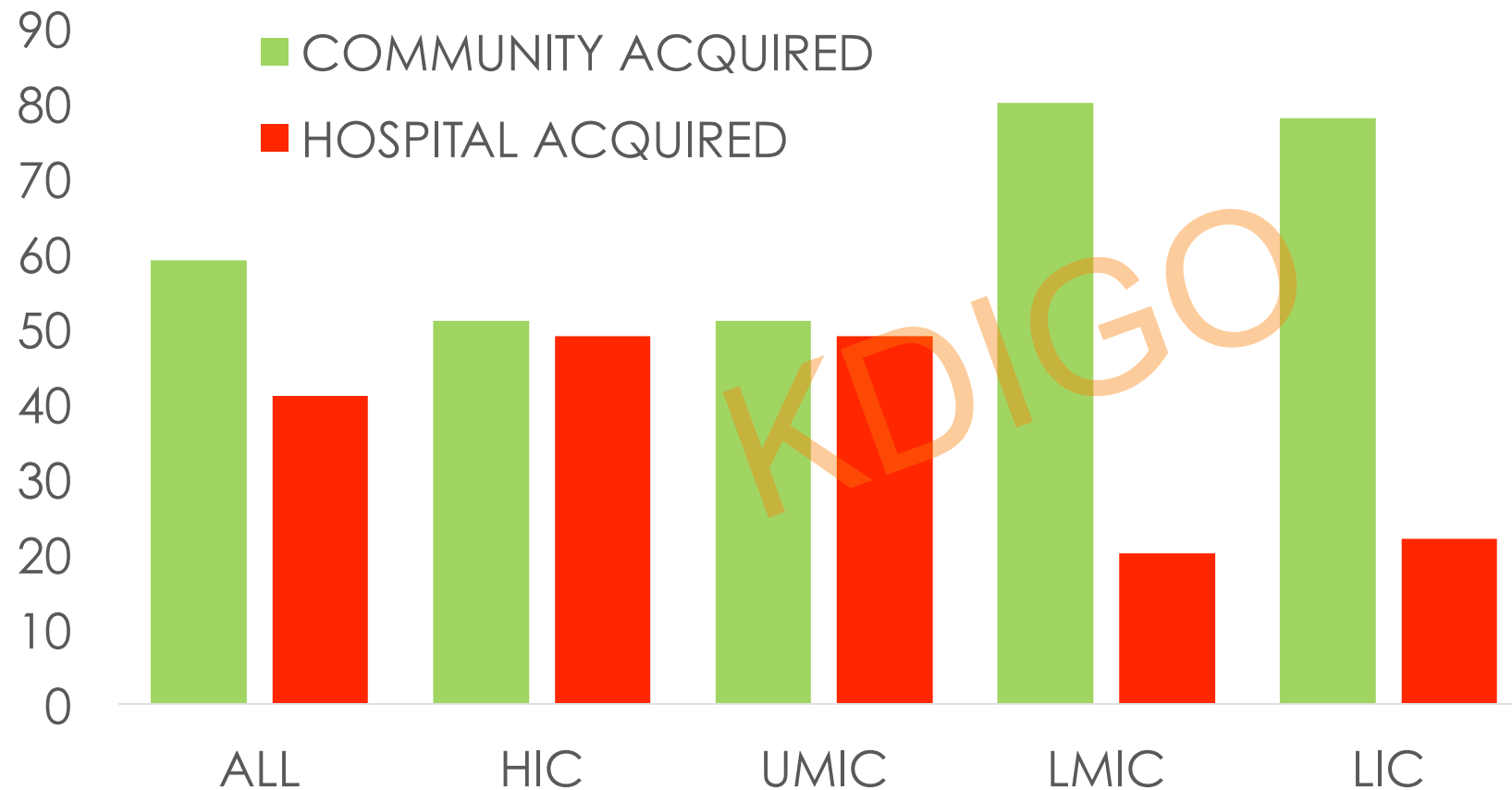
At 90 days	HA -AKI	CAA-AKI	CANA-AKI
No recovery	3.4%	3.5%	12%
Full recovery	45%	49%	34%
Not tested	7%	10%	29%

In CANA -AKI – 30% no sCr assessment in 90 days

- ✓ Applying AKI criteria in non-hospitalized patients may misclassify CKD patients as AKI
- ✓ Lower 30-day mortality -less 'acute' insult in CANA-AKI, reflecting possible CKD.
- ✓ High 1 year mortality suggests that the lack of repeat testing may contribute to worse outcomes

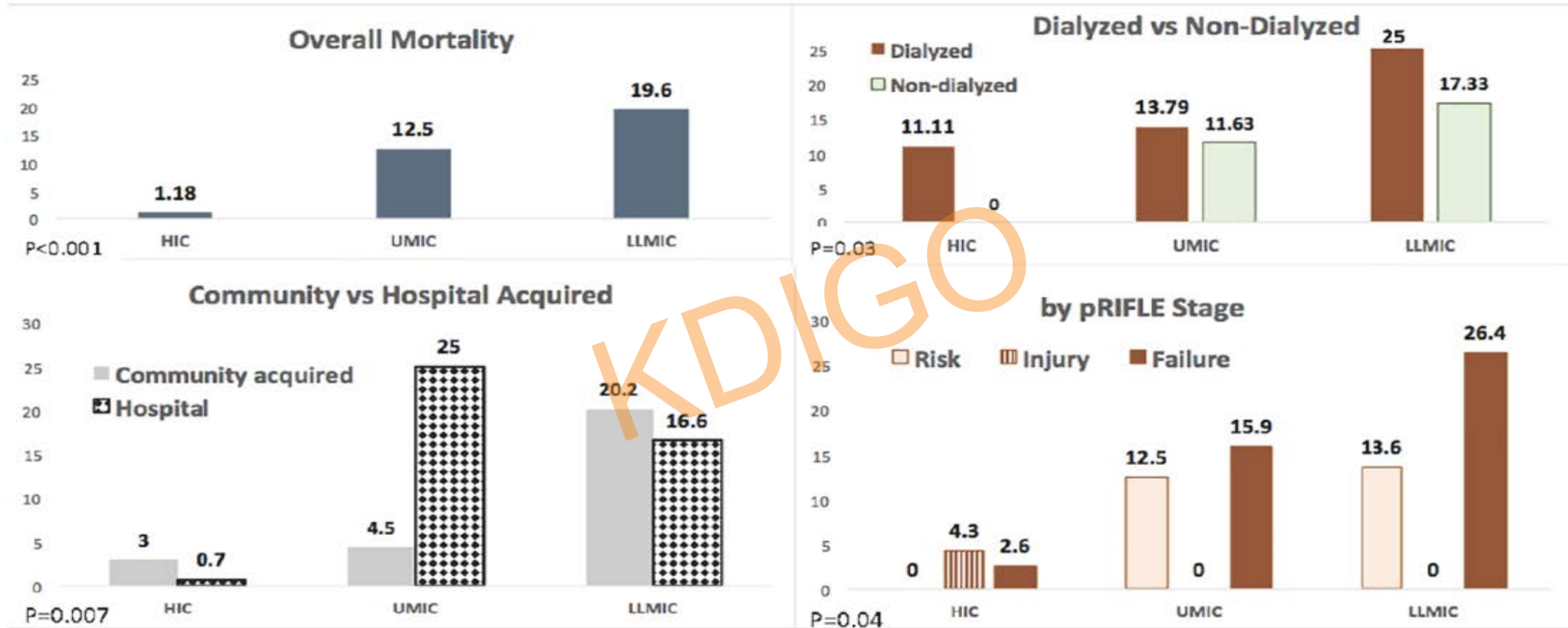
AKI Global Snapshot

Most Patients Developed AKI in the Community



In low-middle and low Income countries, 80% of patients developed AKI in the community

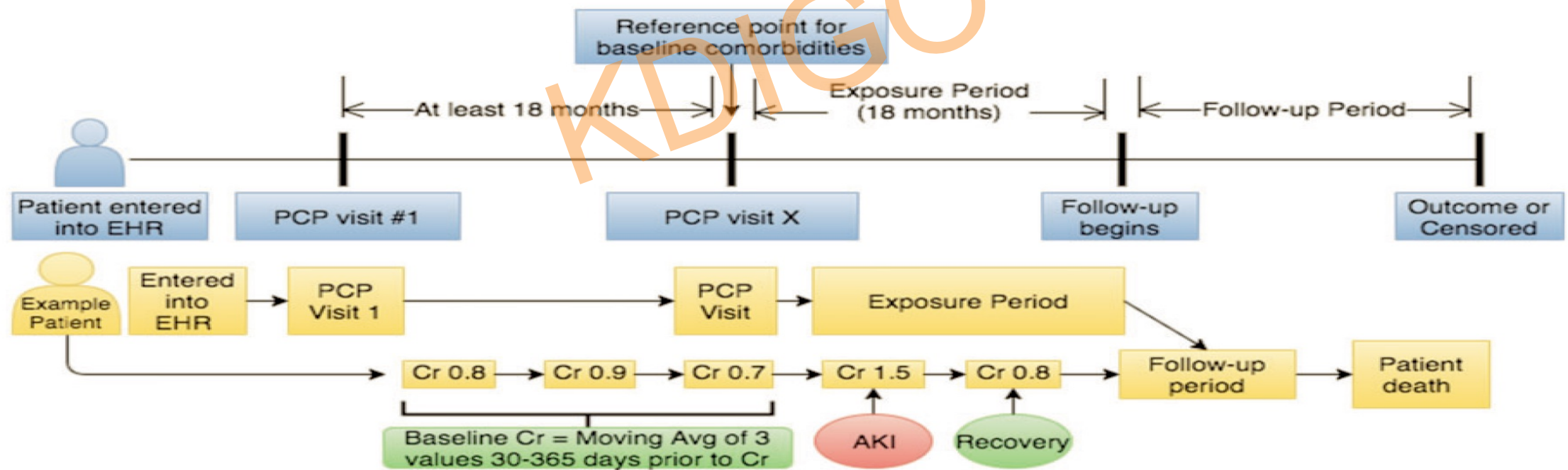
Recognition and management of acute kidney injury in children: The ISN 0by25 Global Snapshot study



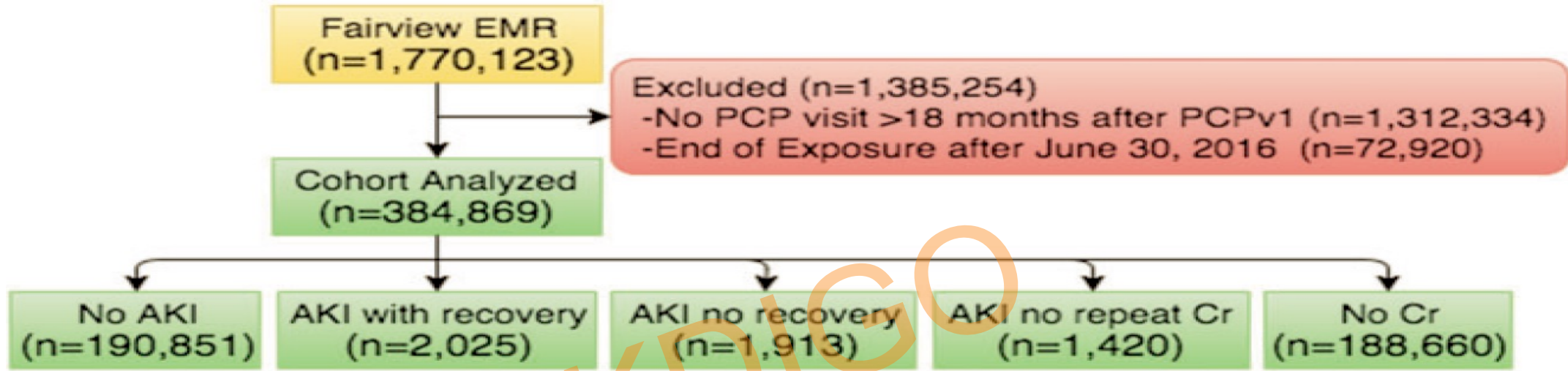
Mortality frequency ranged from 1.2% in HIC patients to 19.6% in LMIC patients.

The impact of outpatient acute kidney injury on mortality and chronic kidney disease: a retrospective cohort study

- ✓ Aim to investigate outcomes patients with outpatient AKI who are not subsequently admitted
- Retrospective study 384,869 outpatient adults receiving primary care at a health system
- Only patients with previous baseline within 12 months



The impact of outpatient acute kidney injury on mortality and chronic kidney disease: a retrospective cohort study

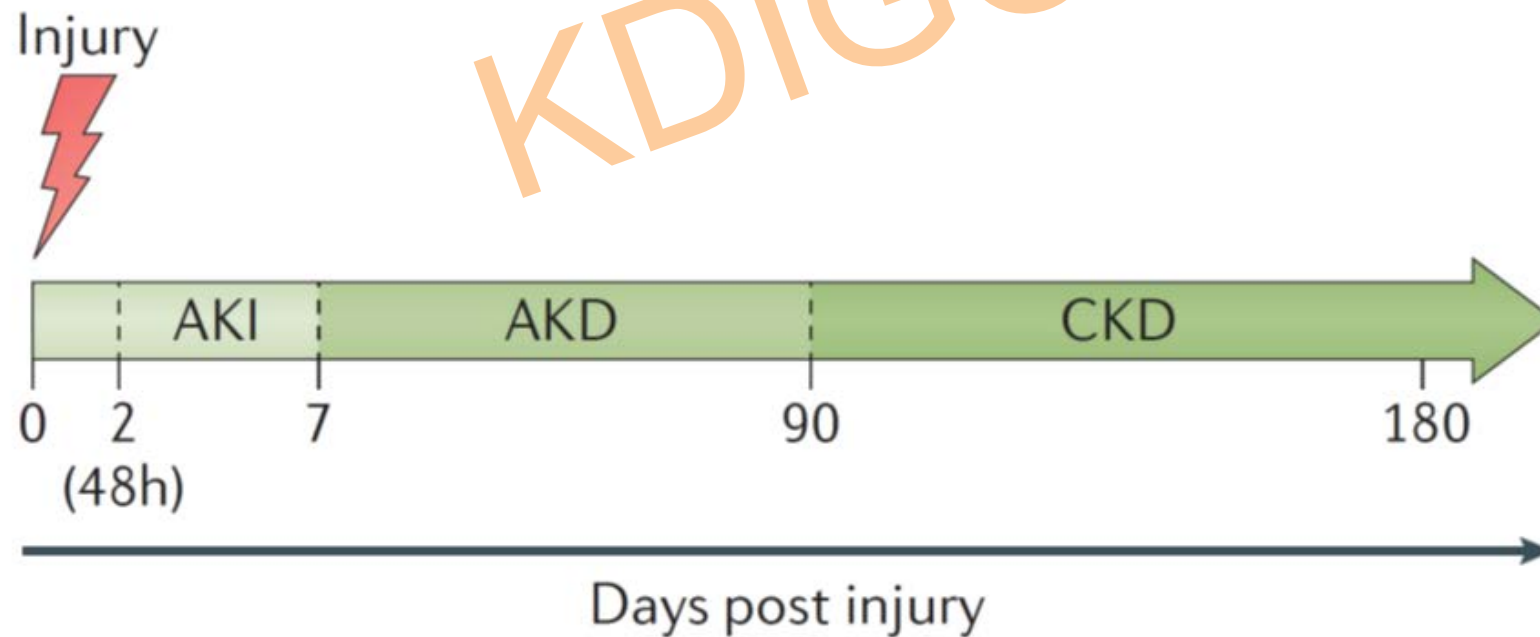


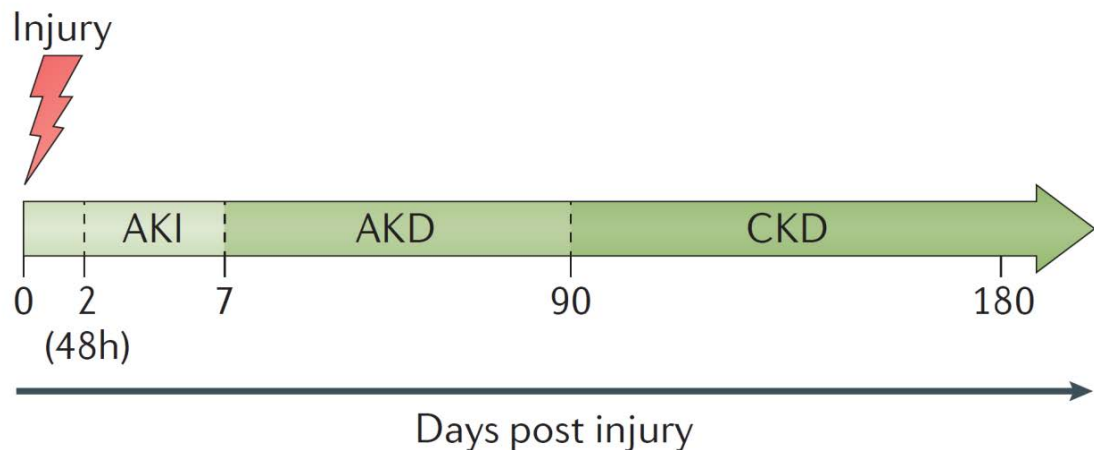
- ✓ Outpatient AKI not requiring hospital admission was common and occurred more than three times as often as hospital AKI.
- ✓ Double the risk of mortality >5 years compared with patients without outpatient AKI
- ✓ Even stage 1 AKI (1.5–1.9 times the baseline Scr) and those that recover their Scr to baseline have a significantly increased risk of mortality, CKD, hospitalization and recurrent AKI.

Global Burden of AKI

What we are Learning

- *Gaps in our diagnostic and staging criteria*
- *Community Acquired AKI is underreported*
- *Acute Kidney Disease is not recognized*



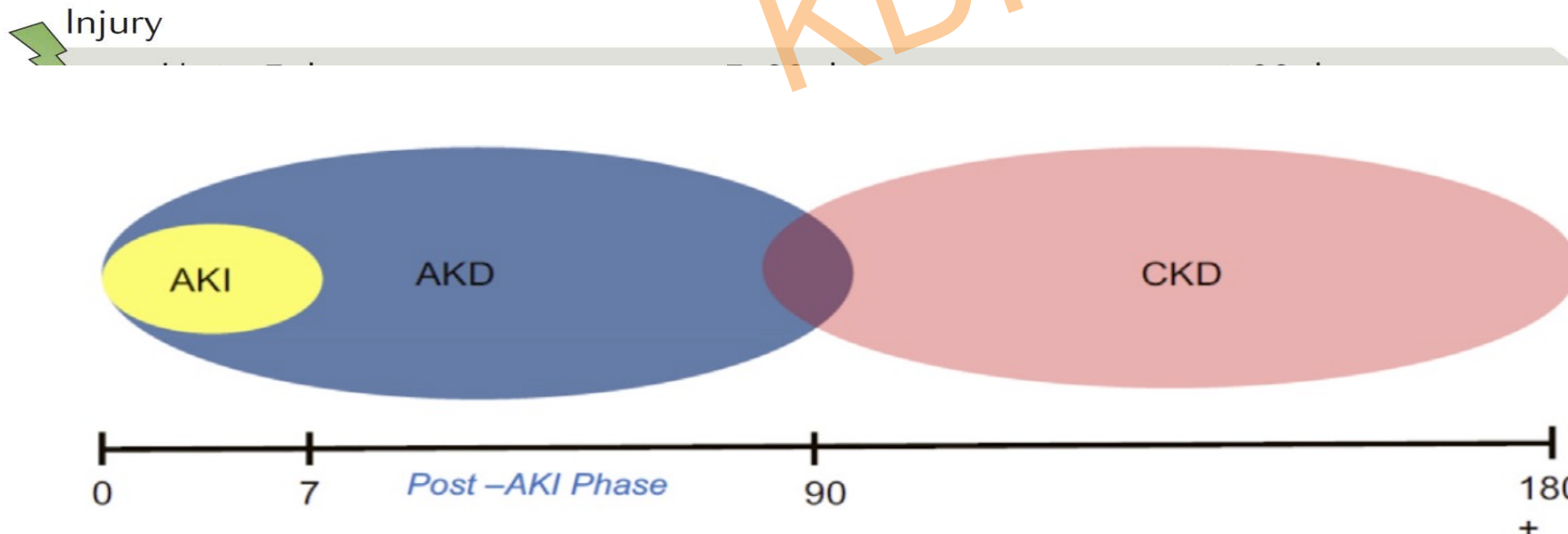
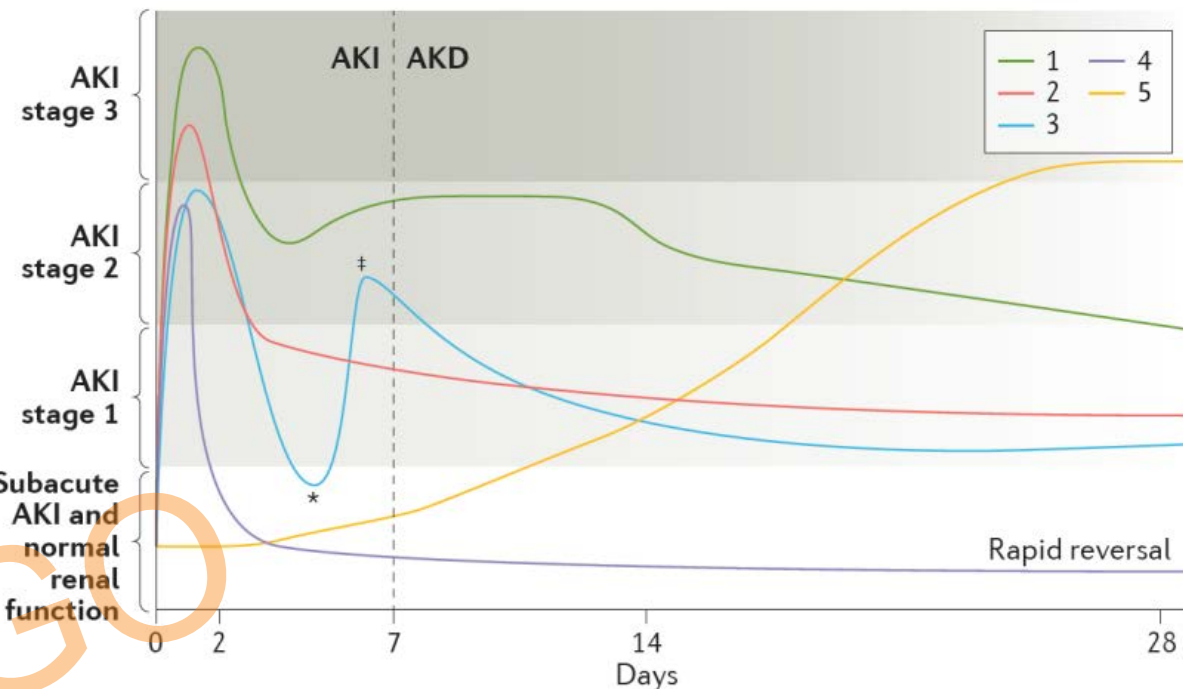


Box 1 | Definitions of AKI and AKD, initial management of AKI, and assessment of kidney function

Consensus statement 1A:

Persistent acute kidney injury (AKI) is characterized by the continuance of AKI by serum creatinine (as defined by KDIGO) beyond 48 h from AKI onset. Complete reversal of AKI by KDIGO criteria within 48 h characterizes rapid reversal of AKI (evidence grade: level 5).

Subacute AKI and normal renal function



0by25 AKI PILOT STUDY

Ran from June 2016
to Dec 2017

Bolivia

Malawi

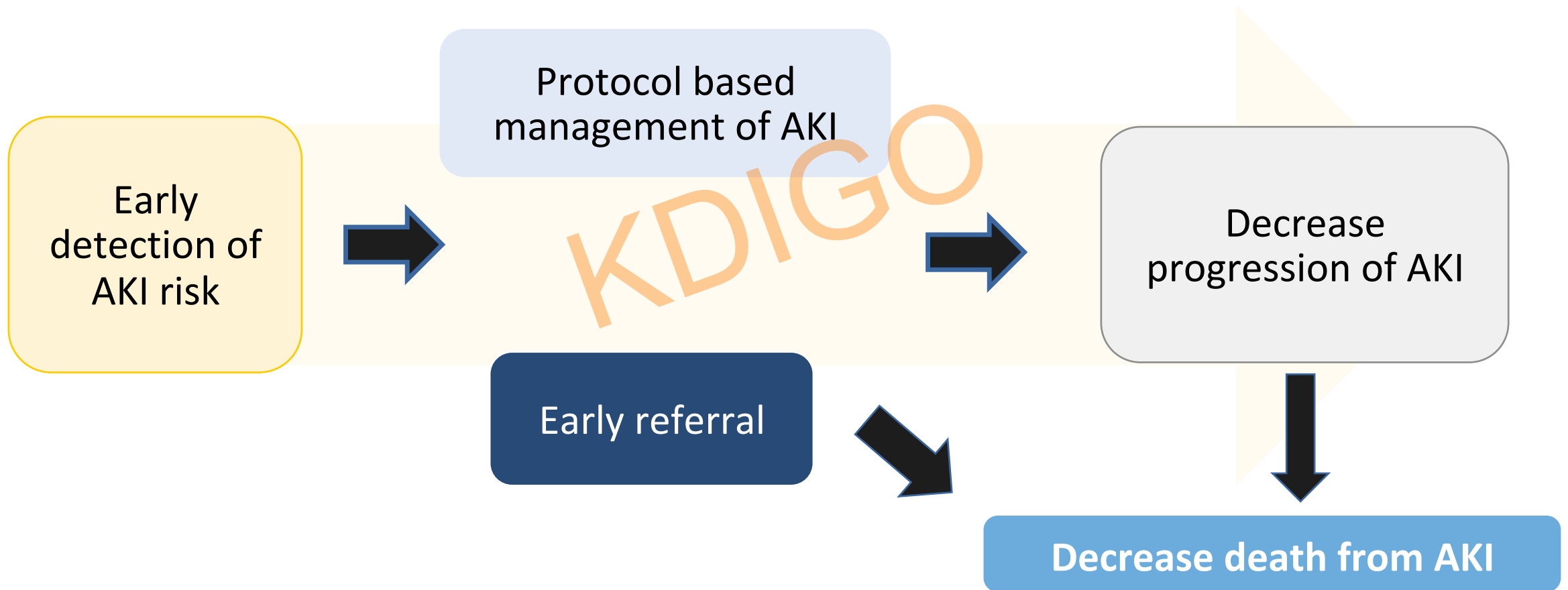
Nepal

8 health care centers
4 regional hospitals
3 University referral
hospitals

Data from 2101 enrolled
patients

Results submitted for publication

Education and Training Program

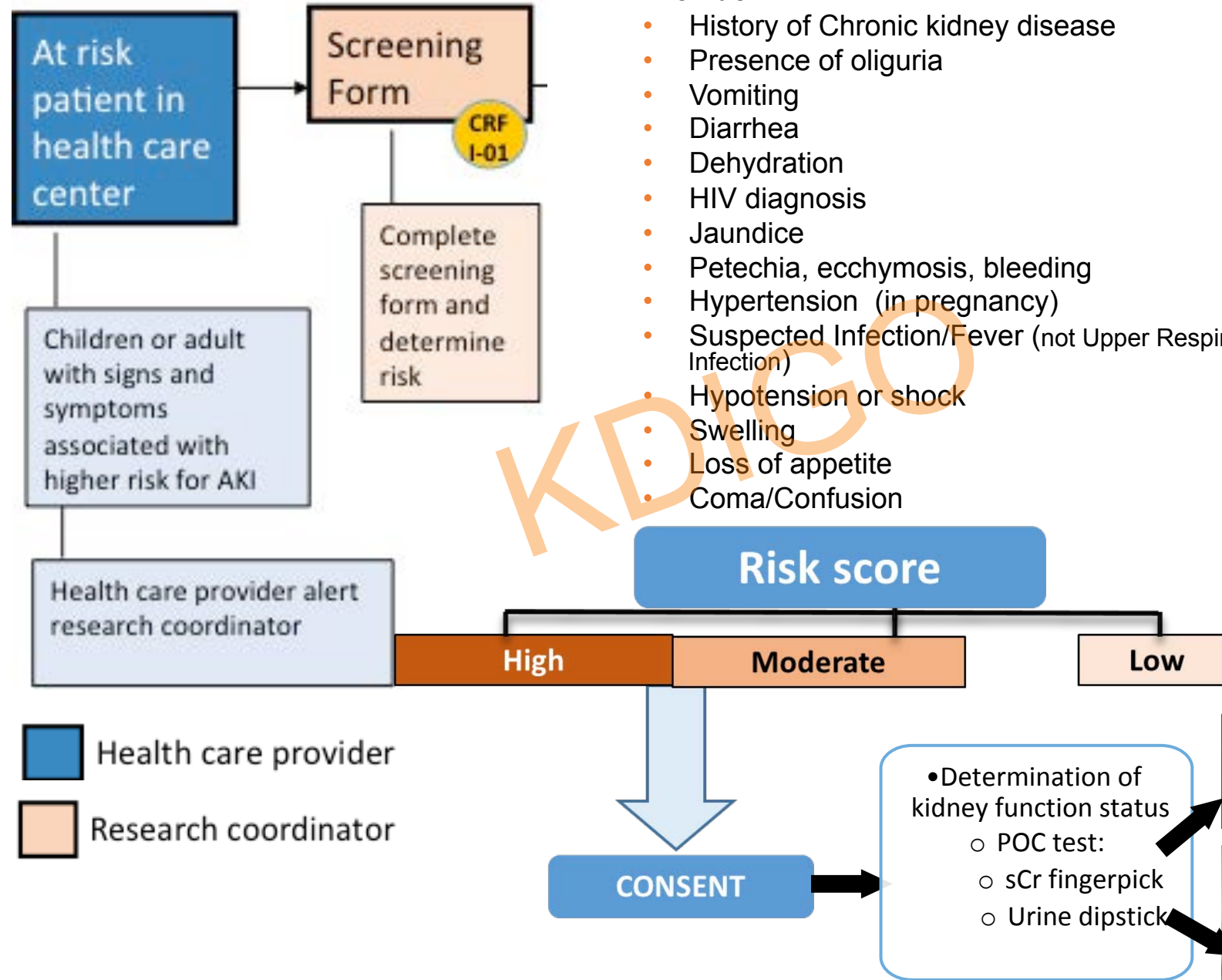


Screening

Health care provider alert research coordinator

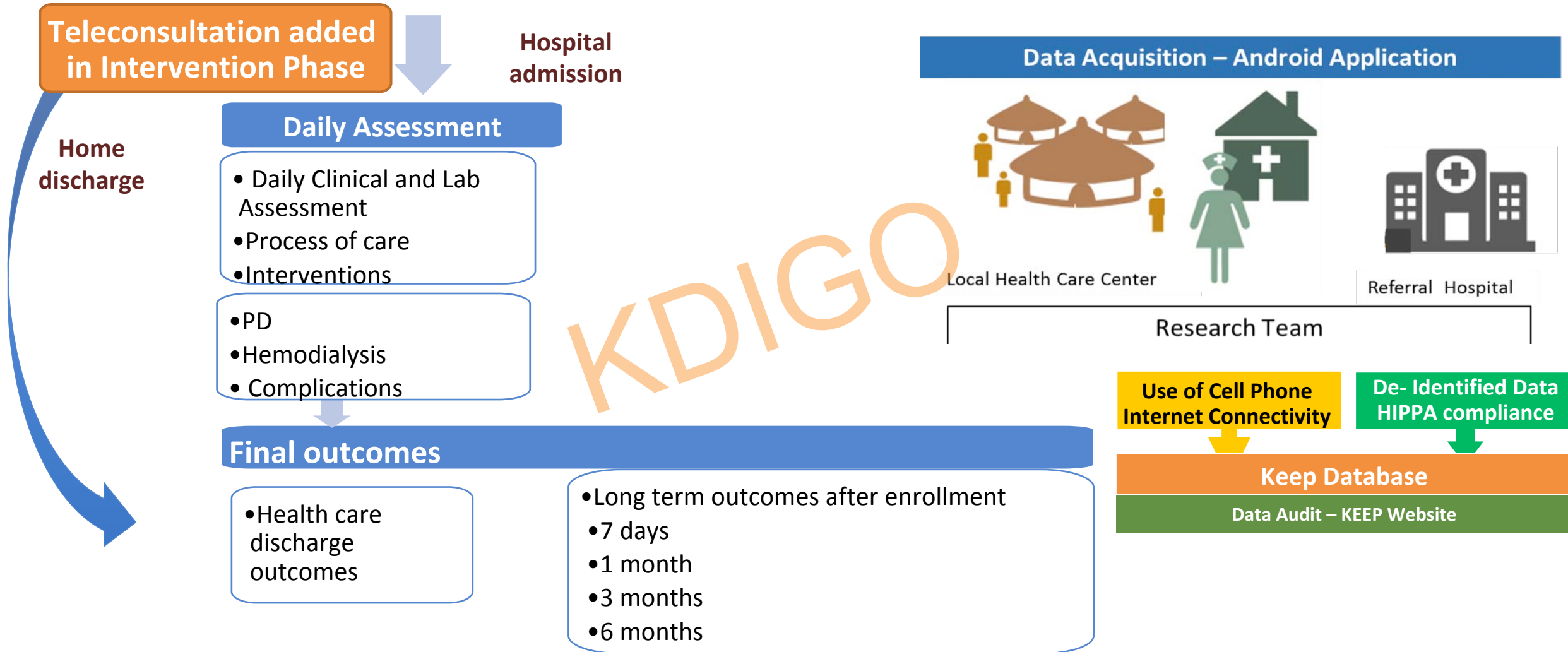
Signs and Symptoms to Alert Health Care Provider

- History of Chronic kidney disease
- Presence of oliguria
- Vomiting
- Diarrhea
- Dehydration
- HIV diagnosis
- Jaundice
- Petechia, ecchymosis, bleeding
- Hypertension (in pregnancy)
- Suspected Infection/Fever (not Upper Respiratory Infection)
- Hypotension or shock
- Swelling
- Loss of appetite
- Coma/Confusion

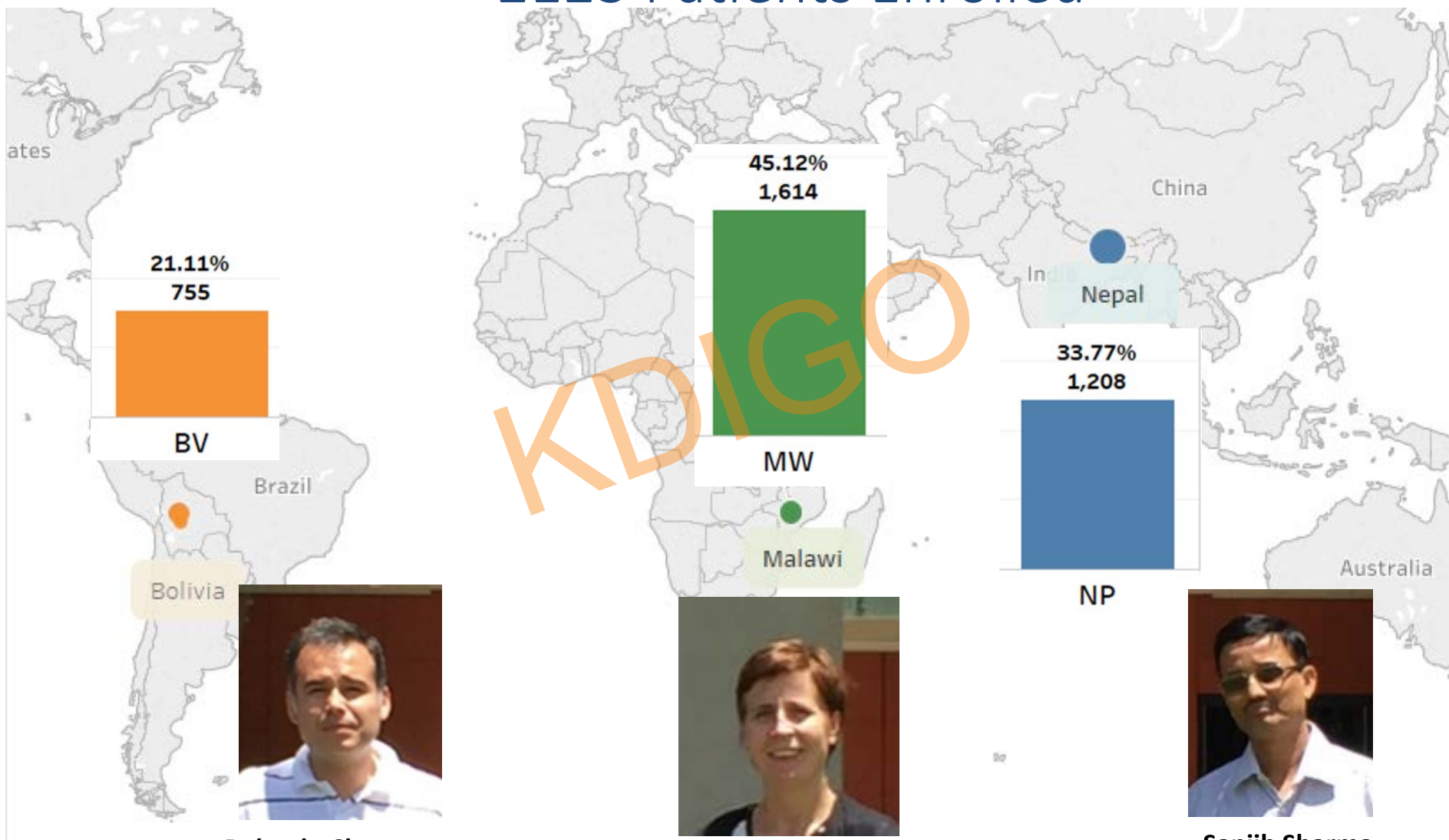


Observation Phase Follow up

Process of Care - during the health care center or hospital stay



3577 Patients Screened 2123 Patients Enrolled



Rolando Claire
Del-Granado

Ulla Hemmila

Sanjib Sharma

Most Frequent Comorbidities and Sign/Symptoms

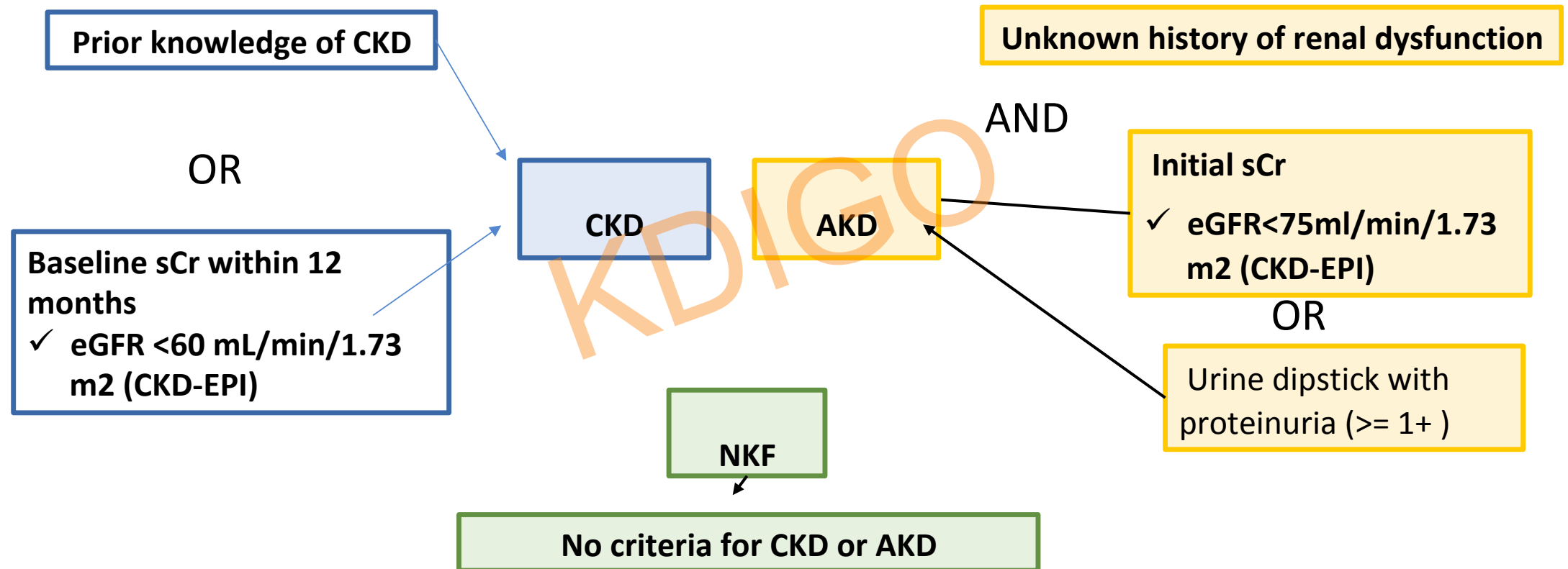
Comorbidities

	Count	%
DM	256	12.2%
Hypertension	418	19.9%
Liver disease	87	4.1%
Heart disease	88	4.2%
Lung disease	119	5.7%
HIV	373	17.8%
Previous diagnosis of anemia	255	12.1%
Cancer	36	1.7%

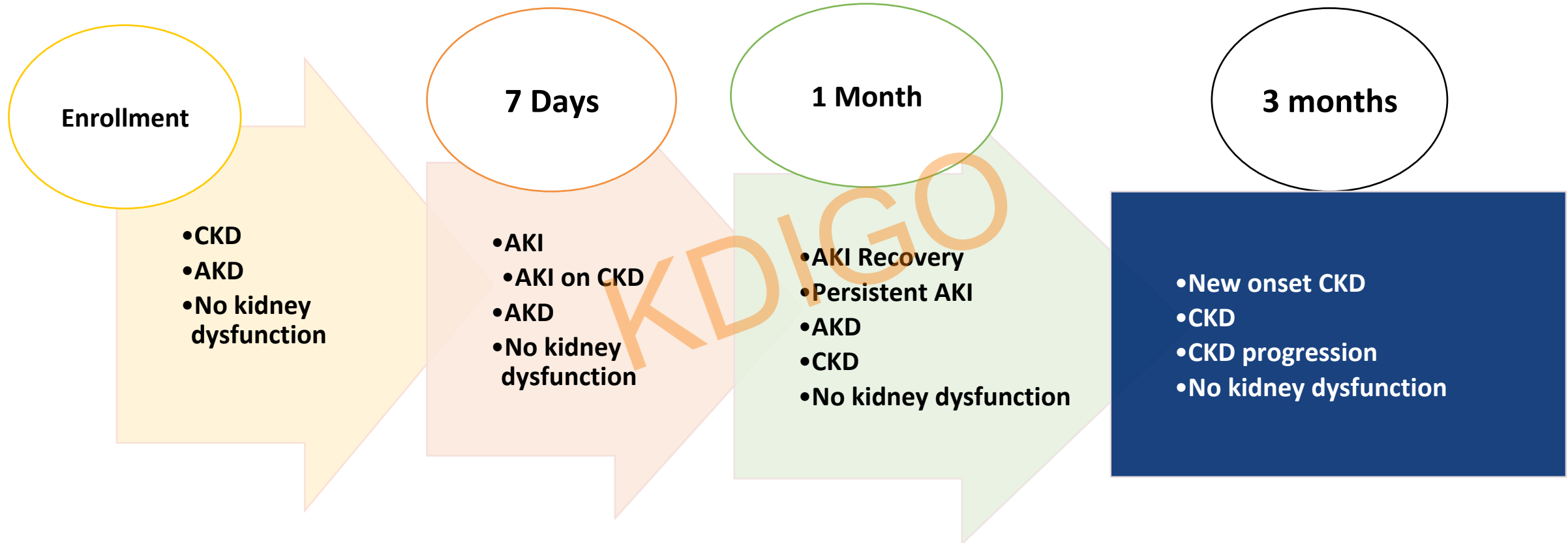
Signs and Symptoms

	Count	%
Weakness	1914	91.1%
Dehydration	1533	73.0%
Infection	1516	72.2%
Vomiting	1050	50.0%
Low intake	1021	48.6%
Oliguria	748	35.6%
Diarrhea	600	28.6%
Hypotension	459	21.8%
GI Infection	410	19.5%
Thirst	396	18.8%
Asthenia	381	18.1%
Use of antibiotic	348	16.6%

Defining Kidney Dysfunction at Admission

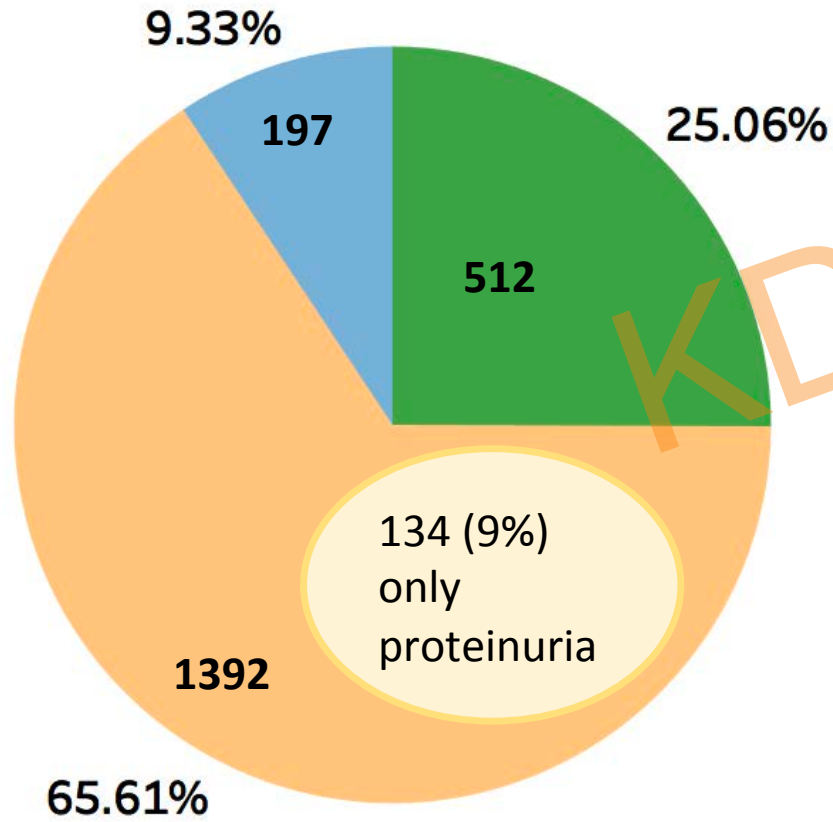


Kidney Functional Stratification



Renal Function Status at Enrollment

■ NKF
■ AKD
■ CKD



CKD – Chronic Kidney Disease

- ✓ Prior knowledge of kidney disease or a baseline serum creatinine determining an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).

AKD – Acute Kidney Disease

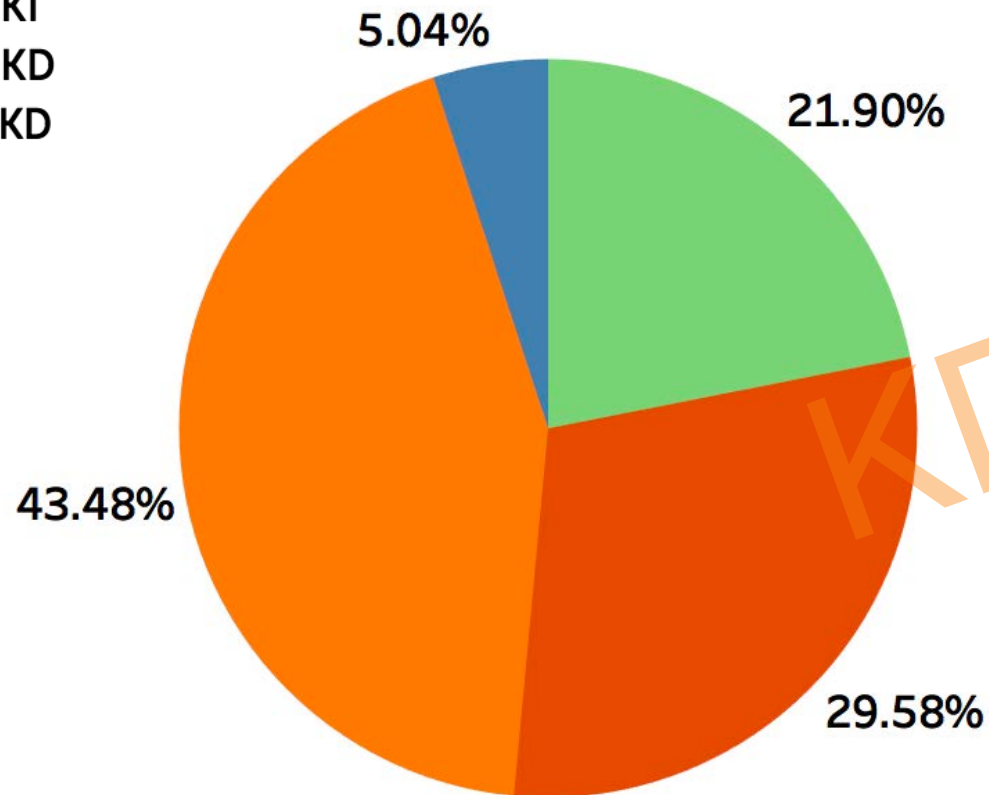
- ✓ Patients with unknown history of renal dysfunction presenting at enrollment:
 - sCr corresponding to an estimated eGFR <75 mL/min/1.73 m² calculated by the CKD-EPI equation.
- OR
- Urine dipstick with proteinuria ($\geq 1+$)

NRF – Normal Kidney Function

- ✓ Patients not fulfilling criteria for CKD or AKD

Renal Function Status at 7 Days

■ NKF
■ AKI
■ AKD
■ CKD



30%

AKI

- ✓ Increase in sCr ≥ 0.3 mg/dl within 48h, or increase to more than 1.5 times the enrollment sCr within 7 days.
- ✓ Decline in sCr ≥ 0.3 mg/dl from the enrollment within 48h.
- ✓ Decline to more than $1.5 \times$ the enrollment sCr within 7 days.

40% of the patients with AKI met decline criterion

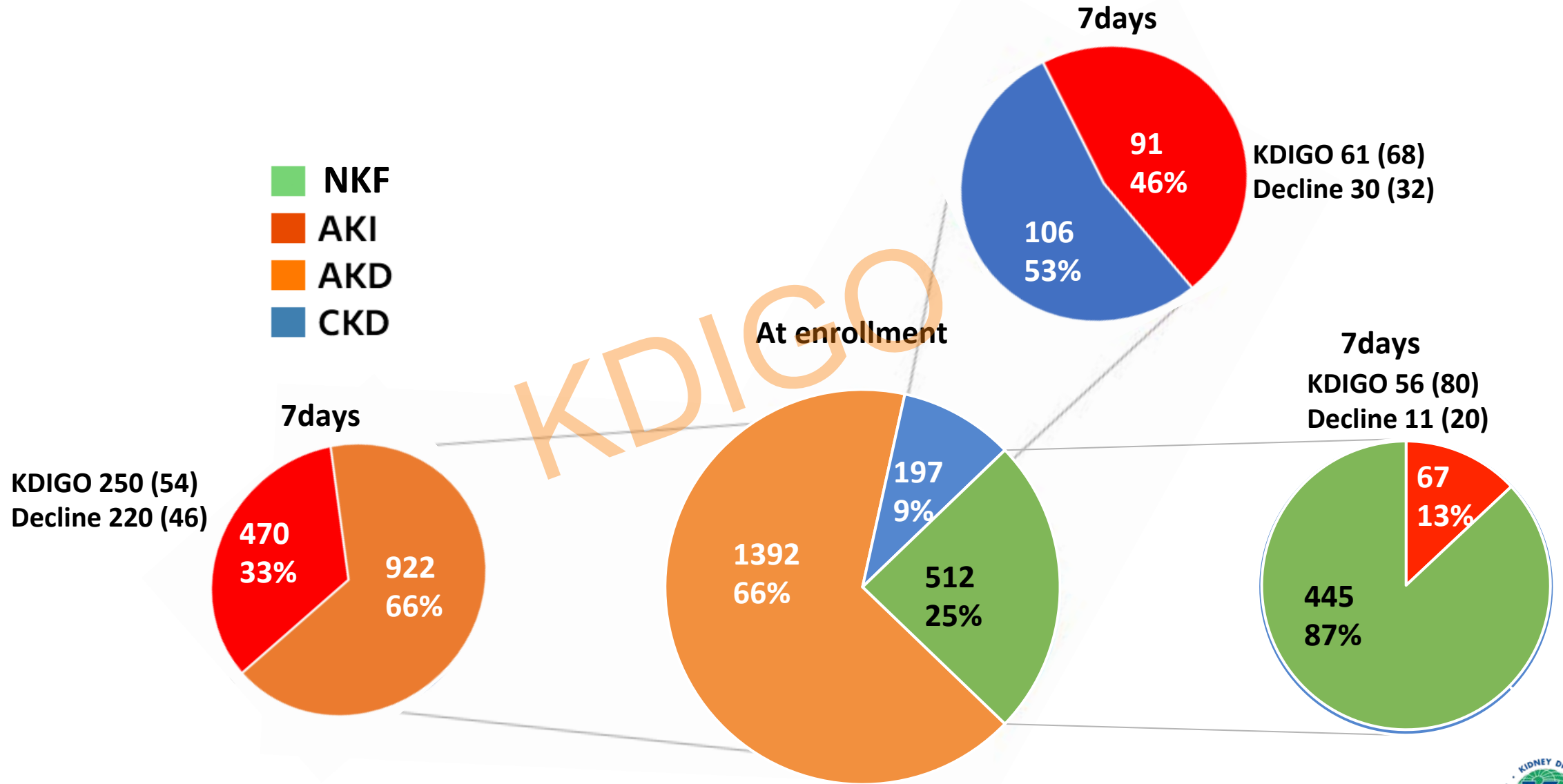
43%

AKD

- ✓ Patients with AKD at enrollment not meeting criteria for AKI within 7 days

The majority of AKI cases 376 (60%) were classified as severe AKI: 138 (22%) stage 2 and 238 (37%) as stage 3.

Renal Function Status at 7 Days



Kidney Recovery During Study Period

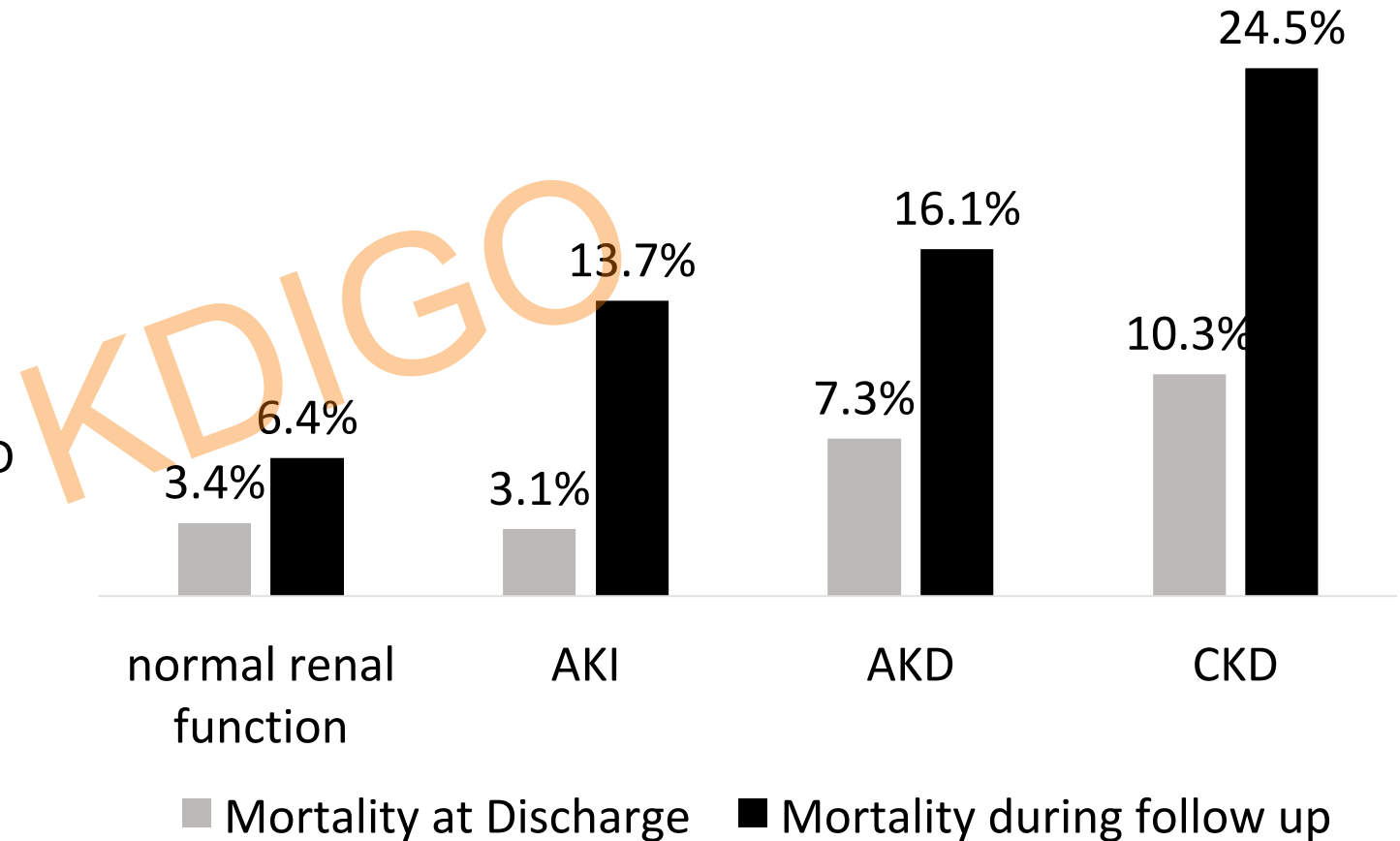
402 with AKI and sCr at 1 month:

- 115 (28%) complete kidney recovery
- 287 (72%) persistent AKI
 - 8 (2%) were on dialysis.

Renal Recovery 6 months	All N=434	Observation N=154	Intervention N=280
new onset CKD	N=168	N=62	N=106
new onset AKD on NKF	12/104 (11)	1/37 (2)	11/67 (16)
new onset CKD in AKD without AKI	75/152 (49)	35/62 (56)	40/90 (44)
new onset CKD in AKI	81/161 (50)	26/49 (53)	55/112 (49)

Mortality by Renal Function at 7-days and Follow up

- ✓ Mortality increased from 5% at discharge to 13% at 6 months
- ✓ Patients with AKI and AKD had higher mortality than those with no renal dysfunction.
- ✓ No significant difference in mortality rate between AKI and AKD group
- ✓ CKD patients had the greatest mortality 24%.



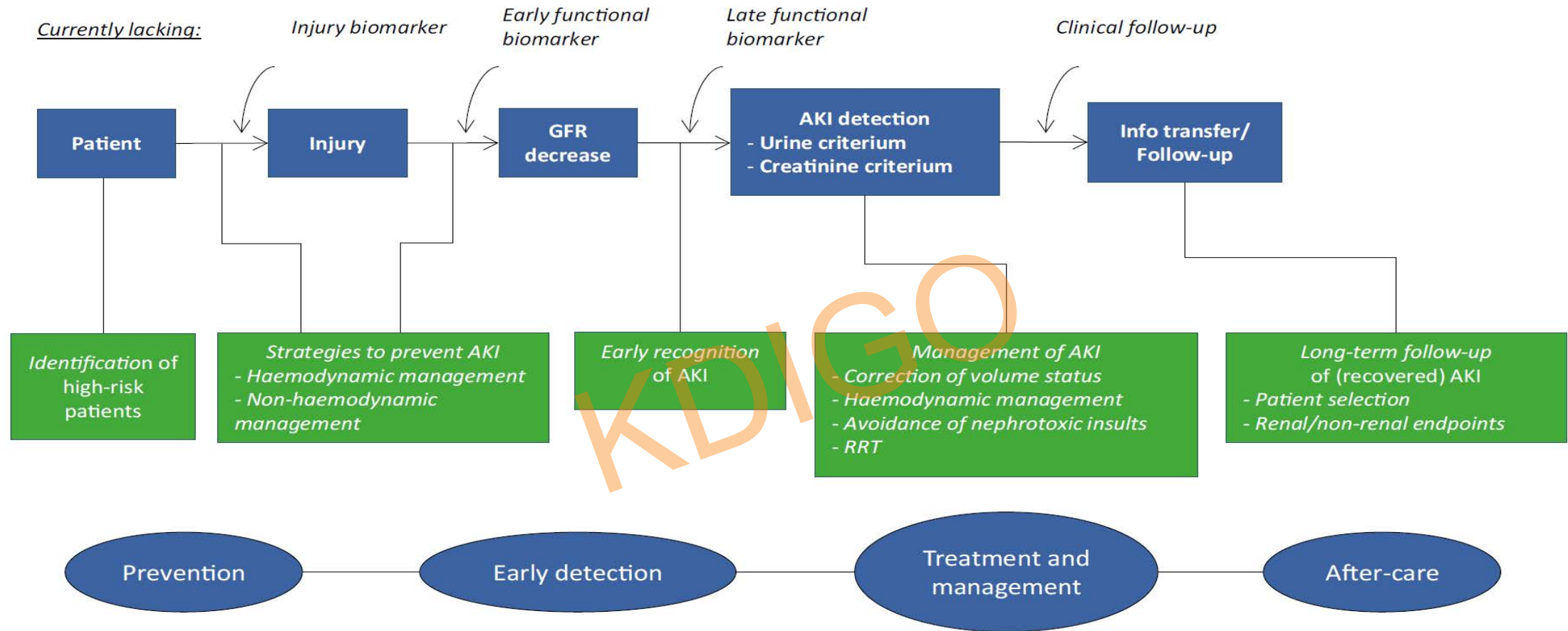
Global Burden of AKI

What we are Learning

- *Gaps in our diagnostic and staging criteria*
- *Community Acquired AKI is underreported*
- *Acute Kidney Disease is not recognized*
- *AKI care is variable and post AKI follow up and care is deficient*

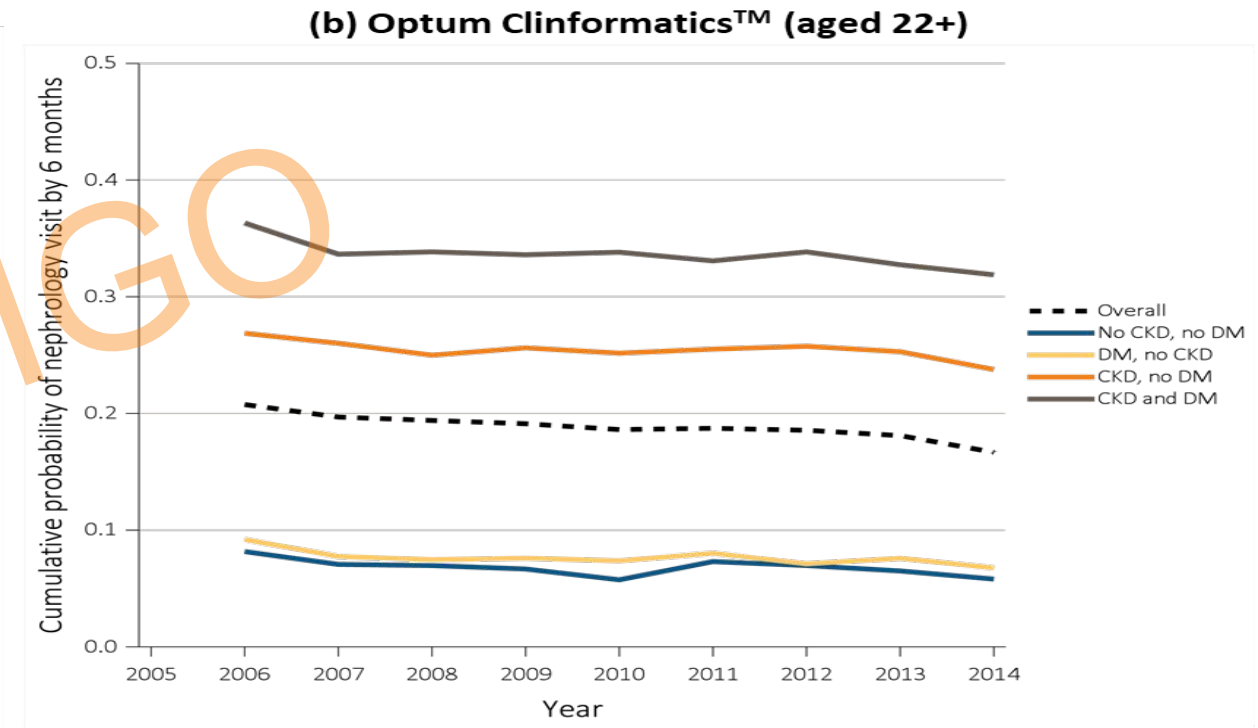
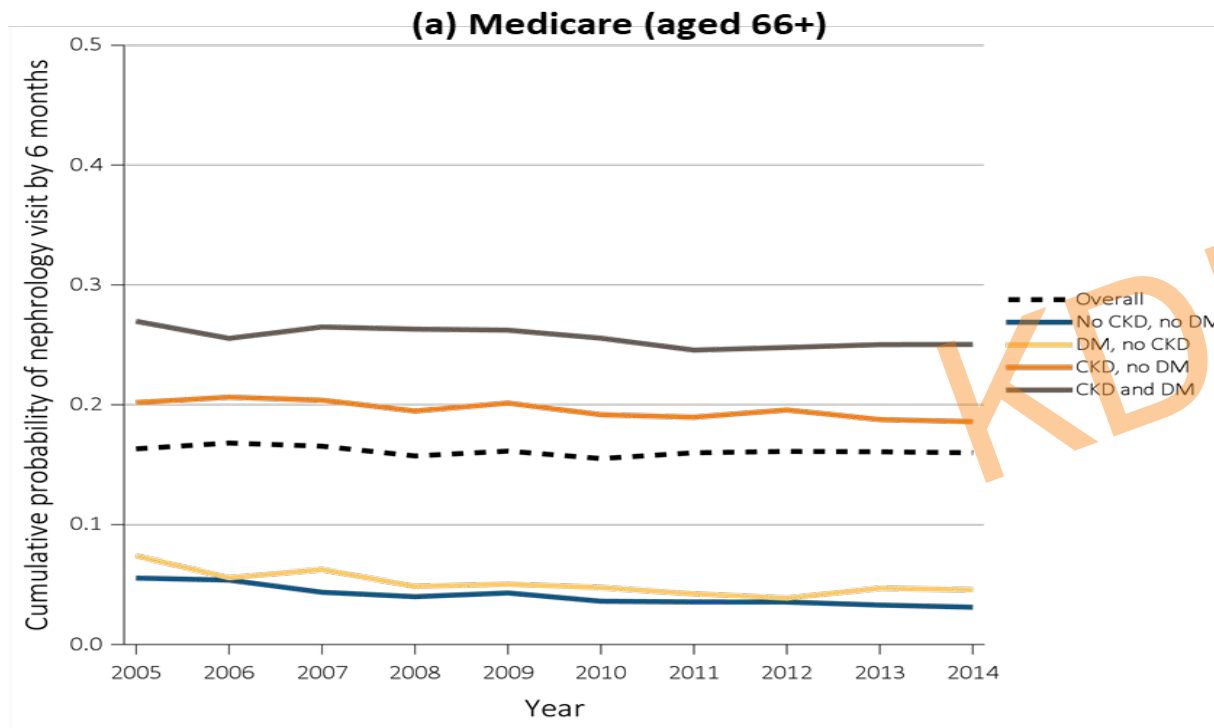


AKI: Current Standard of Care



Current practice is < 50% of the highest risk patients with the most severe forms of AKI receive specialized nephrology follow-up on discharge

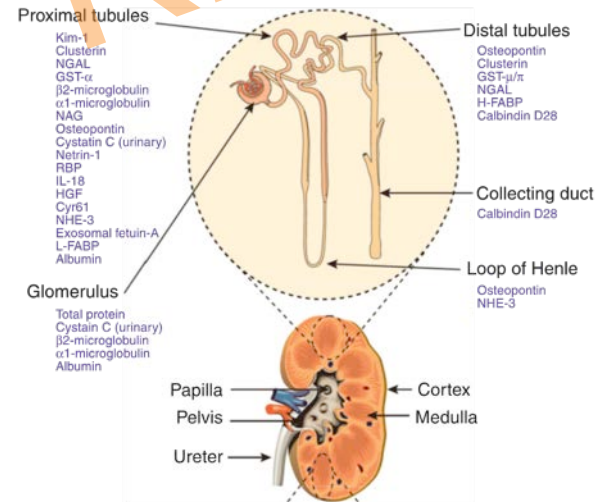
Cumulative probability of a claim for an outpatient nephrology visit within six months of live discharge from first AKI hospitalization, overall and by CKD, DM, 2005-2014



Global Burden of AKI

What we are Learning

- *Gaps in our diagnostic and staging criteria*
- *Community Acquired AKI is underreported*
- *Acute Kidney Disease is not recognized*
- *AKI care is variable and post AKI follow up and care is deficient*
- *Technology is changing how we can improve care*



Global Burden of AKI

Technology can now be leveraged to gather sequential data for recognition application and dynamic adjustments

- Biomarkers
- EHR
- Risk profiling and early recognition
- Decision Support for interventions
- Machine learning and AI
- Telemedicine

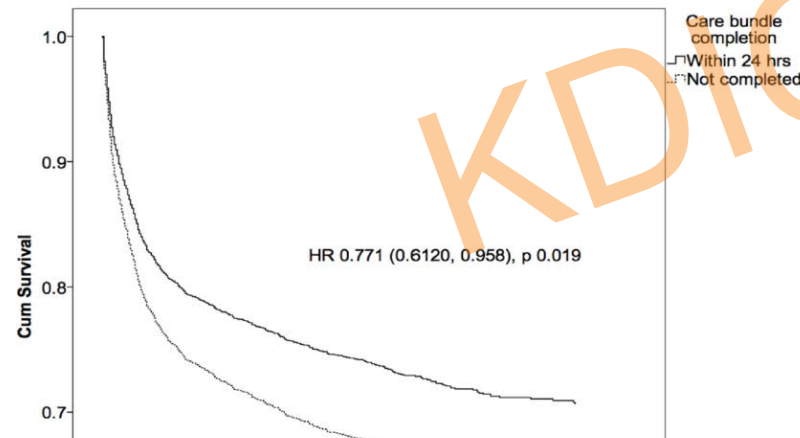
Impact of Compliance with a Care Bundle on Acute Kidney Injury Outcomes: A Prospective Observational Study

- **Design**: Before/After Study (11 months)
- **Population**: 2297 hospitalized patients (2500 AKI episodes)
- **Intervention**:
 - AKI e-alert (interruptive) linked to “care bundle”
 - Interruptive e-alert triggered by attempt to order blood work or medication in a patient identified as having AKI
 - e-Alert would warn provider about AKI and request “care bundle” be completed
 - Once “care bundle” completed – provider could order tests or medications
 - E-alert could be overridden only after provider imputed reason

Results

	Care Bundle completion		P value
	Within 24 hours	Not completed or completed after 24 hours	
Proportion of AKI episodes with progression to higher AKI stage	9 (3.9%)	149 (8.1%)	0.02
Length of stay in days†	11.2 (9.9, 12.4)	12.5 (11.9, 13.1)	0.098
In-hospital case fatality	55 (18%)	506 (23.1%)	0.046
30-day case fatality	77 (25.2%)	626 (28.5%)	0.219
60-day case fatality	83 (27.1%)	673 (30.7%)	0.205

†Mean (95% CI)



Improvement in all outcomes associated with implementation of bundle

No at risk					
ACB completed in 24 hours	306	305	302	271	225
ACB not completed	2194	2028	1845	1654	1418

Fig 3. Adjusted survival curve stratified by timing of completion of AKI Care Bundle.

- In-hospital case-fatality lower in the early CB group (**18% versus 23.1%**, p 0.046).
- Progression to higher AKI stages lower in the early CB group (3.9% vs. 8.1%, p 0.01).
- Patients in the early CB group had lower odds of death at discharge (**0.641; 95% CI 0.46, 0.891**), 30 days (0.707; 95% CI 0.527, 0.950), 60 days (**0.704; 95% CI 0.526, 0.941**) and after a median of 134 days (**0.771; 95% CI 0.62, 0.958**)

- Creatinine tests are largely unavailable at district hospitals and health centres across Malawi
- Only 30% admissions had renal function assessed in rural settings in Ethiopia (Phillips et al, 2013)

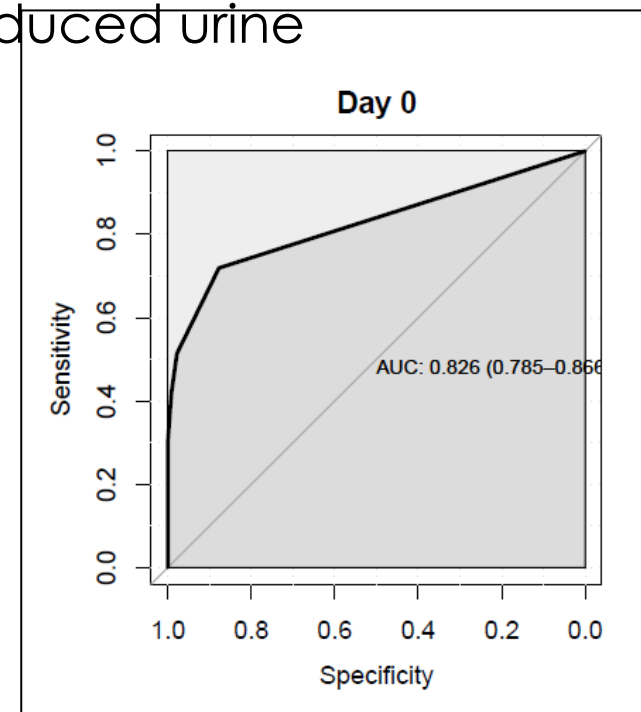


Advantages: cheap, simple, no need electricity, no need refrigerated storage, result in 1 minute

- 742 acute medical admissions at QECH
- 14.7% had kidney disease

To detect kidney disease:

- Sensitivity 71%; Specificity 87% (alone)
- Specificity increased to 97% if used combined with patient reported reduced urine output

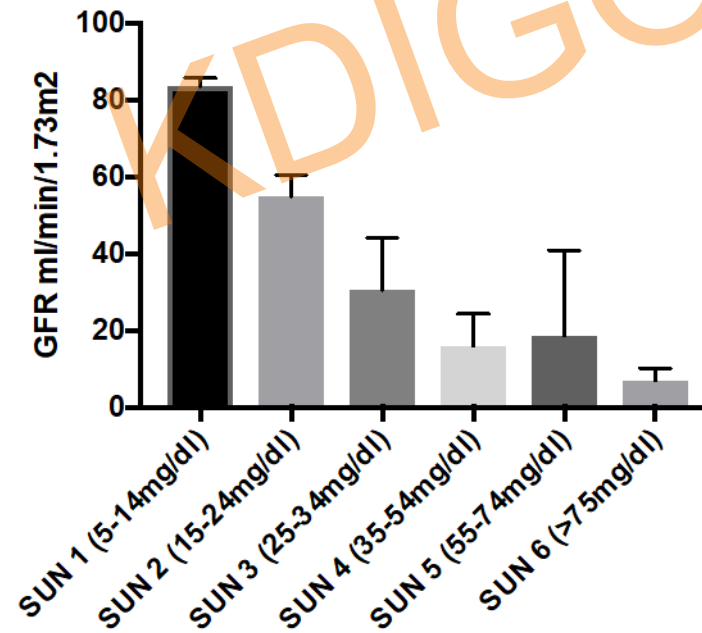


Saliva Urea Nitrogen (SUN) Dipstick Performance in Community Settings in Malawi

- 1479 tests in 774 patients (adults and children) at moderate-high risk of AKI presenting to 1 x central hospital, 1 x district hospital, and 3x health centres in Malawi
- 20% had AKI

To detect $GFR < 30\text{ml/min}$ (presentation):

- Sensitivity 64%; Specificity 85% (alone)
- Area under ROC 0.77 (0.71-0.82)



•Determination of kidney function status

- POC test:
 - sCr fingerpick
 - Urine dipstick
 - Salivary UN



Global Burden of AKI

What is known

What we are learning

- Gaps in our current KDIGO diagnostic criteria lead to a significant % of AKI that is not recognized
- Community acquired AKI is highly prevalent and underreported
- AKD is common and should be considered at initial evaluation and in the course of AKI
- Post AKI care is lacking and often poorly managed even in high resource settings
- Technological advances offer great opportunity to improve recognition and management of AKI

Global Burden of AKI

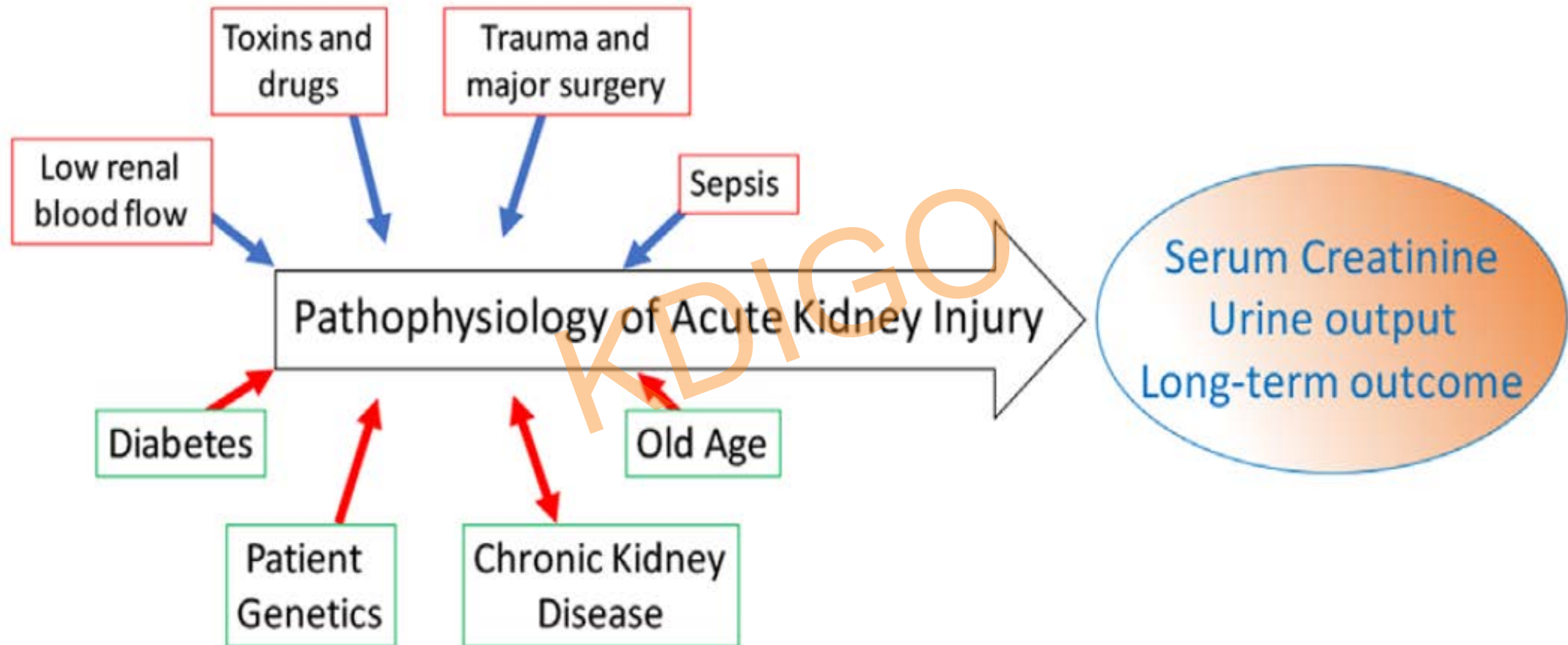
What is known

What we are learning

What we need to know

KDIGO

AKI is still a Conundrum



AKI is still a Conundrum

Does it matter how you get AKI?

- Etiology
- Timing
- Single vs Multiple
- Duration

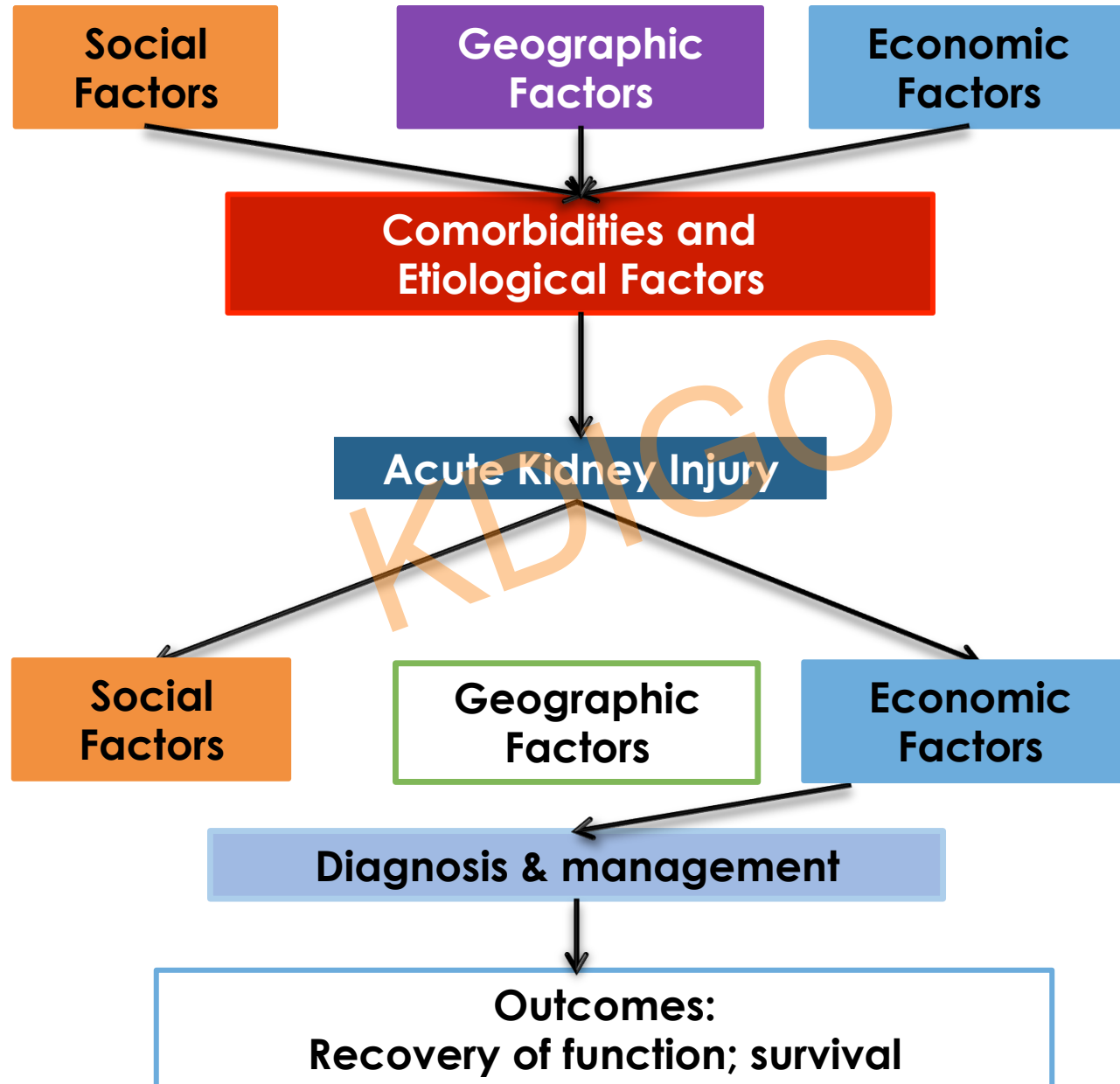
Does the underlying susceptibility matter?

- Genetic
- Comorbidities
- Process of Care

Does what we do for the patient matter?

- Standard of care
- Concurrent care
- Timing of intervention
- Iatrogenic insults

AKI Occurs in a Context:



The diagram illustrates the progression from Population to Patient through the Health care System and Provider, with various factors influencing each stage. The diagram is divided into five vertical columns: Environment, Socioeconomic/Cultural, Process of Care, Exposure, and Inherent. Each column contains a list of factors. A large orange 'X' is drawn across the center, and a blue arrow at the bottom points from 'Resource Limited' to 'Resource Sufficient'.

Population	Health care System	Provider	Patient	
Environment - Water quality - Sanitation - Natural disasters - Earthquake - Famine - Geography - Tropical - High altitude - Politics - War zone	Socioeconomic/Cultural - Housing - Nutrition - Public health - Health care Access - Health insurance - Health care center - Transportation - Health beliefs - Literacy - Access to internet	Process of Care - Level of care - Primary - Tertiary - Timely care - Recognition - Treatment - Follow up - Protocolized care - Checklists - EHR access	Exposure - Infection - Poisoning - Nephrotoxin - Contrast - Antibiotics - NSAIDs - Trauma - Shock - Surgical procedures - Envenomation	Inherent - Age - Gender - Genetics - Comorbidities - Cancer - CKD - Diabetes - Hypertension - Liver disease - Life style

Resource Limited → Resource Sufficient

Settings associated with AKI and Death



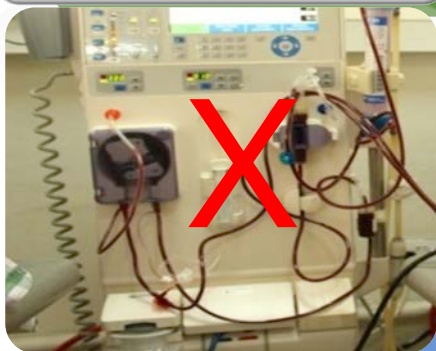
High risk settings

- Lack of clean water
- Envenomation
- Ingestion of toxins
- Endemic infections
- Trauma



Missed or delayed recognition

- No labs to assess renal function
- Inadequate response
- Iatrogenic AKI



No availability for treatment

- Inadequate or no access to dialysis

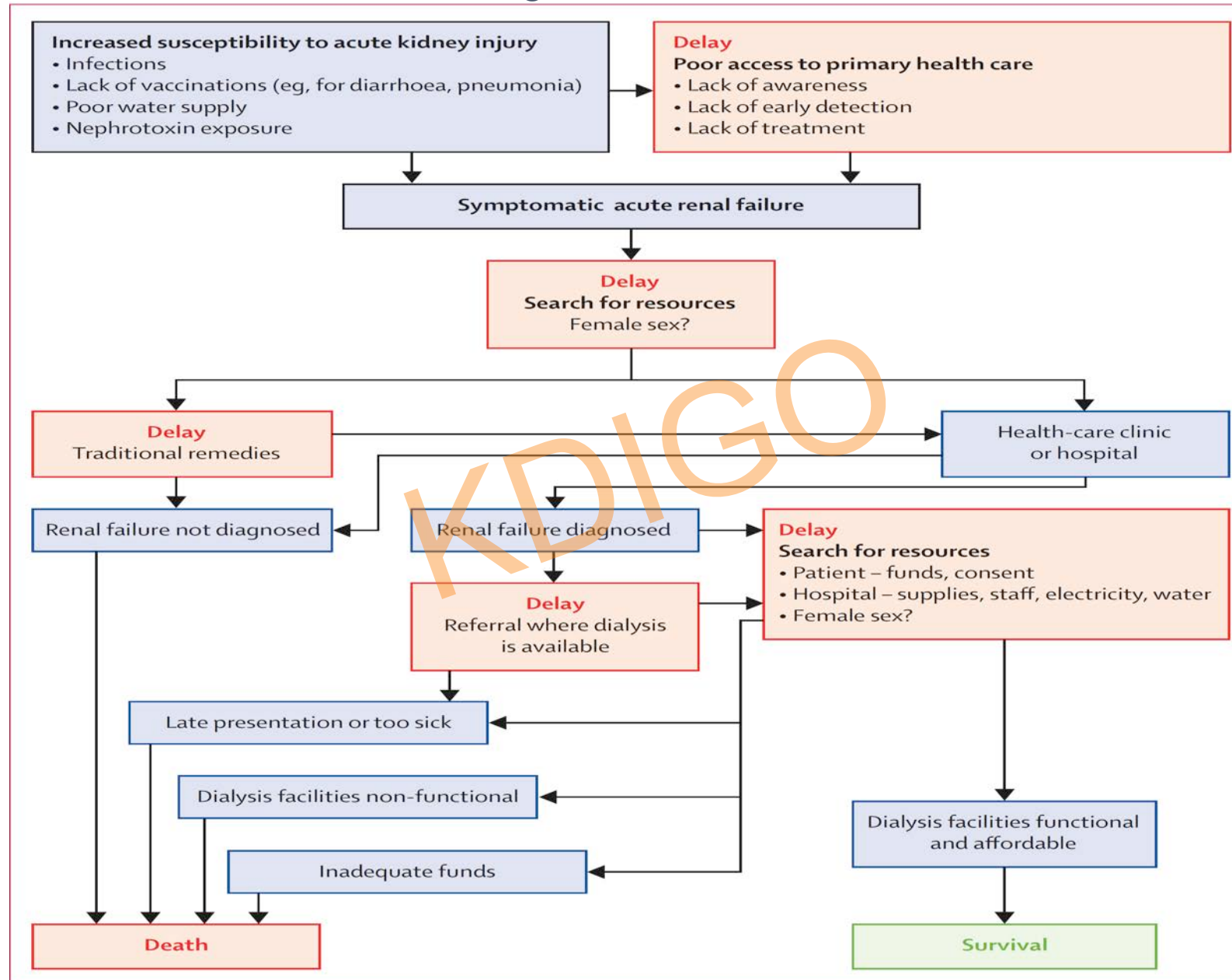
AKI in Africa: Outcomes

	Adult studies			Paediatric studies		
	1990–2009	2010–14	p	1990–2009	2010–14	p
Overall mortality						
Mortality (pooled)	237/639 (37%; n=9)	109/438 (25%; n=8)	<0.0001	285/720 (40%; n=7)	342/1122 (30%; n=14)	<0.0001
Mortality (means of individual studies)	38.7% (20.6)	29.2% (24.5)	0.40	40.5% (8.3)	30.4% (14.4)	0.11
Mortality without dialysis when needed						
Mortality without dialysis when needed (pooled)	43/50 (86%; n=2)	NA	..	179/247 (72%; n=4)	45/57 (79%; n=3)	0.32
Mean mortality without dialysis (means of individual studies)	82.4% (12.8)	NA	..	72.9% (18.8)	90.0% (17.3)	0.27
Mortality with dialysis						
Mortality with dialysis (pooled)	161/500 (32%; n=8)	78/288 (27%; n=6)	0.13	28/119 (24%; n=5)	184/585 (31%; n=10)	0.09
Mean mortality with dialysis (means of individual studies)	28.0% (15.7)	35.1% (26.1)	0.54	16.4% (11.5)	34.6% (20.1)	0.09
Mean mortality haemodialysis (means of individual studies)	27.3% (14.13; n=7)	33.46% (27.00; n=6)	0.61	57.0% (39.9; n=3)		0.27*
Mean mortality peritoneal dialysis (means of individual studies)	25% (n=1)	NA	NA	33.6% (27.4; n=9)		..
Mortality when dialysis not indicated						
Mortality when dialysis not indicated (pooled)	23/43 (53%†; n=2)	NA	..	36/232 (16%; n=4)	43/285 (15%; n=4)	0.84
Mortality, acute kidney injury not needing dialysis (means of individual studies)	30.3% (42.8)	NA	..	22.2% (17.1)	10.2% (8.4)	0.25
Other outcomes						
Recovery of renal function in survivors (pooled)	58/78 (74%; n=2)	72/159 (45%; n=4)	<0.0001	152/172 (88%; n=3)	515/714 (72%; n=8)	<0.0001
Residual chronic kidney disease in survivors (pooled)‡	6/73 (8%; n=1)	18/113 (16%; n=2)	0.1	23/143 (16%; n=2)	45/533 (8%; n=3)	0.007
Left hospital against medical advice (pooled)	0	6/62 (10%; n=1)	..	10/183 (5%; n=2)	33/814 (4%; n=5)	0.4
Lost to follow-up (pooled)	28/264 (11%; n=2)	6/17 (35%; n=1)	..	116/334 (35%; n=2)	20/700 (3%; n=2)	<0.0001

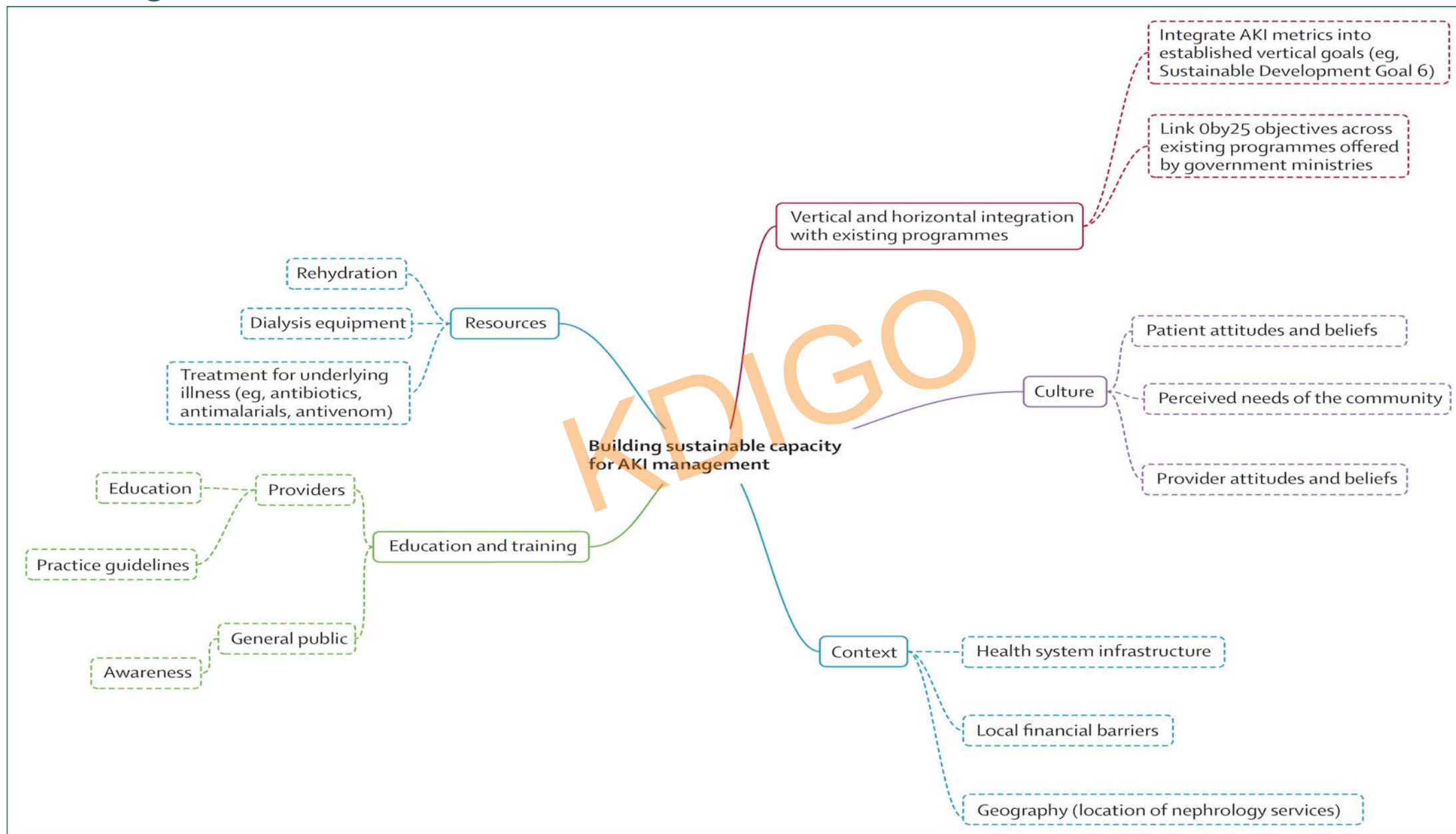
Data are mean % (SD) or mean (%; number of studies with outcome). p values for 1990–2009 versus 2010–14. *Comparison between haemodialysis and peritoneal dialysis in children. †One study included high-comorbidity patients in intensive care units. ‡Chronic kidney disease not specifically defined, generally non-requirement for dialysis but non-return of renal function to normal parameters by discharge or loss to follow-up.

Table 4: Outcomes in children and adults with acute kidney injury

Barriers to Care in AKI in low resource settings

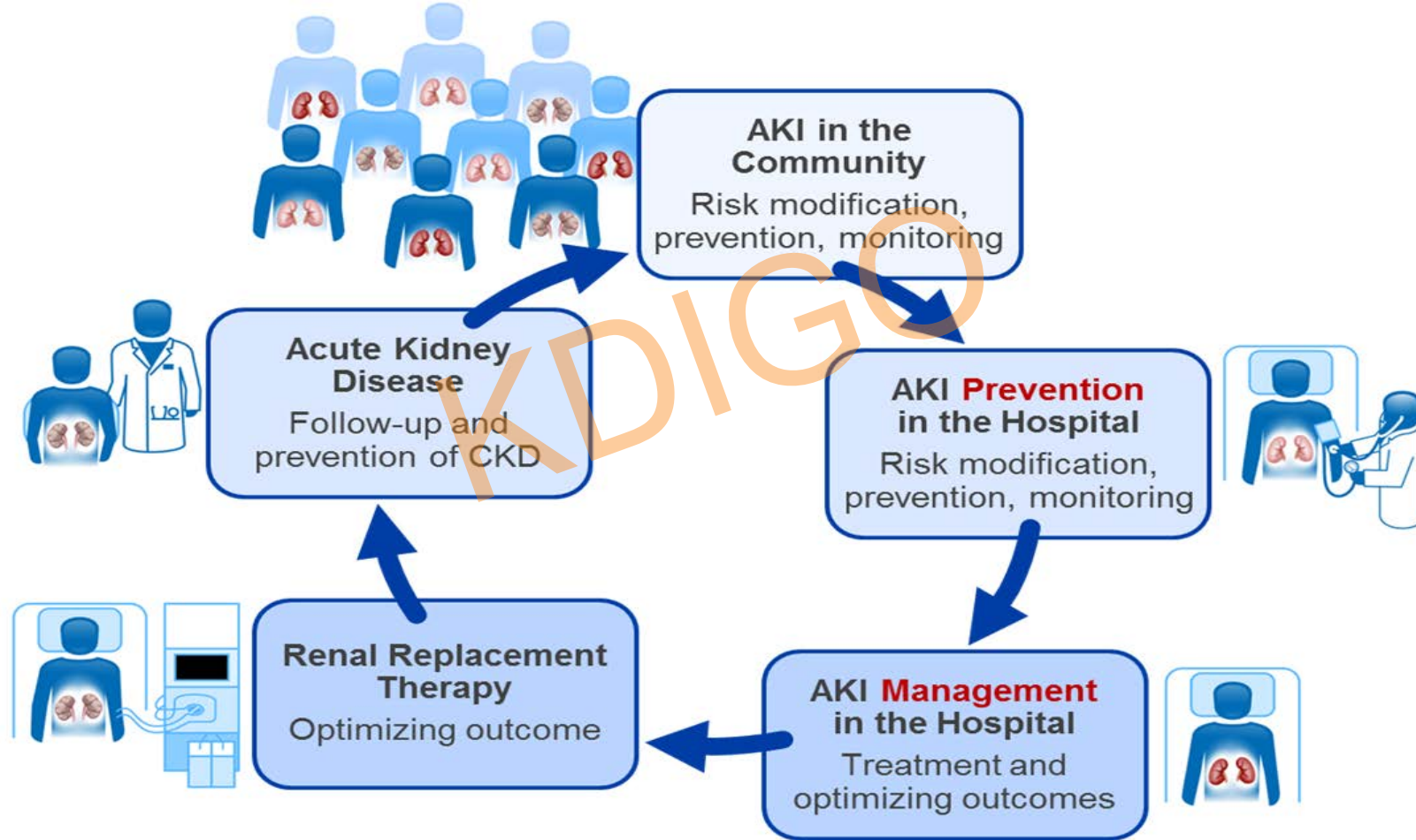


Tackling AKI: What's needed?



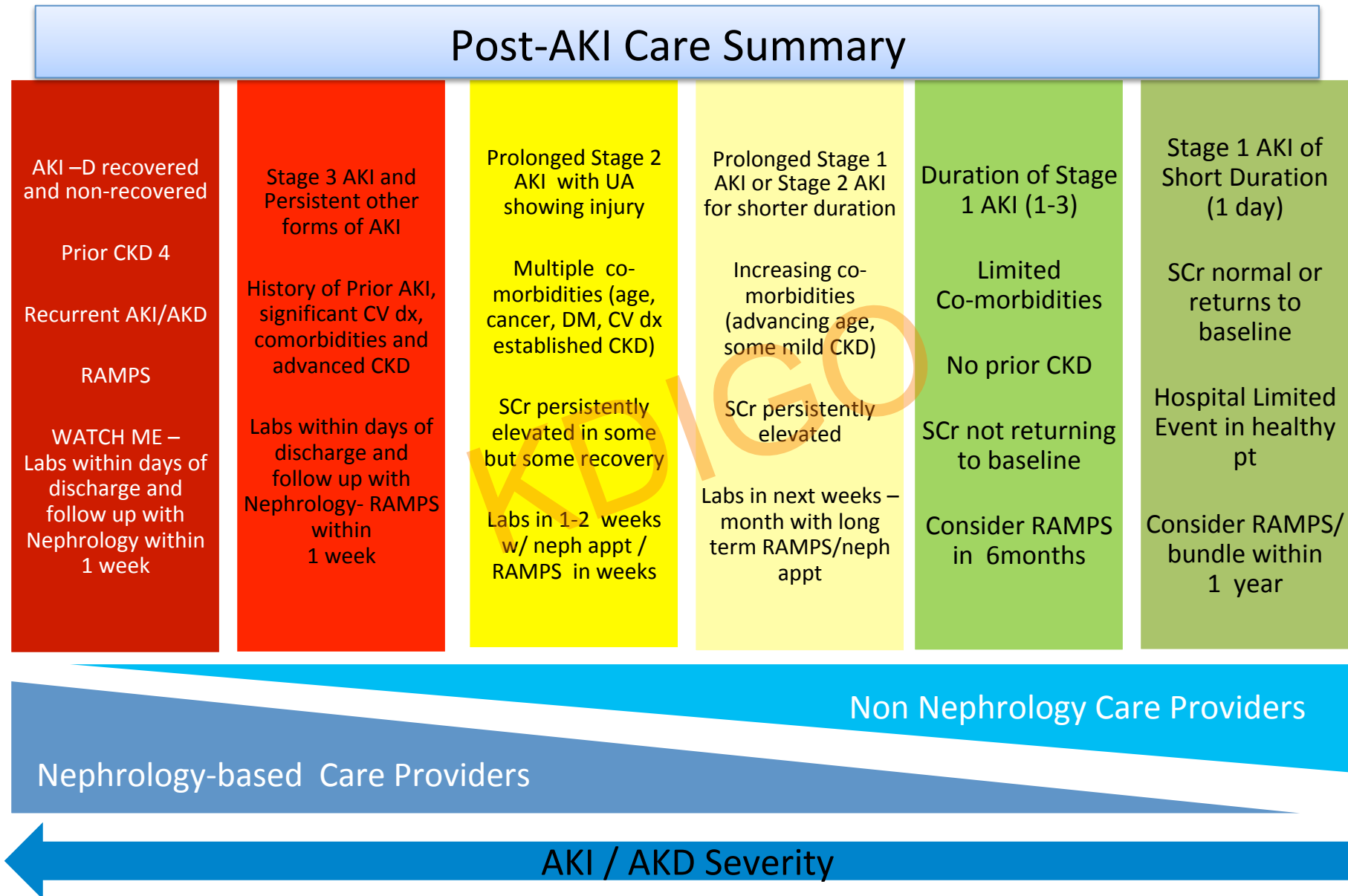
So what is Needed?

AKI care a continuum

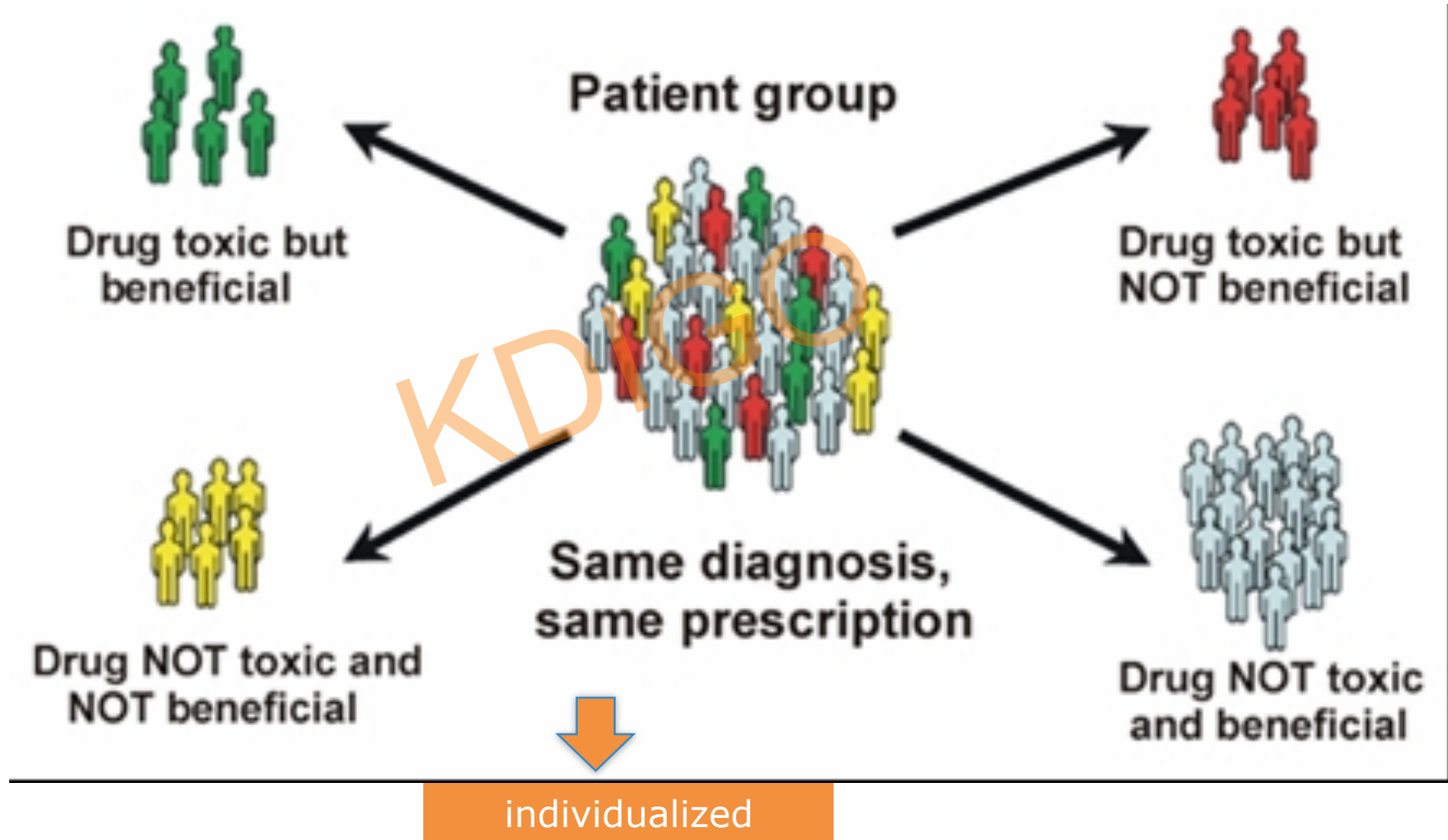


Kashani et al for the ADQI group CJASN 2019 In Press

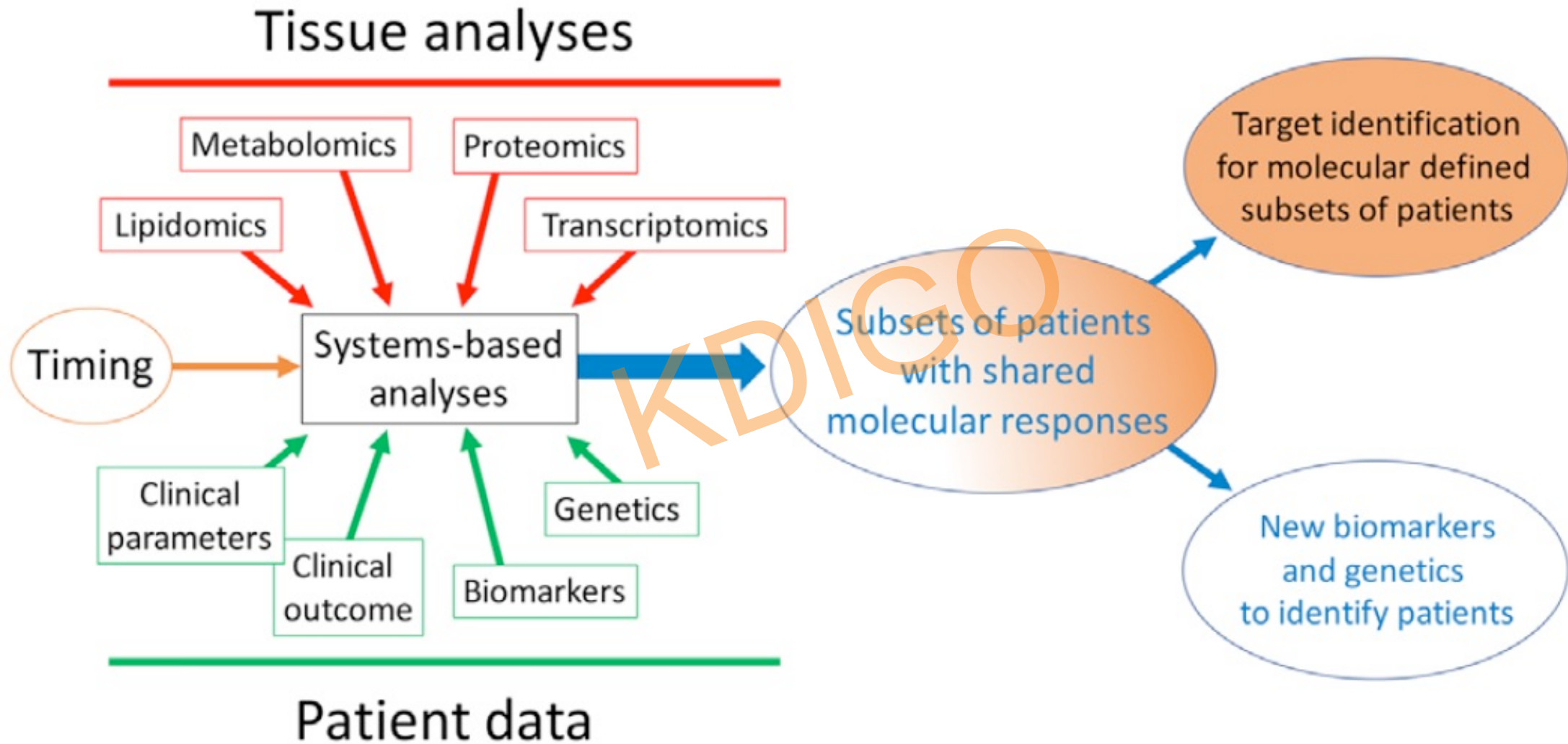
So what is Needed?



Personalized Medicine for AKI



So what is Needed?



Global Burden of AKI

*What is
known*

*What we
are
learning*

What we need to know

- What are determinants of AKI course and outcomes
- How can we personalize care for AKI patients
- What are best approaches for preventing and managing patients across the world
- What are quality metrics for AKI care
- How can we leverage technology to improve patient centered outcomes

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