Online Supplementary Material to:

Acute kidney injury and risk of death after elective surgery: Prospective analysis of data from an international cohort study

H. Chaudery, N. MacDonald, T. Ahmad, S. Chandra, A. Tantri, V. Sivasakthi, M. Mansor, R. Matos, R.M. Pearse and J.R. Prowle on behalf the International Surgical Outcomes Study (ISOS) group*

H. Chaudery	Barts and The London School of Medicine & Dentistry, Queen Mary University of London, UK
N. MacDonald	Department of Anaesthesia, Royal London Hospital, Barts Health NHS Trust, London, UK
T. Ahmad	William Harvey Research Institute, Queen Mary University of London, UK.
S. Chandra	Universitas Indonesia, Ciptomangunkusumo Hospital Jakarta Indonesia.
A. Tantri	Universitas Indonesia, Ciptomangunkusumo Hospital Jakarta Indonesia.
V. Sivasakthi	Ministry of Health of Malaysia, Putrajaya, Malaysia
M. Mansor	University Malaya Medical Centre, Kuala Lumpur, Malaysia
R. Matos	Unidade de Cuidados Intensivos Polivalente Neurocríticos, Hospital de S. José, Centro Hospitalar de Lisboa Central, E.P.E, Lisboa, Portugal
R.M. Pearse	Barts and The London School of Medicine & Dentistry, Queen Mary University of London, UK
J. R. Prowle	Barts and The London School of Medicine & Dentistry, Queen Mary University of London, UK

The ISOS Investigators

Collaborating organisations

- South Yorkshire Surgical Research Group
- Yorkshire Surgical Research Group
- West Midlands Research Collaborative
- Welsh Barbers Research Group
- London Surgical Research Group
- South Yorkshire Hospitals Audit and Research Collaboration (anaesthesia)

Collaborators

Steering committee

- Rupert M. Pearce (chief investigator)
- Scott Beattie
- Pierre-Alain Clavien
- Nicolas Demartines
- Lee A. Fleisher
- Mike Grocott (independent, chair)
- James Haddow
- Andreas Hoeft
- Peter Holt
- Rui Moreno
- Naomi Pritchard (independent, patient representative)
- Andrew Rhodes
- Duminda Wijeyesundera
- Matt Wilson (independent)

Study management group

- Tahania Ahmed (statistician)
- Kirsty Everingham
- Russell Hewson (study websites and information governance)
- Marta Januszewska (study coordinator)
- Rupert M. Pearce (chief investigator)
- Mandeep-Kaur Phull

National Co-ordinators

- Australia: Richard Halliwell, Mark Shulman and Paul Myles
- Austria: Werner Schmid and Michael Hiesmayr
- Belgium: Patrick Wouters and Stefan de Hert
- Brazil: Suzana Lobo
- Canada: Scott Beattie and Duminda Wijesundera
- China: Xiangming Fang
- Denmark: Lars Rasmussen
- France: Emmanuel Futier, Matthieu Biais, Aurélien Venara and Karem Slim
- Germany: Michael Sander
- Greece: Despoina Koulenti and Kostoula Arvaniti
- Hong Kong: Mathew Chan
- India: Atul Kulkarni
- Indonesia: Susilo Chandra and Aida Tantri
- Iraq: Emad Geddoa and Muntadhar Abbas
- Italy: Giorgio Della Rocca
- Malaysia: Datin Sivasakthi and Marzida Mansor
- Mexico: Pastor Luna
- Netherlands: Arthur Bouwman and Wolfgang Buhre
- New Zealand: Vanessa Beavis, Douglas Campbell and Tim Short
- Nigeria: Tunde Osinaike
- Portugal: Ricardo Matos
- Romania: Ioana Grigoras
- Russia: Mikhail Kirov and Denis Protsenko
- South Africa: Bruce Biccard
- Spain: Cesar Aldecoa
- Sweden: Michelle Chew
- Switzerland: Christoph Hofer and Martin Hubner
- Uganda: James Ditai
- United Kingdom: Tamas Szakmany
- United States of America: Lee Fleisher

A full list of investigators can be downloaded from:

[http://isos.org.uk/docs/ISOS%20list%20of%20collaborators%20for%20the%20website 20.02.17.pdf](http://isos.org.uk/docs/ISOS%20list%20of%20collaborators%20for%20the%20website%2020.02.17.pdf)

Supplementary table 1: Outcomes modelling cohort by hospital discharge survival (censored at 30d post-operatively). AKI - Acute kidney Injury, ASA – American Society of Anaesthesiologists, COPD - chronic obstructive pulmonary disease, eGFR – estimated glomerular filtration rate, OR - Odd ratio.

Variables Median (IQR) or n (% of group)	Survived Hospital	Died in Hospital	Univariate ORs (95% CI)	P	Missing
Number of Patients	36161 (99.5)	196 (0.5)			
Age (Years – median, IQR)	58 (45-69)	69 (60-78)	1.055 (1.044-1.067)	<0.001	
Age (Years – mean, range)	56.7 (28-93)	69.0 (18-102)			
High Income Country	22041 (99.3)	145 (0.7)	Reference		
Middle Income Country	14120 (99.6)	51 (0.4)	0.549 [0.399-0.756]	<0.001	
Male sex	17042 (47.1)	118 (60.2)	1.697 (1.274-2.261)	<0.001	
Smoker	6442 (17.9)	41 (21.0)	1.222 (0.865-1.727)	0.295	148
Pre-op Haemoglobin g dl⁻¹	12 (10-13)	13 (12-14)	0.700 (0.657-0.747)		491
Pre-op eGFR ml min⁻¹ 1.73m⁻²	88 (73-91)	67 (43-92)	0.974 (0.969-0.978)	<0.001	
ASA Fitness Grade					45
1-2	26290 (72.8)	34 (17.3)	Reference		
3	8902 (24.6)	110 (56.1)	9.555 (6.499-14.046)	<0.001	
4	924 (2.6)	52 (26.5)	43.52 (28.10-67.38)	<0.001	
Surgical Speciality				<0.001	5
Orthopaedic	7536 (20.8)	22 (11.2)	Reference		
Abdominal	6429 (17.8)	72 (36.7)	3.836 (2.377-6.191)	<0.001	
Cardiothoracic	2658 (7.4)	49 (25.0)	6.315 (3.811-10.463)	<0.001	
Urology & Kidney	4179 (11.6)	9 (4.6)	0.714 (0.41-1.243)	0.442	
Vascular	1433 (4.0)	15 (7.7)	0.738 (0.339-1.604)	<0.001	
Other	13921 (38.5)	29 (14.8)	3.586 (1.856-6.928)	0.233	
Laparoscopic Surgery	6006 (16.6)	15 (7.7)	0.416 (0.245-0.705)	<0.001	9
Co-morbid Disease					
Coronary Artery Disease	3989 (11.1)	63 (32.1)	3.811 (2.819-5.152)	<0.001	81
Heart Failure	1646 (4.6)	47 (24.0)	6.599 (4.736-9.194)	<0.001	81
COPD / Asthma	3255 (9.0)	40 (20.4)	2.586 (1.824-3.667)	<0.001	81
Diabetes Mellitus	5111 (11.5)	58 (28.2)	2.817 (2.06-3.854)	<0.001	80
Stroke	1286 (3.6)	37 (18.9)	6.296 (4.384-9.043)	<0.001	81
Metastatic Cancer	1500 (4.2)	36 (18.4)	6.296 (4.384-9.043)	<0.001	81
Cirrhosis	296 (0.8)	9 (4.6)	5.187 (3.60-7.474)	<0.001	81
Grade of Surgery					
Minor	6404 (17.7)	14 (7.1)	Reference		17
Intermediate	15954 (44.1)	50 (25.5)	1.434 (0.792-2.595)	0.2341	
Major	13786 (38.1)	132 (67.3)	4.38 (2.523-7.604)	<0.001	
AKI					2
None	35490 (98.1)	122 (62.6)	Reference		
Stage 1	393 (1.1)	12 (6.2)	8.88 (4.869-16.25)	<0.001	
Stage 2	175 (0.5)	20 (10.3)	33.20 (20.25-54.57)	<0.001	
Stage 3	102 (0.3)	41 (21.0)	116.90 (78.09-175.08)	<0.001	
Any AKI by Country Income					

<i>All Countries</i>	670 (1.9)	73 (37)	31.7 (23.5-42.8)	<0.001
<i>High Income</i>	587 (2.7)	49 (33.8)	18.9 (13.2 -26.9)	<0.001
<i>Middle Income</i>	83 (0.59)	24 (47.1)	150.3 (83.3-271.4)	<0.001

Supplementary table 2: Odds ratios associated with AKI in the single level multivariable logistic regression (figure 1) and a similarly specified mixed-effects logistic regression model with a random intercept for country and in the single level model with an interaction term between AKI and country income status.
AKI, Acute Kidney Injury; OR, Odds Ratio

	Single Level Model	Mixed Effects with Random Intercept for Country	Interaction term for Country Income Status	
			<i>High Income</i>	<i>Middle Income</i>
No AKI	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
AKI 1	2.57 (1.33 -4.96)	2.63 (1.62-4.29)	2.08 (1.01-4.29)	8.48 (1.82-39.5)
AKI 2	8.64(4.95- 15.1)	8.47 (5.60-12.8)	3.87 (1.80-8.33)	51.20 (20.1-130.2)
AKI 3	30.1 (18.5- 49.0)	31.9 (22.1-45.9)	19.7 (11.4-33.7)	331.5 (96.7-1136.3)

Box 1: Full specification of logistic regression model for hospital mortality. Prior to variable selection the full model had 28 degrees of freedom and a log likelihood ratio Chi-squared of 720, a shrinkage estimate of $(720-28)/720 = 0.95$ (>0.90), suggests data reduction prior to variable selection was not required to avoid over-fitting (Harrell, FE 2015 Regression Modelling Strategies 2nd edition, Springer, New York section 4.7.7).

Logistic Regression Model for Hospital Mortality							
		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	35722	LR chi2	721.98	R2	0.309	C	0.917
1	35530	d.f.	22	g	1.618	Dxy	0.835
2	192	Pr(> chi2)	<0.0001	gr	5.044	gamma	0.875
max deriv	7e-06			gp	0.009	tau-a	0.009
				Brier	0.005		
				Coef	S.E.	Wald Z	Pr(> Z)
Intercept				-4.4989	1.1181	-4.02	<0.0001
baseline_ASA=3				1.0950	0.2205	4.97	<0.0001
baseline_ASA=4				1.9348	0.2758	7.01	<0.0001
meta_cancer=1				1.0456	0.2195	4.76	<0.0001
baseline_stroke=1				1.0492	0.2152	4.87	<0.0001
baseline_Severityofsurgery=2				0.4084	0.3241	1.26	0.2077
baseline_Severityofsurgery=3				0.7952	0.3102	2.56	0.0104
baseline_Laparoscopicsurgery=1				-0.7108	0.2934	-2.42	0.0154
baseline_Age				0.0001	0.0140	0.01	0.9951
baseline_Haemoglobin				-0.1710	0.0392	-4.36	<0.0001
baseline_Surgical_procedure=Abdominal				1.2453	0.2724	4.57	<0.0001
baseline_Surgical_procedure=Cardiothoracic				0.7752	0.2935	2.64	0.0083
baseline_Surgical_procedure=Other				0.0479	0.3084	0.16	0.8767
baseline_Surgical_procedure=Urology & Kidney				-0.3838	0.4291	-0.89	0.3711
baseline_Surgical_procedure=Vascular				0.3343	0.3646	0.92	0.3591
eGFR				-0.0431	0.0140	-3.07	0.0021
eGFR'				0.0053	0.0348	0.15	0.8782
eGFR''				0.3834	0.3629	1.06	0.2907
eGFR'''				-1.1192	0.8456	-1.32	0.1857
AKI=AKI Stage 1				0.9432	0.3363	2.80	0.0050
AKI=AKI Stage 2				2.1565	0.2839	7.60	<0.0001
AKI=AKI Stage 3				3.4058	0.2479	13.74	<0.0001
baseline_Age * eGFR				0.0005	0.0002	2.49	0.0128
Wald Statistics							
Factor		Chi-Square		d.f.	P		
baseline_ASA		49.28		2	<.0001		
meta_cancer		22.70		1	<.0001		
baseline_stroke		23.76		1	<.0001		
baseline_Severityofsurgery		8.86		2	0.0119		
baseline_Laparoscopicsurgery		5.87		1	0.0154		
baseline_Age (Factor+Higher Order Factors)		23.58		2	<.0001		
All Interactions		6.20		1	0.0128		
baseline_Haemoglobin		18.98		1	<.0001		
baseline_Surgical_procedure		43.01		5	<.0001		
eGFR (Factor+Higher Order Factors)		14.85		5	0.0110		
All Interactions		6.20		1	0.0128		
Nonlinear		13.45		3	0.0038		
AKI		212.28		3	<.0001		
baseline_Age * eGFR (Factor+Higher Order Factors)		6.20		1	0.0128		
TOTAL NONLINEAR + INTERACTION		14.75		4	0.0052		
TOTAL		661.44		22	<.0001		

Box 2: Full specification of logistic regression model for AKI Stages 1-3

Logistic Regression Model for AKI Stages 1-3									
		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes			
Obs	35722	LR chi2	1432.47	R2	0.217	C	0.857		
FALSE	34991	d.f.	19	g	1.634	Dxy	0.715		
TRUE	731	Pr(> chi2)	<0.0001	gr	5.122	gamma	0.727		
max lderiv	1e-07			gp	0.028	tau-a	0.029		
				Brier	0.019				
				Coef	S.E.	Wald Z	Pr(> Z)		
Intercept				-2.7829	0.3295	-8.45	<0.0001		
baseline_Gender=M				0.4058	0.0849	4.78	<0.0001		
baseline_ASA=3				0.4667	0.0979	4.77	<0.0001		
baseline_ASA=4				1.0371	0.1463	7.09	<0.0001		
baseline_heart_failure=1				0.4285	0.1092	3.92	<0.0001		
baseline_cirrhosis=1				0.9969	0.2286	4.36	<0.0001		
baseline_Severityofsurgery=2				0.7651	0.1863	4.11	<0.0001		
baseline_Severityofsurgery=3				1.5662	0.1797	8.72	<0.0001		
baseline_Laparoscopicsurgery=1				-0.3540	0.1278	-2.77	0.0056		
baseline_Haemoglobin				-0.1237	0.0207	-5.97	<0.0001		
baseline_Surgical_procedure=Abdominal				0.9273	0.1365	6.79	<0.0001		
baseline_Surgical_procedure=Cardiothoracic				0.9444	0.1390	6.79	<0.0001		
baseline_Surgical_procedure=Other				-0.1901	0.1528	-1.24	0.2136		
baseline_Surgical_procedure=Urology & Kidney				0.6339	0.1493	4.25	<0.0001		
baseline_Surgical_procedure=Vascular				0.4943	0.1747	2.83	0.0047		
eGFR				-0.0128	0.0033	-3.89	0.0001		
eGFR'				-0.0686	0.0171	-4.00	<0.0001		
eGFR''				0.7248	0.1986	3.65	0.0003		
eGFR'''				-1.6629	0.5274	-3.15	0.0016		
Income=Middle				-0.7157	0.1128	-6.34	<0.0001		
Wald Statistics									
Factor		Chi-Square		d.f.	P				
baseline_Gender		22.86	1	<.0001					
baseline_ASA		51.19	2	<.0001					
baseline_heart_failure		15.39	1	0.0001					
baseline_cirrhosis		19.01	1	<.0001					
baseline_Severityofsurgery		126.02	2	<.0001					
baseline_Laparoscopicsurgery		7.67	1	0.0056					
baseline_Haemoglobin		35.69	1	<.0001					
baseline_Surgical_procedure		104.08	5	<.0001					
eGFR		215.72	4	<.0001					
Nonlinear		16.04	3	0.0011					
Income		40.22	1	<.0001					
TOTAL		1176.67	19	<.0001					

Supplementary figure 1: Data selection for the ISOS AKI secondary study. Of the initial 30 countries 3 were excluded for having <8 hospitals and 1 (the only low income nation) was excluded as no surgical patients had baseline creatinine measurements leaving data from 26 high and 7 middle income nation or administrative regions.

Supplementary figure 2: The effect of pre-operative eGFR, Age and AKI status on risk of hospital mortality in a mixed effects model with random intercept by country, values plotted for an ASA 3 patient, undergoing major abdominal surgery in the country with mean risk of death closest to the overall study mean, all other co-variables and factors at median/reference values. Risk prediction is near-identical to the single level model in the main analysis (c.f. Main Figure 2). Note error margins are not shown as there are no accepted methods for computing standard errors of predictions from generalized linear mixed models because it is difficult to define an efficient method that incorporates uncertainty in the variance parameters. Probability of death in hospital is plotted versus eGFR at ages 35, 58 and 76 representing the 12.5th, 50th and 87.5th centiles (mid Q1, median and mid Q4). AKI, Acute Kidney Injury; eGFR, estimated glomerular filtration rate.

Supplemental figure 3: Modelling effect of age, pre-operative eGFR and AKI status in high and middle income countries, while risk of death is similar in the absence of AKI. AKI diagnosis appears to confer significantly greater risk of death in middle income settings, however small numbers of patients with AKI and potential for bias toward making diagnosis of AKI only in sicker patients in more resource limited settings mean this finding should be interpreted with caution. Probability of death in hospital is plotted versus eGFR at ages 35, 58 and 76 representing the 12.5th, 50th and 87.5th centiles (mid Q1, median and mid Q4). AKI, Acute Kidney Injury; eGFR, estimated glomerular filtration rate.

Supplementary figure 4: Logistic Regression for AKI Stages 1-3. Reference category noted where appropriate, odds ratios, limits of the 95% confidence interval and corresponding p-values are shown. For continuous variables a comparison between a specific value and a reference value is shown to illustrate the spread of risk over the majority of the population. For pre-operative GFR this is from 90 (population median) to 60 (boundary of CKD stage 3). For pre-operative haemoglobin this was chosen at 10g dl⁻¹ (close to the 10th centile) vs. the median 13g dl⁻¹ as reference. Full model specified in Box S2. AKI-Acute kidney Injury, ASA – American Society of Anaesthesiologists, COPD - chronic obstructive pulmonary disease, eGFR – estimated glomerular filtration rate.

Supplementary figure 5: Relationship between pre-operative eGFR and risk of AKI in multivariable modelling illustrating the restricted cubic spline with increasing risk of AKI from GFR $<90\text{ mL min}^{-1} 1.73\text{ m}^{-2}$. Adjusted to ASA 3, Abdominal Surgery, Major Surgery, High Income Nation, medians/reference value for other covariates/factors. Full model specified in Box S2. AKI-Acute kidney Injury, eGFR – estimated glomerular filtration rate.