Renal safety of hydroxyethyl starch 130/0.42 after cardiac surgery: A retrospective cohort analysis

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Table S1: Variables extracted during the retrospective analysis, the corresponding units and operationalization, the definition and measurement, and the data source.

	Variable	Unit/ Operationalization	Definition& Measurement	Data source
Patient	Age	n/a	Taken as reported in the electronic health record.	Electronic health record
	Sex	Male/female	Taken as reported in the electronic health record.	Electronic health record
	90-Day mortality	Binary yes/no	Patient death within 90 days from surgery. Measured during 90 day follow-up and documented in electronic health record.	Electronic health record
	Comorbidities			
Comorbidities	Atrial fibrillation	Binary yes/no	A reported persistent, intermittent, or chronic atrial fibrillation was defined as an atrial fibrillation.	Electronic health record
	Body mass index	n/a	Calculated from the patient's weight at admission and the patient's height.	Electronic patient char
	Current or previous smoking	Binary yes/no	Current smoking or reported previous smoking as reported in the electronic health record.	Electronic patient char
	Diabetes	Binary yes/no	A reported Typ I or Typ II diabetes without treatment, treated with insulin or oral medication, or treated by dietary measures was defined as diabetes.	Electronic health record
	Hyperlipidemia	Binary yes/no	Defined as a reported hyperlipidemia in the electronic health record.	Electronic health record
	Hypertension	Binary yes/no	Hypertension was taken as reported in the electronic health record. Categories untreated hypertension and treated hypertension were grouped as arterial hypertension.	Electronic health record
	Left ventricular function:	[%]	Left ventricular function was available in different stages: good > 50 %, medium 31-50 %, bad 21-30 %, and very bad ≤ 20 %.	Electronic health record

	Logistic EUROSCORE		EUROSCORE as defined by Eur J Cardiothorac Surg. 2012 41(4):734.	Electronic health record
	NYHA	Categorical	NYHA classification in the categories I, II, II-III, III, and IV as defined by the New York Heart Association.	Electronic health record
	Peripheral artery disease	Binary yes/no	A reported peripheral artery disease in the electronic health record.	Electronic health record
	Pulmonary arterial hypertension	Binary yes/no	A reported pulmonary hypertension as reported in the electronic health record.	Electronic health record
	Systolic Arterial Pressure	[mmHg]	Systolic arterial pressure defined as the measured blood pressure on admission to the ICU.	Electronic patient char
	Laboratory parameters			
Laboratory	Serum creatinine	[mg/dl]	Urea as measured during stay in 12 h intervals and reported in the laboratory software.	Laboratory software
	Max. creatinine on ICU	[mg/dl]	Max. serum creatinine during the ICU stay as measured in the hospital laboratory.	Laboratory software
	(Preoperative) creatinine	[mg/dl]	Serum creatinine measurement at patient hospital admission.	Laboratory software
	Estimated glomerular filtration rate	[mL/min]	Glomerular filtration rate was estimated with the CKD-EPI formula of the ‘chronic kidney disease epidemiology collaboration’ and calculated in the laboratory software.	Laboratory software
	Hemoglobin	[g/dl]	Hemoglobin as measured during stay in 12 h intervals and reported in the laboratory software.	Laboratory software
	Lactate	[mg/dl]	Serumlactate as measured during stay in 12 h intervals and reported in the laboratory software.	Laboratory software

	Leucocytes	[/nl]	Leucocytes as measured during stay in 12 h intervals and reported in the laboratory software.	Laboratory software
	Thrombocytes	[/nl]	Thrombocytes as measured during stay in 12 h intervals and reported in the laboratory software.	Laboratory software
	Urea	[mg/dl]	Urea as measured during stay in 12 h intervals and reported in the laboratory software.	Laboratory software
	Surgical parameters			
Surgical parameters	Aortic clamp time	[min]	Aortic cross clamp time was defined as time from the clamping start to release of the aorta.	Electronic health record
	Bypass time	[min]	Cardiopulmonary bypass time was defined as time on cardiopulmonary bypass.	Electronic health record
	Intraoperative blood transfusion	[mL]	Total volume of erythrocytes concentrate which was substituted during surgery.	Electronic health record
	Intraoperative fresh-frozen plasma substitution	[mL]	Total volume of fresh-frozen plasma which was substituted during surgery.	Electronic health record
	Intraoperative thrombocyte concentrate substitution	[mL]	Total volume of thrombocyte concentrates which was substituted during surgery.	Electronic health record
	Surgery time	[min]	Surgery time was defined as time from skin cut until skin suture.	Electronic health record
	ICU parameters			
ICU	Drain losses	[ml]	Defined as the cumulative volume lost over indwelling drains measured at bedside and documented in the electronic patient chart.	Electronic patient chart

	Mean arterial pressure	[mmHg]	Measured at bedside and taken in 12 h intervals as reported in the electronic patient chart.	Electronic patient chart
	Postoperative blood transfusion	[ml]	Defined as the cumulate volume of erythrocyte concentrates administered postoperatively.	Electronic patient chart
	Ventilation time	[min]	Time patient was mechanically ventilated on ICU until extubation.	Electronic patient chart
	Systolic arterial pressure	[mmHg]	Measured at bedside and taken in 12 h intervals as reported in the electronic patient chart.	Electronic patient chart
	Urine output	[ml]	Urine output during ICU stay in ml/h. Measurements were summed up in 12 h intervals.	Electronic patient chart
	Medication			
Medication	Catecholamine	Binary yes/no	The administration of noradrenaline, adrenaline, dobutamine during the ICU stay was grouped as binary indicator catecholamine.	Electronic patient chart
	HES dose	[mL]	The administered volume of HES. HES was used as a 130/0.42 solution	Electronic patient chart
	Crystalloid dose	[mL]	The total dose of administered crystalloid infusion (ringer solution)	Electronic patient chart
	Furosemide	Binary yes/no	Defined as the administration of furosemide as reported in the patient chart during the ICU stay	Electronic patient chart
	Mannitol	Binary yes/no	Defined as the administration of mannitol as a binary indicator	Electronic patient chart
	Nephrotoxic drugs	Binary yes/no	The administration of vancomycin, gentamicin, tobramycin, amikacin, piperacillin/tazobactam, colistin, cotrimoxazole, lithium, acyclovir, tacrolimus, ciclosporine, etoricoxib, diclofenac, and ibuprofen was defined as the binary indicator nephrotoxic drugs	Electronic patient chart

Abbreviations: HES: Hydroxyethylstarch | **ICU:** Intensive Care Unit

Table S2: STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8, supplementary
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of	6-8, supplementary

		assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	7-9
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	n/a
		(*e*) Describe any sensitivity analyses	8-9. supplementary
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-10, table 1
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10, supplementary
		(b) Indicate number of participants with missing data for each variable of interest	8, 9-10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10-11

		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a
		Cross-sectional study—Report numbers of outcome events or summary measures	10-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10, supplementary
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page

Tab. S3: Matching table describing cohort generation by patient characteristics before and after matching (sensitivity analysis).

Matching variable (mean or proportion)	HES before	Control before	HES matched	Control matched	Percent Balance Improvement
Age	69.85	69.05	69.78	69.79	98.57 %
Sex	0.73	0.77	0.73	0.72	90.29 %
Body-mass index	28.49	27.85	28.56	27.97	9.40 %
Preoperative serum creatinine	1.09	0.95	1.06	1.05	93.16 %
EUROSCORE	6.99	6.37	6.91	6.99	87.39 %
Left ventricular function	1.47	1.4	1.46	1.47	71.59 %
Atrial fibrillation	0.22	0.14	0.21	0.23	66.78 %
Diabetes	0.36	0.34	0.36	0.34	31.02 %
Catecholamines	0.62	0.77	0.63	0.64	98.34 %
Nephrotoxic drugs	0.06	0.08	0.06	0.06	86.54 %
Furosemide	0.96	0.97	0.96	0.96	16.71 %
Mannitol	0.01	0	0.01	0.01	36.04 %
Drain-losses	882.95	1158.89	889.81	878.91	96.05 %
Mean arterial pressure	109.78	109.58	110.06	110.41	-72.50 %
Systolic blood pressure	159.15	159.49	159.11	158.59	-55.11 %
Intraoperative blood transfusion	200.29	349.69	200.3	204.94	96.89 %
All blood transfusion	282.07	353.46	284.43	305.69	70.22 %
Surgery time	197.72	223.87	199.85	199.96	99.58 %

Tab. S4: Propensity-weighted and propensity-matched analysis for sensitivity analysis.

Propensity-score weighted analysis (N = 2188)	**Odds Ratio**	**Confidence Interval 95 %**
Hydroxyethylstarch infusion[a]	0.93	[0.89-0.97]
Propensity-score matched analysis (N = 1014)	**Odds Ratio**	**Confidence Interval 95 %**
Hydroxyethylstarch infusion[a]	0.85	[0.77-0.94]

a: Per 500 mL

Analysis: In particular, the propensity-weighted analysis was based on average treatment effect (ATE) weights assigned to groups with HES (1/eˆ˙(x))) or without HES (1/(1-eˆ˙(x))). The propensity-matched analysis was based on a linear logit model to select HES patients and controls at a 3:1 ratio with a caliper of 0.1 in a nearest neighbour matching.

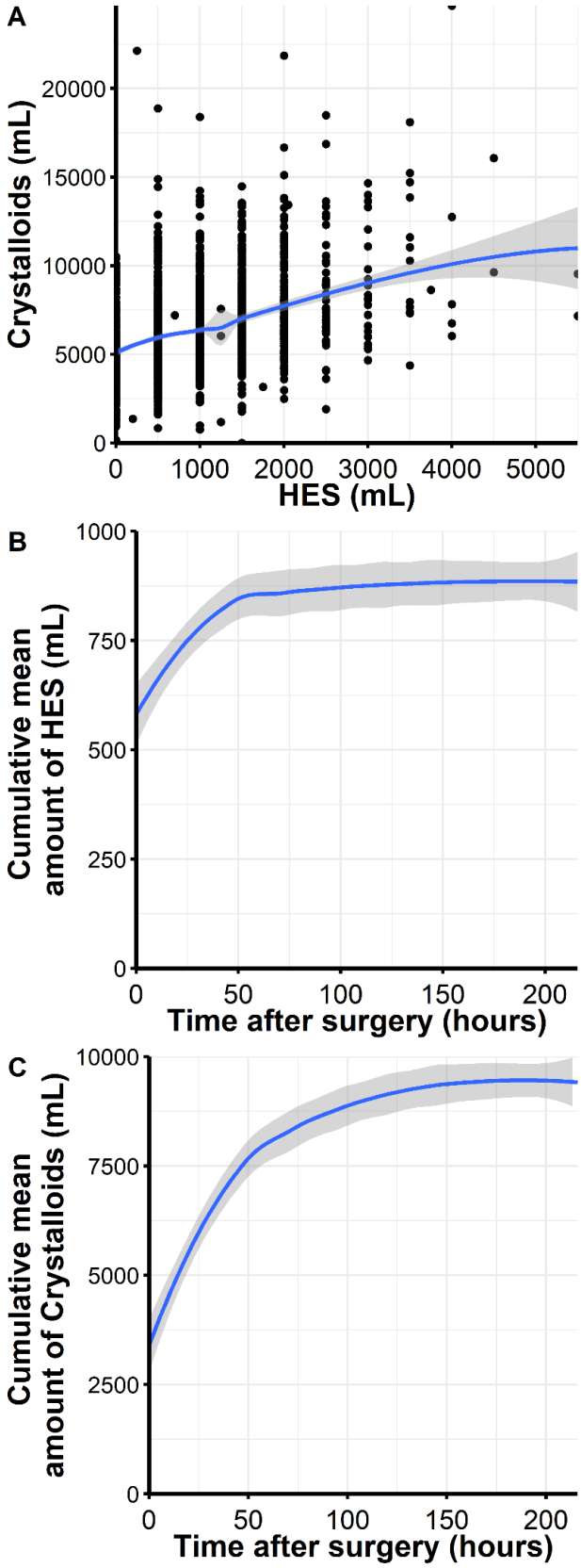

Fig. S1 Scatter plot of crystalloid and hydroxyethylstarch 130/0.42 doses administered after cardiac surgery per patient and the cumulative dosage of HES and crystalloids.

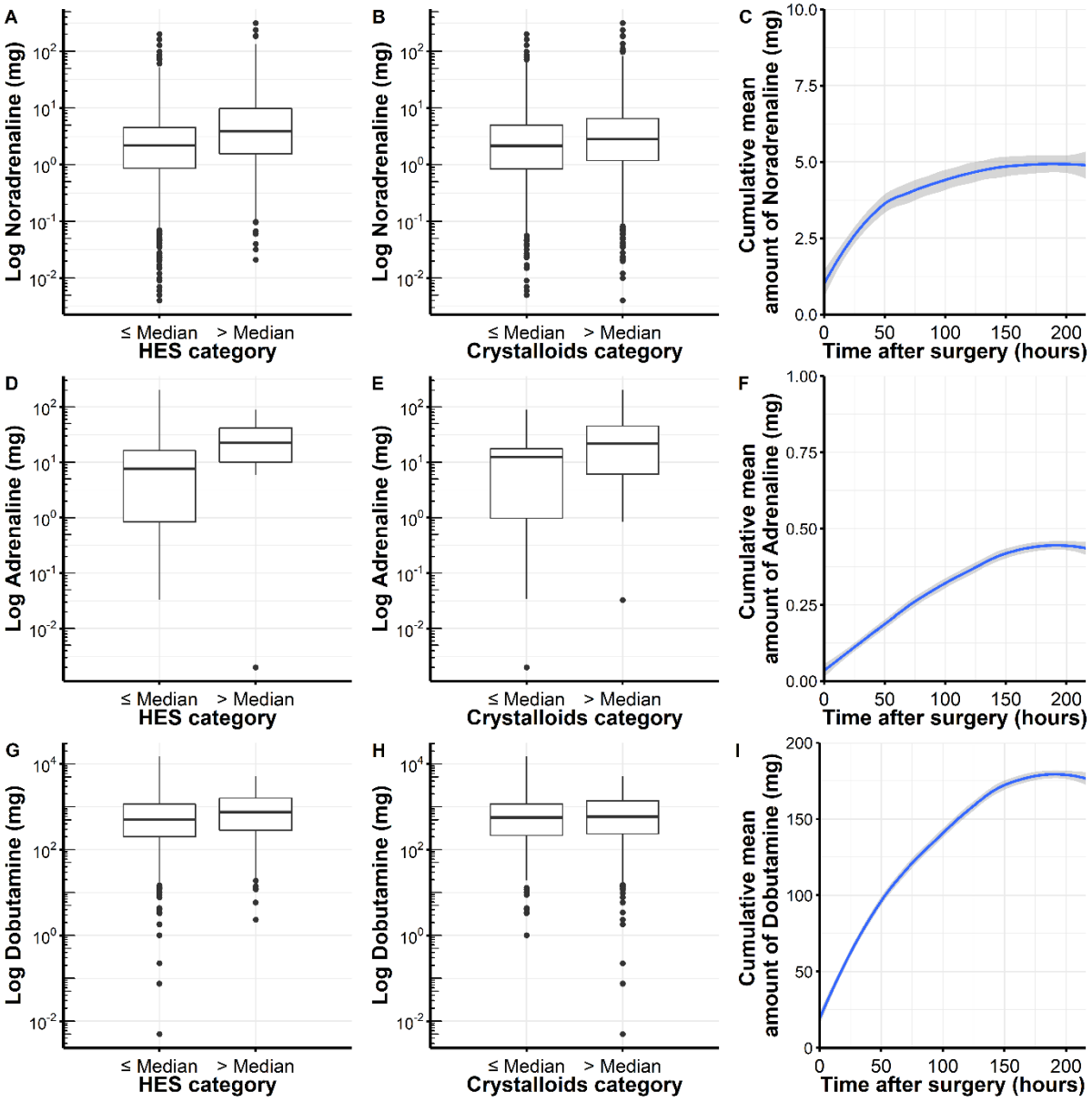

Fig. S2: Detailed information on vasopressor and inotrope doses and timing of administration on the ICU. The HES and crystalloid cohorts are divided according to the administered dose in ≤ median dose and >median dose.

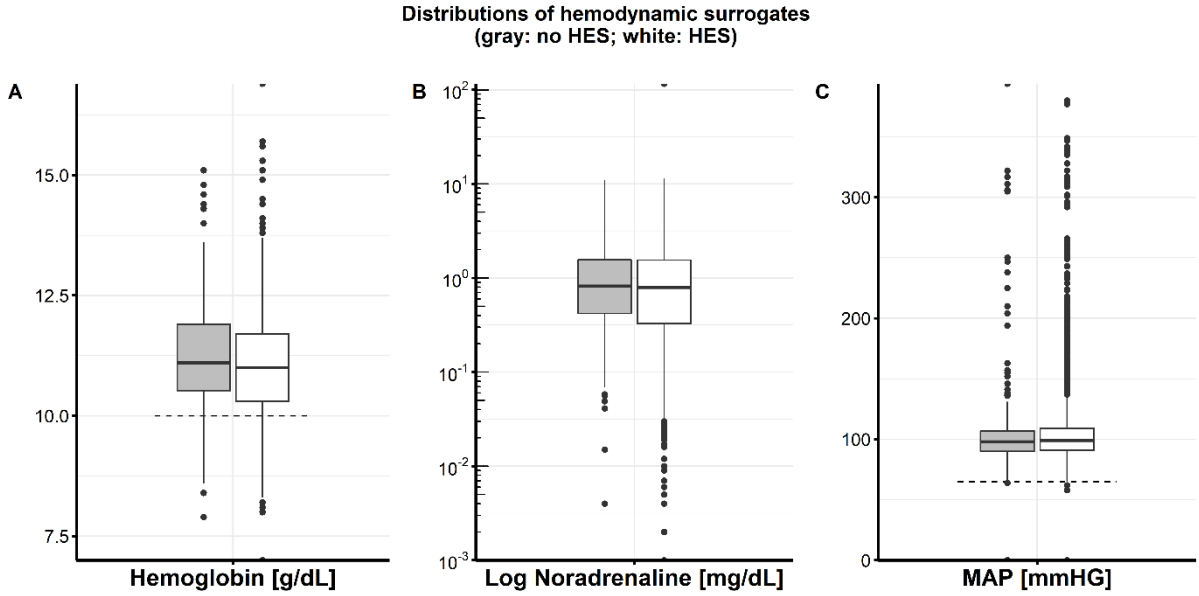

Fig. S3: Hemodynamic surrogates of the HES and crystalloid cohort at admission on the ICU. Gray: Crystalloid | White: HES

Tab. S5: Dose and postoperative administration time points of patients receiving hydroxyethylstarch 130/0.42

HES dosage	**Number of patients**
< 1000 mL	1292
1000-2000 ml	483
> 2000 ml	99
Cumulative HES Dosage per patient	
1091 mL ± 649 mL	
Time of HES administration	**Number of patients**
< 24 h after surgery	1839
24-72 h after surgery	24
>72 h after surgery	11

Abbreviations: HES: Hydroxyethylstarch

Tab. S6: Associations of HES with bleeding incidents and reoperations after multivariate adjustment

	Odds Ratio for bleeding	**Confidence interval**	**p-value**
HES per 500 ml	0.93	[0.76, 1.13]	0.466
	Odds Ratio for reoperation	**Confidence interval**	**p-value**
HES per 500 ml	0.94	[0.77, 1.13]	0.506

Tab. S7: All estimates selected by the LASSO-framework, corresponding standard errors, p-values, and confidence intervals of the cross-sectional acute kidney injury model. All values are rounded to the last digit.

Co-variate	Estimate	Standard error	z value	p value	95 % Confidence interval
Age[a]	0.120	± 0.057	2.111	0.035	[0.01, 0.23]
Atrial fibrillation	0.592	± 0.138	4.274	<0.001	[0.32, 0.86]
Body mass index	0.006	± 0.005	1.255	0.210	[0.00, 0.02]
Crystalloid infusion[b]	-0.024	± 0.012	-2.024	0.043	[-0.05, -0.00*]
Diabetes	0.341	± 0.103	3.325	<0.001	[0.14, 0.54]
Furosemide	0.264	± 0.284	0.930	0.352	[-0.28, 0.84]
Hydroxyethylstarch infusion[c]	-0.115	± 0.040	-2.897	0.004	[-0.19, -0.04]
Intraoperative blood transfusion[d]	0.037	± 0.037	0.996	0.319	[-0.04, 0.11]
Left ventricular function	0.088	± 0.079	1.111	0.266	[-0.07, 0.24]
Mannitol	1.028	± 1.135	0.906	0.365	[-0.92, 4.02]
Mean arterial pressure[e]	-0.041	± 0.020	-2.013	0.044	[-0.08, -0.00**]
Nephrotoxic drugs	0.645	± 0.203	3.173	0.002	[0.24, 1.04]
Postoperative blood transfusion[f]	0.155	± 0.031	4.938	<0.001	[0.10, 0.22]
Pre-operative serum creatinine[g]	0.131	± 0.020	6.590	<0.001	[0.09, 0.17]
Sex	-0.248	± 0.129	-1.920	0.055	[-0.50, 0.01]
Surgery time[h]	0.192	± 0.014	13.251	<0.001	[0.16, 0.22]

Legend: a: Per 10 years | **b:** Per 500 mL | **c:** Per 500 mL | **d:** Per 300 mL | **e:** Per 10 mmHg | **f:** Per 300 mL | **g:** Per 10 mg/dl | **h:** Per 15 min | * = -0.001 | ** = -0.003

Tab. S8: All estimates selected by the LASSO-framework, corresponding standard errors, p-values, and confidence intervals of the cross-sectional mortality model. All values are rounded to the last digit.

Co-variate	Estimate	Standard error	z value	p value	95 % Confidence interval
Age[a]	0.497	0.245	2.027	0.04	[0.03, 0.99]
Atrial fibrillation	1.018	0.304	3.346	<0.001	[0.41, 1.61]
Crystalloid infusion[b]	0.055	0.026	2.141	0.03	[0.00*, 0.10]
EuroSCORE	0.133	0.06	2.340	0.02	[0.02, 0.24]
Hydroxyethylstarch infusion[c]	0.053	0.091	0.553	0.580	[-0.13, 0.22]
Intraoperative blood transfusion[d]	0.047	0.071	0.658	0.510	[-0.10, 0.18]
Left ventricular function	0.314	0.186	1.688	0.09	[-0.06, 0.67]
Nephrotoxic drugs	0.416	0.371	1.119	0.263	[-0.33, 1.12]
Postoperative blood transfusion[e]	0.260	0.042	6.195	<0.001	[-0.18, 0.35]
Pre-operative serum creatinine[f]	0.010	0.030	0.335	0.74	[-0.05, 0.07]
Systolic arterial pressure[g]	-0.114	0.081	-1.411	0.16	[-0.28, 0.04]

Legend: a: Per 10 years | **b:** Per 500 mL | **c:** Per 500 mL | **d:** Per 300 mL | **e:** Per 300 ml | **f:** Per 10 mg/dl | **g:** Per 10 mmHg | * = 0.003

Tab. S9: All estimates of the longitudinal renal function trajectories, corresponding standard errors, and p-values.

Co-variate	Estimate	Standard error	df	t value	p value
Age	-7.567e-01	± 2.240e-02	2.012e+03	-33.78	< 0.001
Aortic cross clamp time	2.751e-02	± 1.038e-02	1.993e+03	2.650	0.008
Crystalloid infusion	2.653e-04	± 8.678e-05	2.093e+03	3.058	0.002
Diabetes	-5.965e-01	± 1.658e-01	1.991e+03	-3.597	< 0.001
EuroSCORE (logarithmic)	1.675e-02	± 2.415e-02	1.985e+03	0.694	0.488
Hydroxyethylstarch infusion	-1.417e-03	± 2.477e-04	9.033e+03	-5.720	< 0.001
Intraoperative blood transfusion	-2.797e-05	± 4.466e-04	1.989e+03	-0.063	0.950
Left ventricular function	3.420e-01	± 2.778e-01	1.983e+03	1.231	0.218
Postoperative blood transfusion	-6.049e-04	± 3.534e-04	2.003e+03	-1.712	0.087
Postoperative Days	-1.540e+00	± 7.276e-02	2.669e+03	-21.16	< 0.001
Pre-operative serum creatinine	-2.642e+01	± 5.955e-01	2.299e+03	-44.36	< 0.001
Sex	6.022e+00	± 4.958e-01	1.988e+03	12.15	< 0.001
Surgery time	-8.608e-03	± 4.061e-03	1.981e+03	-2.120	0.034
Transfusion of platelets	2.058e-03	± 8.097e-04	1.983e+03	2.542	0.011
Urea	-3.225e-01	± 5.484e-03	1.105e+04	-58.80	< 0.001
Urine output	2.207e-04	± 4.059e-05	1.147e+04	5.438	< 0.001
Ventilation time	-2.023e-05	± 6.846e-05	1.994e+03	-0.296	0.768
Postoperative Days: Hydroxyethylstarch infusion[c]	4.282e-04	± 6.274e-05	2.728e+03	6.824	< 0.001