



Fluid balance and AKI – a single centre observational study Stata Oceania Conference

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Purpose

- Observational study based on methodology of RELIEF trial
- This was a RCT from 2018 which randomised elective major abdominal surgery to zero fluid balance (restrictive) versus positive fluid balance (liberal)
- They found an increased hazard ratio for acute kidney injury (defined by 1.5x baseline creatinine – KDIGO)
- Our study looked at emergency patients undergoing major general surgery (emergency laparotomy) or major orthopaedics (major lower limb fractures)
- We analysed the association between AKI and fluid balance and timing of recovery by measuring fluid balance at days 0, 3 and 7 and comparing this with the change in kidney function measured by serum creatinine

Table 3. Primary and Secondary Outcomes.*

Outcome	Restrictive Fluid (N=1490)	Liberal Fluid (N=1493)	Hazard or Risk Ratio (95% CI) [†]	P Value
Primary outcome				
Disability-free survival at 1 yr — no. (%) [‡]	1223 (81.9)	1232 (82.3)	1.05 (0.88–1.24)	0.61
Death or persistent disability — no.	267	261		
Death	95	96		
Persistent disability	172	165		
Secondary outcomes[§]				
Composite septic outcome or death — no./total no. (%) [¶]	323/1481 (21.8)	295/1487 (19.8)	1.10 (0.96–1.27)	0.19
Surgical-site infection — no./total no. (%)	245/1481 (16.5)	202/1487 (13.6)	1.22 (1.03–1.45)	0.02
Sepsis — no./total no. (%)	157/1481 (10.6)	129/1487 (8.7)	1.22 (0.98–1.52)	0.08
Anastomotic leak — no./total no. (%)	49/1481 (3.3)	35/1487 (2.4)	1.41 (0.92–2.16)	0.12
Pneumonia — no./total no. (%)	54/1481 (3.6)	57/1487 (3.8)	0.95 (0.66–1.37)	0.79
Acute kidney injury — no./total no. (%) ^{**}	124/1443 (8.6)	72/1439 (5.0)	1.71 (1.29–2.27)	<0.001
Renal-replacement therapy — no./total no. (%)	13/1460 (0.9)	4/1462 (0.3)	3.27 (1.01–13.8)	0.048
Pulmonary edema — no./total no. (%)	20/1481 (1.4)	32/1487 (2.2)	0.63 (0.36–1.09)	0.10
Unplanned admission to ICU — no./total no. (%)	161/1487 (10.8)	145/1491 (9.7)	1.11 (0.90–1.38)	0.32
Median peak serum lactate level (IQR) — mmol per liter ^{††}	1.6 (1.1–2.5)	1.6 (1.1–2.4)	NA	NA
Median C-reactive protein level on day 3 (IQR) — mg per liter ^{‡‡}	136 (82–198)	133 (80–200)	NA	0.66
Median duration of mechanical ventilation (IQR) — hr ^{§§}	17 (5–65)	14 (3–31)	NA	0.07
Median score on quality-of-recovery scale (IQR) ^{¶¶}	106 (89–121)	107 (90–122)	NA	0.31
Median duration of stay in HDU or ICU (IQR) — days	1.8 (1.0–3.1)	1.4 (0.9–2.9)	NA	0.13
Median duration of hospital stay (IQR) — days	6.4 (3.6–10.6)	5.6 (3.6–10.5)	NA	0.26
Death — no. (%)[‡]				
At 90 days	31 (2.1)	18 (1.2)	1.73 (0.97–3.10)	0.06
At 12 mo	95 (6.5)	96 (6.6)	1.03 (0.78–1.36)	0.86

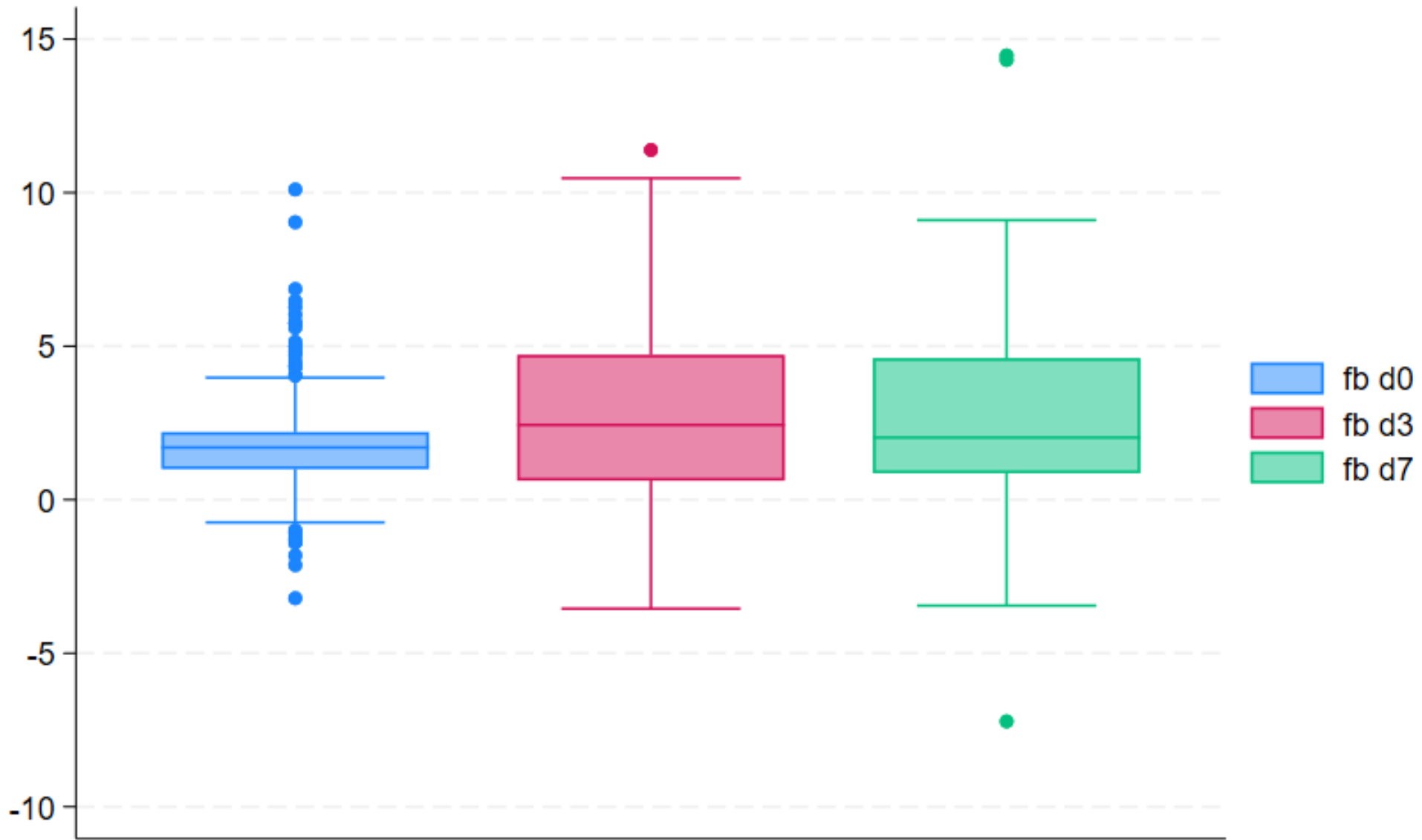
SECONDARY OUTCOMES

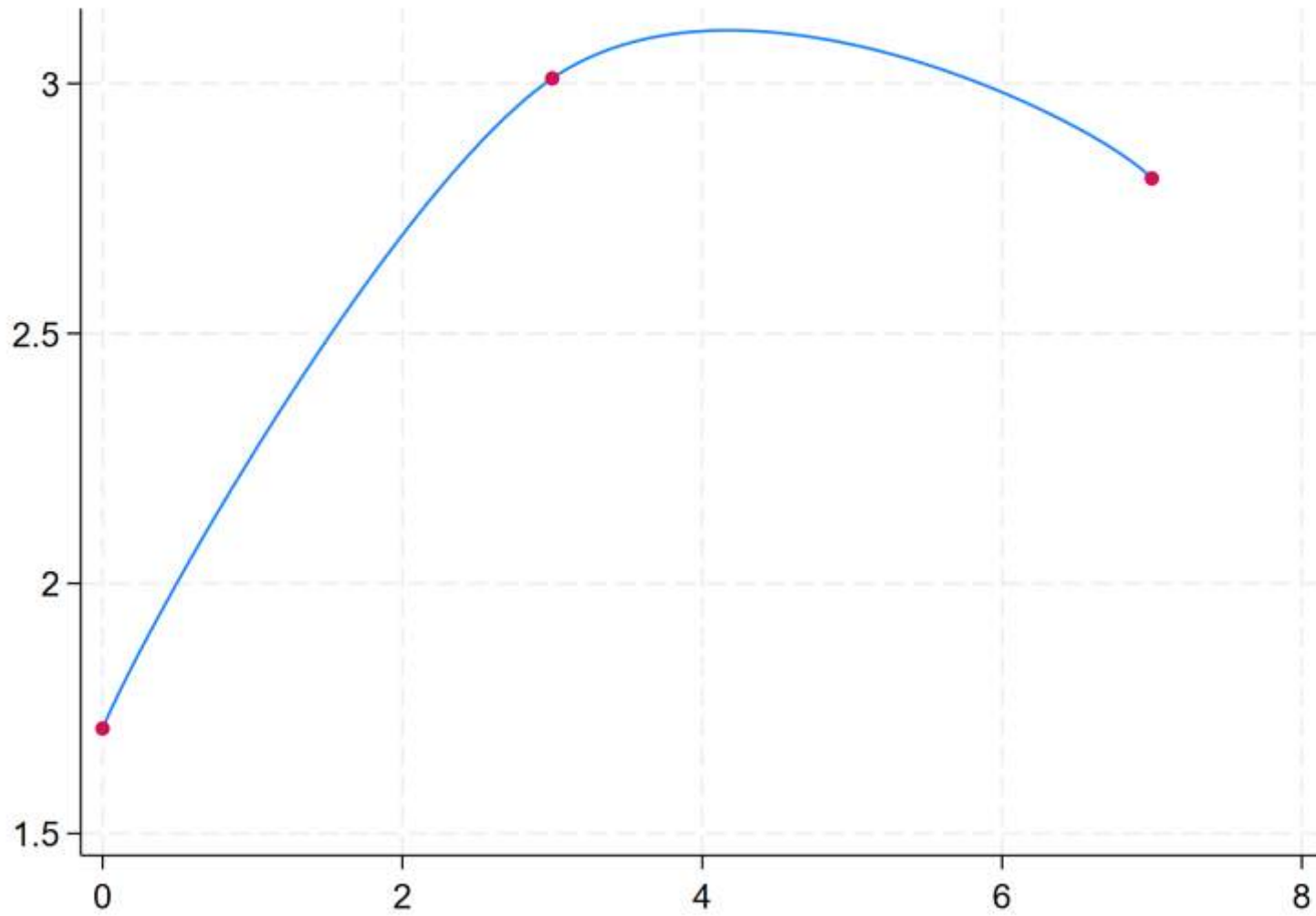
Acute kidney injury occurred in 124 patients (8.6%) in the restrictive fluid group and in 72 patients (5.0%) in the liberal fluid group (P<0.001),

Table 2. Blood Loss and Administered Intravenous-Fluid Volumes.*

Variable	Restrictive Fluid (N=1490)	Liberal Fluid (N=1493)	P Value
At 24 hr after surgery			
Median cumulative total for intravenous fluids (IQR) — ml	3671 (2885 to 4880)	6146 (5000 to 7410)	<0.001
Median fluid balance (IQR) — ml¶	1380 (540 to 2338)	3092 (2010 to 4241)	<0.001†
Median weight gain (IQR) — kg	0.3 (-1.0 to 1.9)	1.6 (0.0 to 3.6)	ND

RELIEF results at 24 hrs

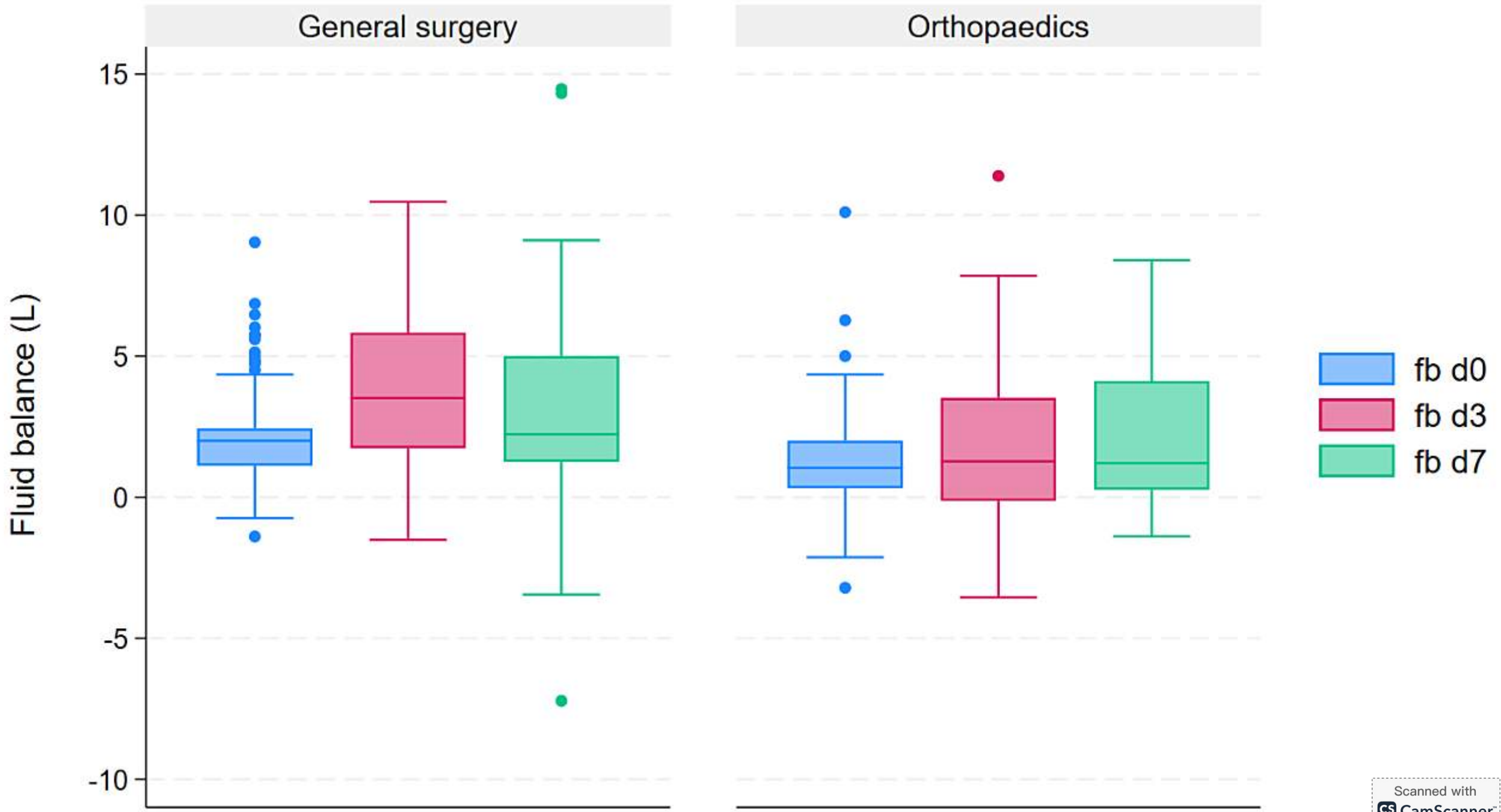


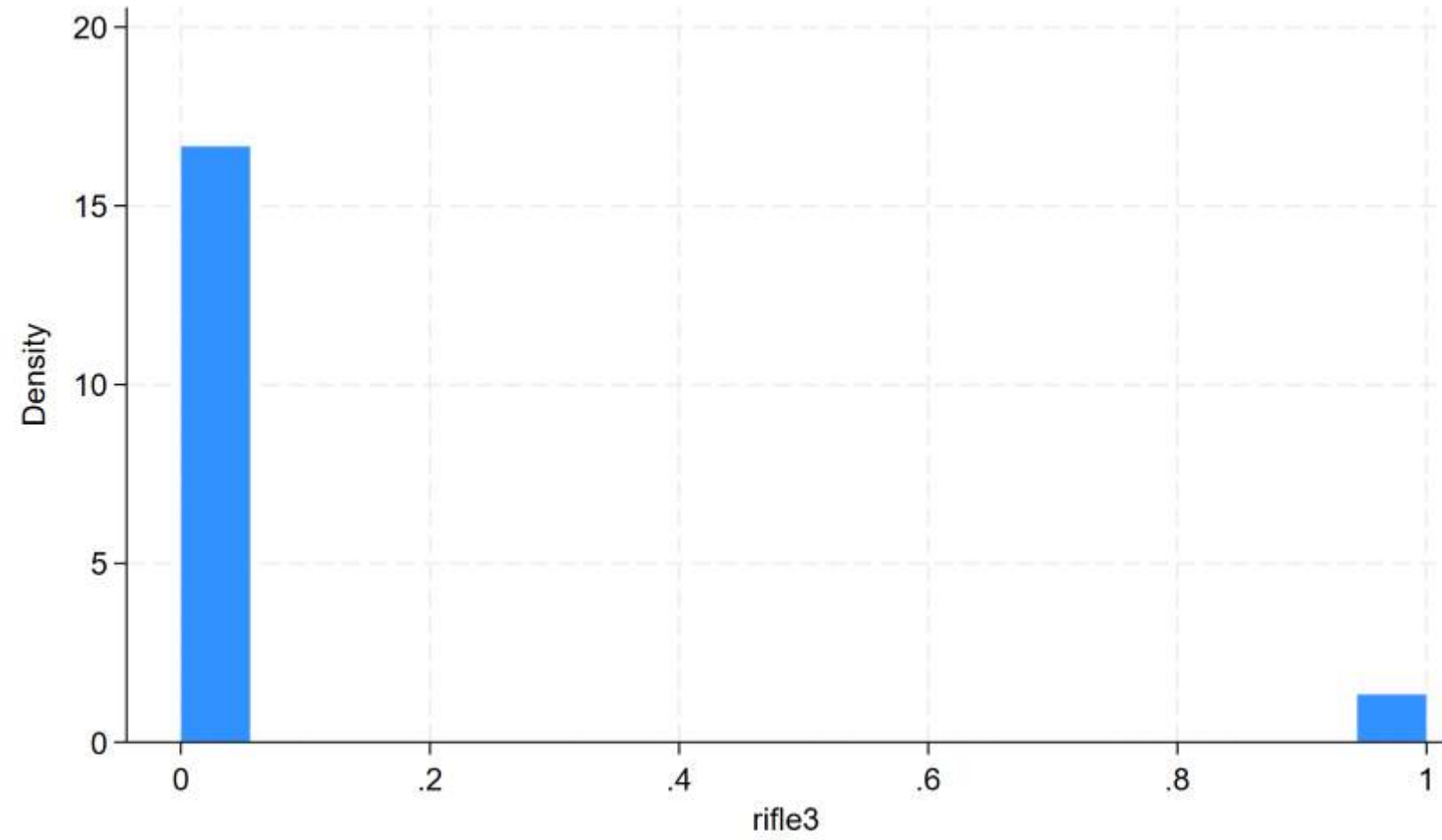


splinefit y x

— y_pts
• y

After fitting a cubic spline
to the means of the data
X – days post-op
Y – fluid balance

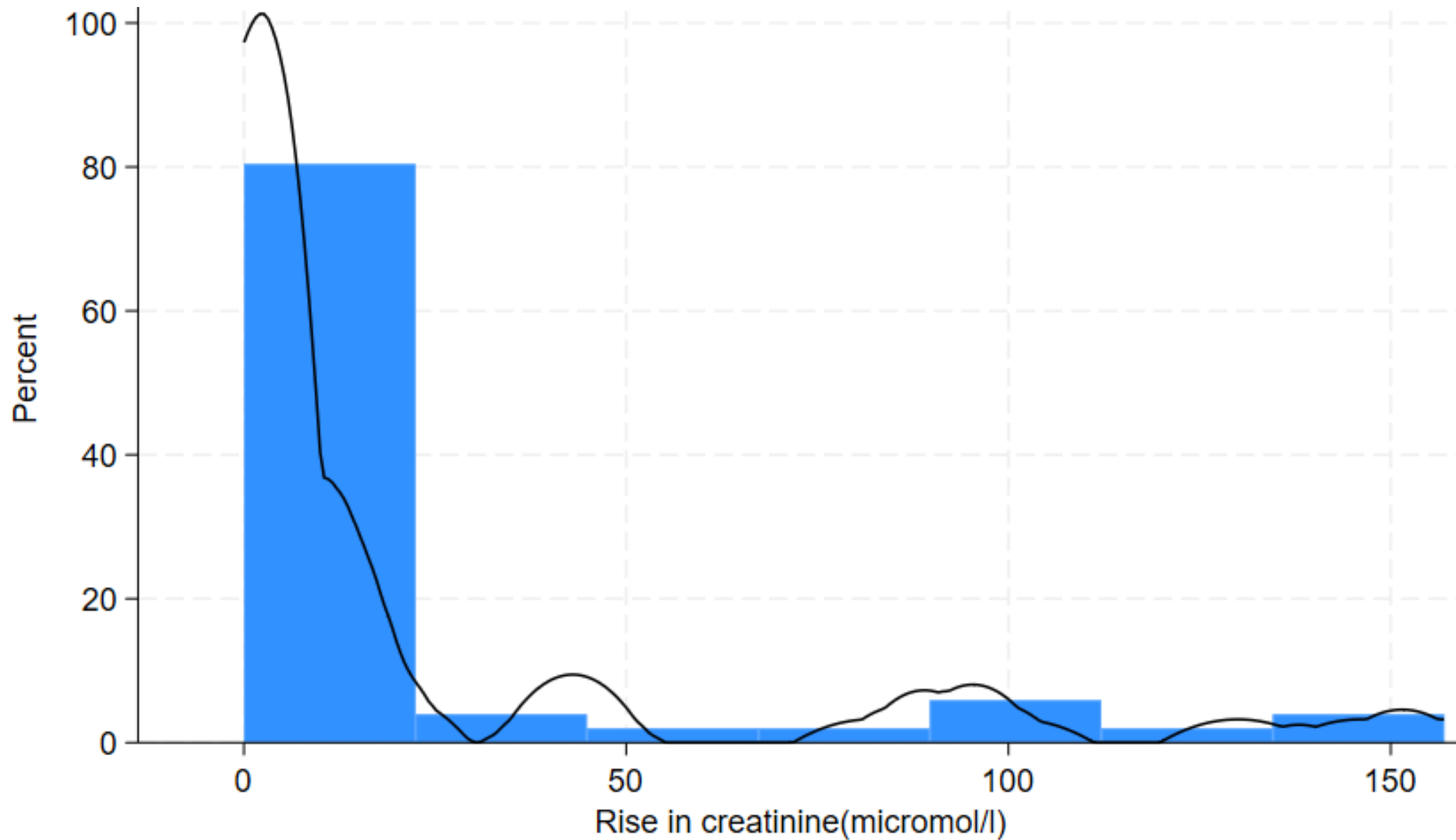




7.4% AKI

```
. summarize rifle3
```

Variable	Obs	Mean	Std. dev.	Min	Max
rifle3	338	.0739645	.2621011	0	1

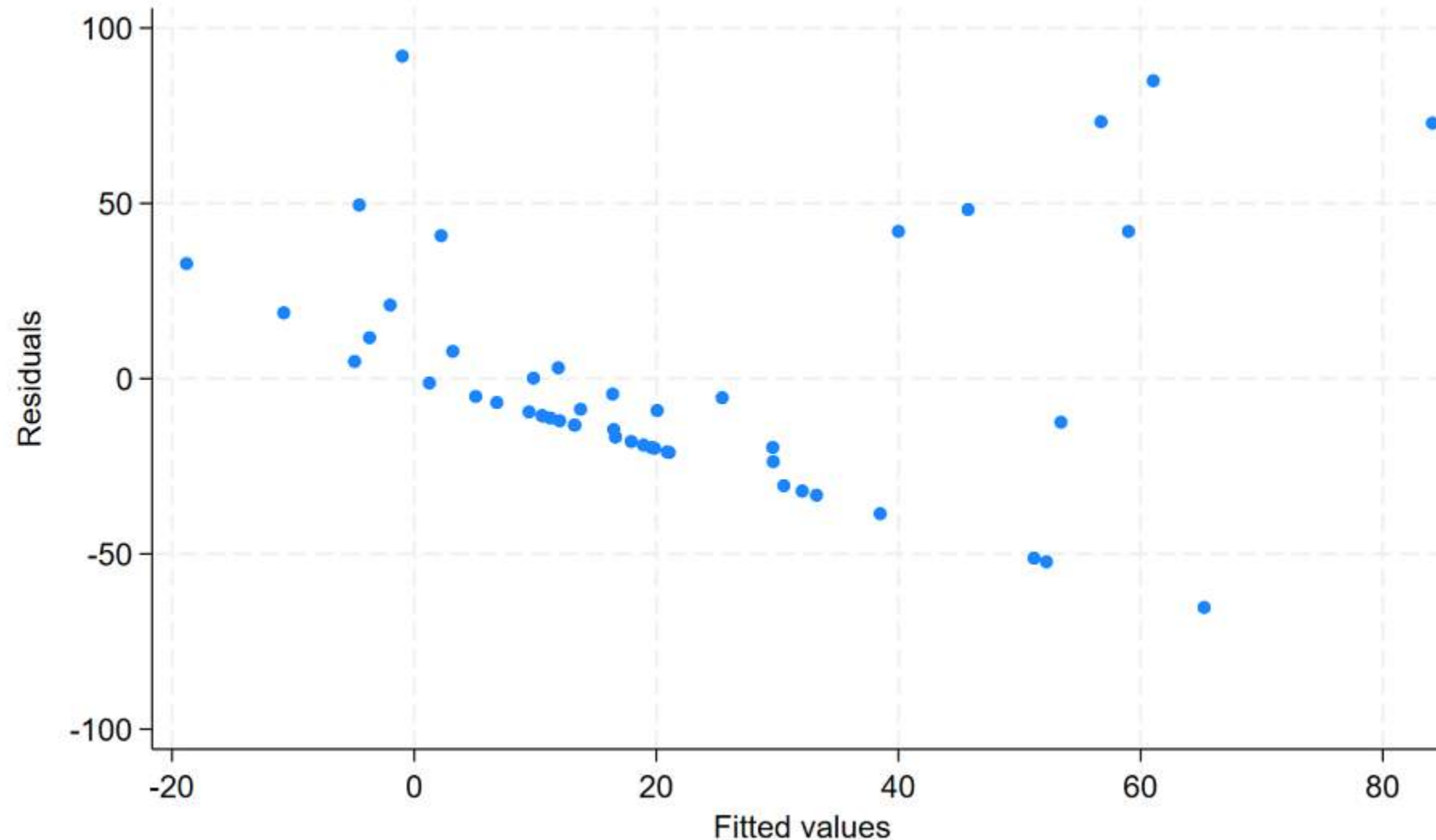


```
. regress deltacr fbd0 fbd3 fbd7
```

Source	SS	df	MS	Number of obs	=	50
Model	23049.6808	3	7683.22693	F(3, 46)	=	6.09
Residual	58002.0992	46	1260.9152	Prob > F	=	0.0014
Total	81051.78	49	1654.11796	R-squared	=	0.2844
				Adj R-squared	=	0.2377
				Root MSE	=	35.509

deltacr	Coefficient	Std. err.	t	P> t	[95% conf. interval]
fbd0	8.697013	2.959469	2.94	0.005	2.739912 14.65411
fbd3	1.258978	2.465393	0.51	0.612	-3.703601 6.221557
fbd7	1.567789	1.764507	0.89	0.379	-1.98398 5.119557
_cons	-6.422156	8.562787	-0.75	0.457	-23.65815 10.81384

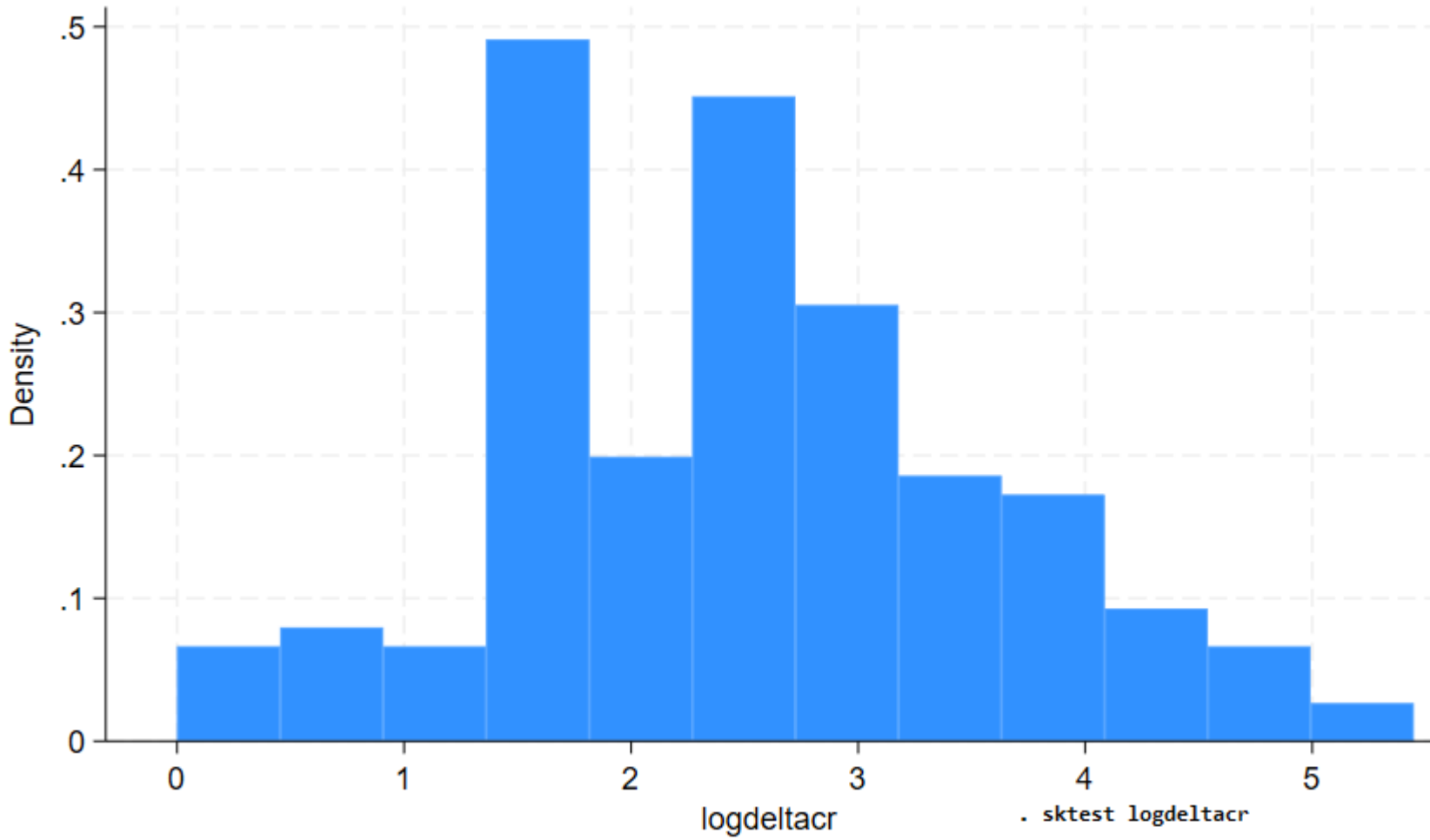
Subgroup of 50 in whom 7d of FB data available
 Assumption no correlation between FB d0, d3, d7 (part of 'iid' assumption of OLS regression)



This is a RVF plot
 It checks the assumptions of the linear relationship by plotting the error term against the values.
 It is supposed to be randomly distributed above and below line of zero.
 Here it is downwardly sloped and has an 'hour-glass' shape
 This can be tested with a White's test for non-constant variance (heteroskedasticity), which is positive (below)

```
. whitest
```

```
White's general test statistic : 22.94311 Chi-sq( 9) P-value = .0063
```



Log transformation of
deltacr variable

Now more 'normal'

? Two underlying normal
distributions

. sktest logdeltacr

Skewness and kurtosis tests for normality

Variable	Obs	Pr(skewness)	Pr(kurtosis)	Joint test	
				Adj chi2(2)	Prob>chi2
logdeltacr	166	0.4022	0.8853	0.73	0.693

*H₀ = normal
∴ not rejected*

```
. xtgee logdeltacr fbd0 fbd3 fbd7, family(gaussian) link(identity) corr(exchangeable) vce(robust)
```

```
Iteration 1: Tolerance = .00804964
Iteration 2: Tolerance = .00481987
Iteration 3: Tolerance = .00268006
Iteration 4: Tolerance = .00138481
Iteration 5: Tolerance = .00068312
Iteration 6: Tolerance = .00032864
Iteration 7: Tolerance = .00015613
Iteration 8: Tolerance = .00007372
Iteration 9: Tolerance = .00003471
Iteration 10: Tolerance = .00001632
Iteration 11: Tolerance = 7.668e-06
Iteration 12: Tolerance = 3.602e-06
Iteration 13: Tolerance = 1.692e-06
Iteration 14: Tolerance = 7.945e-07
```

```
GEE population-averaged model
Group variable: surteam
Family: Gaussian
Link: Identity
Correlation: exchangeable
```

```
Number of obs   = 24
Number of groups = 2
Obs per group:
    min = 6
    avg = 12.0
    max = 18
Wald chi2(1)   = .
Prob > chi2    = .
```

```
Scale parameter = .9538696
```

(Std. err. adjusted for clustering on surteam)

logdeltacr	Coefficient	Robust std. err.	z	P> z	[95% conf. interval]
fbd0	.226665	.0364127	6.22	0.000	.1552974 .2980326
fbd3	.0721995	.0274701	2.63	0.009	.0183591 .12604
fbd7	.0479411	.0125831	3.81	0.000	.0232787 .0726034
_cons	2.372687	.6074734	3.91	0.000	1.182061 3.563313

This made a big difference

Now all variables are significantly assoc with logdeltacr

Interpretation of coefficient= % change in creatinine (not log creatinine) for each unit change in fluid balance

e.g. for FB day 0 +1L creatinine rises by 23%

FB day 3 +1L creatinine rises by

7%

FB day 7 +1L creatinine rises by

5%

```
. xtgee logdeltacr fbd0 if fbd7 !=., family(gaussian) link(identity) vce(robust)
```

```
Iteration 1: Tolerance = .01171443  
Iteration 2: Tolerance = .00554629  
Iteration 3: Tolerance = .00180387  
Iteration 4: Tolerance = .00044084  
Iteration 5: Tolerance = .00009615  
Iteration 6: Tolerance = .00002036  
Iteration 7: Tolerance = 4.282e-06  
Iteration 8: Tolerance = 8.994e-07
```

```
GEE population-averaged model  
Group variable: surteam  
Family: Gaussian  
Link: Identity  
Correlation: exchangeable
```

```
Number of obs    =    25  
Number of groups =     2  
Obs per group:  
    min =     7  
    avg =    12.5  
    max =    18  
Wald chi2(1)    =    13.91  
Prob > chi2     = 0.0002
```

```
Scale parameter = 1.053305
```

(Std. err. adjusted for clustering on surteam)

logdeltacr	Coefficient	Robust std. err.	z	P> z	[95% conf. interval]	
fbd0	.2826111	.0757857	3.73	0.000	.1340737	.4311484
_cons	2.391364	.3017144	7.93	0.000	1.800015	2.982714

Reducing the number of parameters to 1 but still using same ptns with 7 days fluid balance data

This allows a Wald test of the model to be done (the no parameters needs to be *less* than the no groups)

. fmm 2: regress logdeltacr fbd0 fbd3 fbd7

— checks whether 2 normal dist

Finite mixture model
Log likelihood = -30.149023

Number of obs = 24

	Coefficient	Std. err.	z	P> z	[95% conf. interval]	
1.Class	(base outcome)					
2.Class						
_cons	.5751926	.5910863	0.97	0.330	-.5833153	1.7337

Class: 1
Response: logdeltacr
Model: regress

	Coefficient	Std. err.	z	P> z	[95% conf. interval]	
logdeltacr						
fbd0	-.9327039	.3259107	-2.86	0.004	-1.571477	-.2939305
fbd3	.2278574	.2563876	0.89	0.374	-.274653	.7303678
fbd7	-.1241362	.1727133	-0.72	0.472	-.462648	.2143756
_cons	3.65125	.6119584	5.97	0.000	2.451834	4.850667
var(e.logdeltacr)	.5004084	.2966882			.1565503	1.59954

Class: 2
Response: logdeltacr
Model: regress

	Coefficient	Std. err.	z	P> z	[95% conf. interval]	
logdeltacr						
fbd0	.3063086	.0628673	4.87	0.000	.183091	.4295262
fbd3	-.014239	.0605713	-0.24	0.814	-.1329566	.1044786
fbd7	.0846913	.0364696	2.32	0.020	.0132123	.1561703
_cons	2.429331	.2692316	9.02	0.000	1.901647	2.957016
var(e.logdeltacr)	.2279628	.130367			.0743157	.6992744

. estat lcpob

Latent class marginal probabilities

Number of obs = 24

Class	Delta-method			
	Margin	std. err.	[95% conf. interval]	
1	.3600395	.1361928	.1501149	.6418299
2	.6399605	.1361928	.3581701	.8498851

36% obs in first dist, 64% in second

. lcstats fmm2 fmm1

Latent class statistics

	Classes	N	ll	Rank	Entropy	df	LMR	P>LMR
fmm2	2	24	-30.15	11	0.6849	6	5.67	0.350
fmm1	1	24	-33.13	5				

LMR is the Lo-Mendell-Rubin-adjusted likelihood-ratio test statistic.
Likelihood-ratio tests compare the given model versus the same model with one less latent class.

this says NO

```
. ksmirnov logdeltacr, by(surteam)
```

```
Two-sample Kolmogorov-Smirnov test for equality of distribution functions
```

Smaller group	D	p-value
General surgery	0.2079	0.028
Orthopaedics	-0.0639	0.714
Combined K-S	0.2079	0.056

```
Note: Ties exist in combined dataset;  
there are 55 unique values out of 166 observations.
```

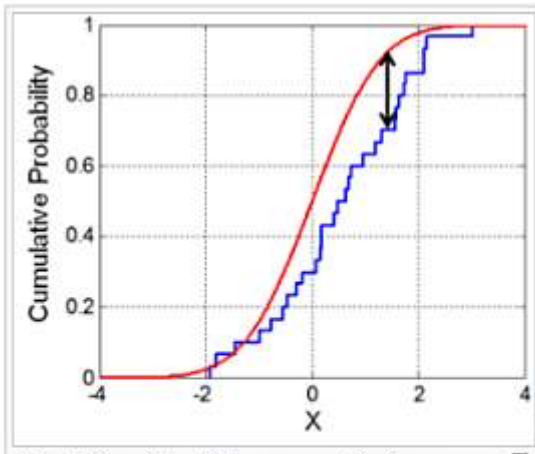


Illustration of the Kolmogorov-Smirnov statistic. The red line is a model CDF, the blue line is an empirical CDF, and the black arrow is the KS statistic.

Another way of doing it – the Kolmogorov-Smirnov test

This checks whether the logdeltacr variable is distributed the same across surgical teams

D is the max distance between the two functions

In this case Gen surg is *smaller* than ortho for logdeltacr variable

The opposite hypothesis that ortho is *larger* (D negative) is not proven

The combined K-S statistic is the hypothesis that *both* are true i.e. gen surg is smaller and ortho is larger for logdeltacr

This provides some evidence for two distributions

```
. stcox fbd0
```

```
Failure _d: rifle3  
Analysis time _t: timetobase
```

```
Iteration 0: Log likelihood = -73.741158  
Iteration 1: Log likelihood = -71.568045  
Iteration 2: Log likelihood = -71.523032  
Iteration 3: Log likelihood = -71.523023  
Refining estimates:  
Iteration 0: Log likelihood = -71.523023
```

```
Cox regression with Breslow method for ties
```

```
No. of subjects = 138  
No. of failures = 22  
Time at risk = 436
```

```
Number of obs = 138
```

```
Log likelihood = -71.523023
```

```
LR chi2(1) = 4.44  
Prob > chi2 = 0.0352
```

_t	Haz. ratio	Std. err.	z	P> z	[95% conf. interval]	
fbd0	1.225299	.113608	2.19	0.028	1.021692	1.469482

Time to recovery from AKI (defined as >1.5x baseline creatinine) was significantly longer with more fluid
Excluded (censored) those with missing data and end before/on day of surgery leaving 138 pts

Summary

- Positive fluid balance was associated with renal dysfunction in post-operative patients in our data
- When data adjusted for skew using log transformation positive relationship between fluid balance and rise in creatinine was demonstrated using GEE model
- Relationship stronger for general surgery patients than orthopaedic patients
- Association between positive fluid balance and slower time to renal recovery using Cox PH model

Anaesthesia and Intensive Care Journal response

- This is a retrospective analysis of the relationship between postoperative creatinine changes and fluid balance in a heterogeneous (abdominal and orthopaedic) emergency surgical population sample of 333 patients at one centre over a 12 month period.

The aim of the study is not made clear, with no primary endpoint nominated. The sample size seems to be an arbitrary one, so the likelihood of adequate statistical power to demonstrate relationships is unclear.

The results are not well articulated or summarised, instead with reference to a series of 8 tables which are not well labelled to allow the reader to understand where each fits into the outcomes of interest.

The clinical meaning of the “weak relationship” between degree of positive fluid balance and AKI incidence is quite obscure, particularly give the multiplicity of statistical testing performed, and it seems impossible to imply causality in this sort of retrospective analysis.