Understanding the RELIEF results - greater fluid administration volume is associated with increased endothelial injury

Shailesh Bihari[1,2]*, Dani-Louise Dixon[1,2], Thomas Painter[3,4], Paul Myles[5,6], Andrew D Bersten[1,2]

[1] College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia.

[2] Intensive and Critical Care Unit, Southern Adelaide Local Health Network, Adelaide, SA, Australia.

[3] Royal Adelaide Hospital, Adelaide, SA, Australia.

[4] Discipline of Acute Care Medicine, University of Adelaide, Adelaide, SA, Australia.

[5] Alfred Hospital and [6] Monash University, Melbourne, VIC, Australia.

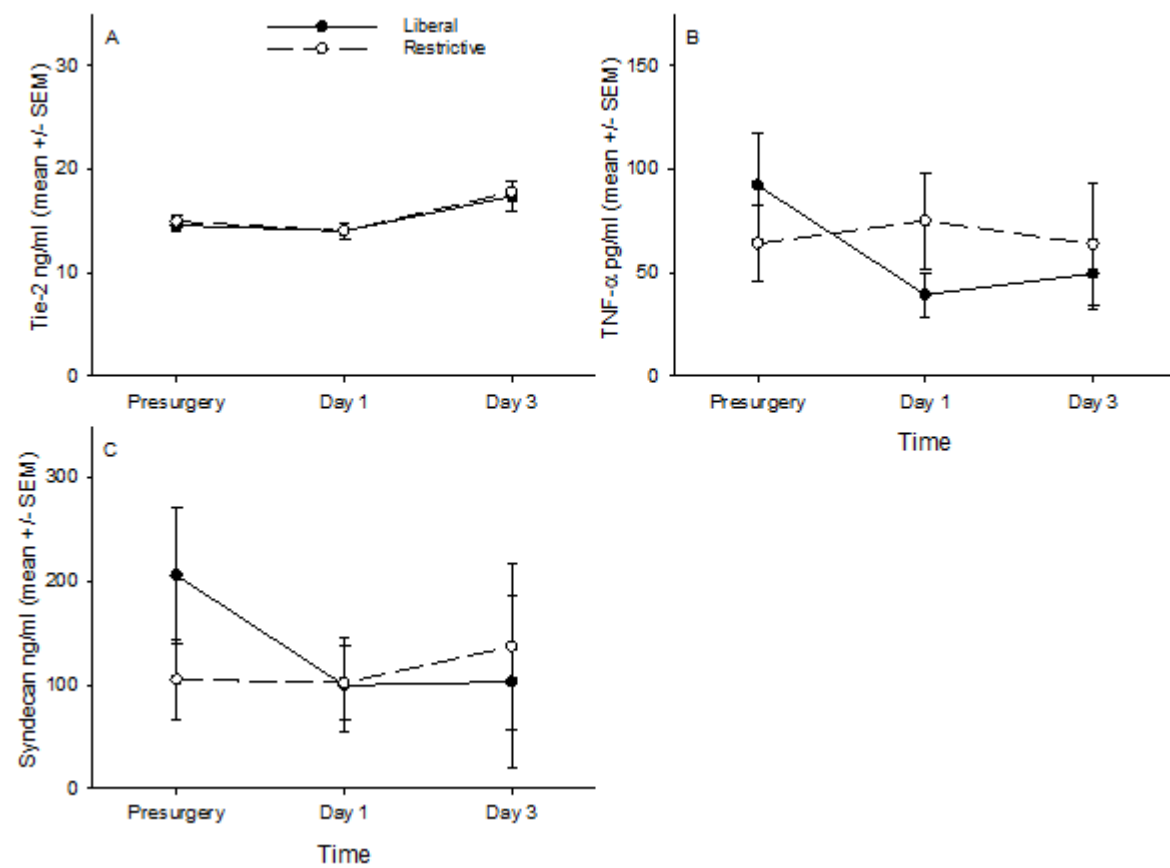**Electronic Supplementary Material**

Figure S1

Fig. S1 Plasma biomarkers, normalised for change in plasma volume, by treatment groups during the first three days from surgery. *SEM,* standard error of the mean; *sTie-2,* soluble Angiopoietin-1 receptor; *TNF-α*, tumor necrosis factor alpha.
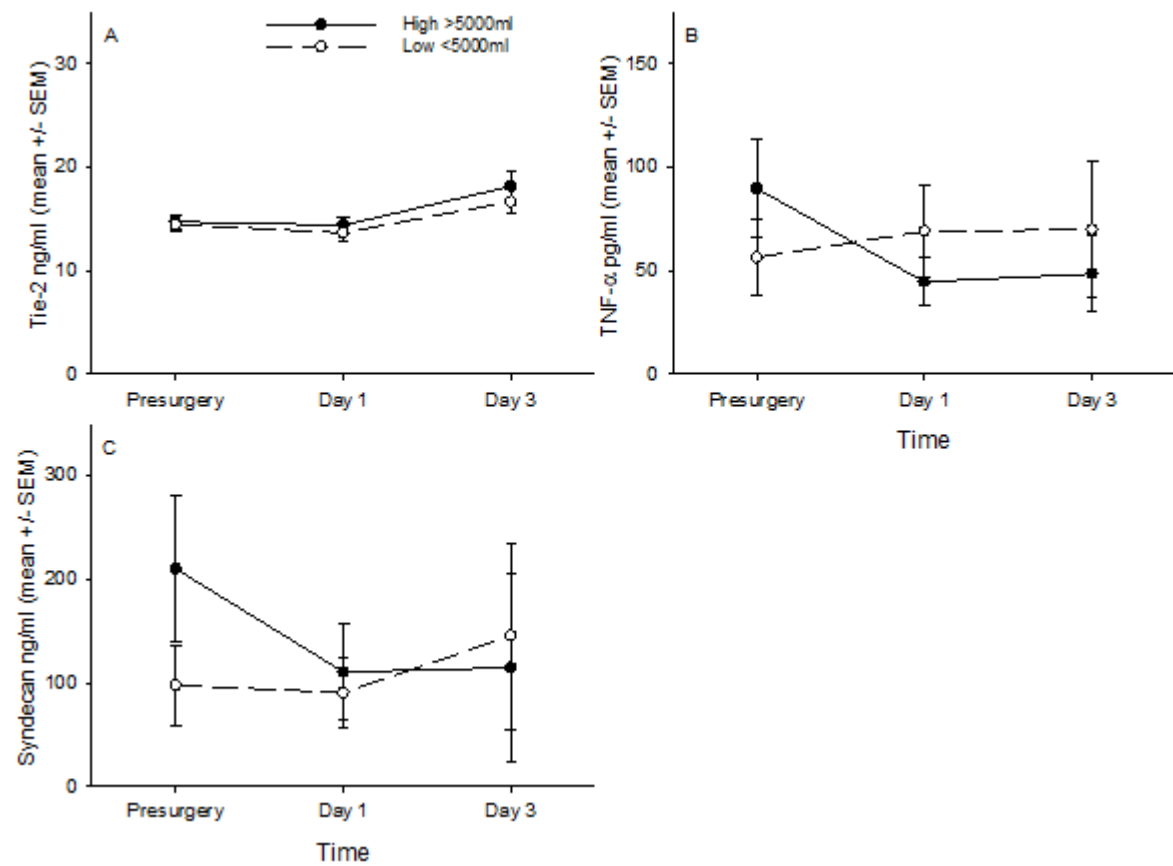
Figure S2

Fig. S2 Plasma biomarkers, normalised for change in plasma volume, by total intravenous fluid administered, dichotomised into High >5000ml and Low <5000ml groups, during the first three days from surgery. *SEM,* standard error of the mean; *sTie-2,* soluble Angiopoietin-1 receptor; *TNF-α,* tumor necrosis factor alpha.

Table S1. Primary and secondary outcomes of the patients by enrolment and total fluid administered groups

Outcome	Restrictive Fluid (N=75)	Liberal Fluid (N=86)	P
Primary outcome			
Disability-free survival at 1yr, n (%)	56 /70 (80)	66/84 (54)	0.845
Death or persistent disability, n	19	20	
Death	3	2	
Persistent disability	16	18	
Secondary outcomes			
Pneumonia, n (%)	6 (8.0)	6 (7.0)	1.000
Acute kidney injury, n (%)	12 (16.2)	10 (12.3)	0.646
Pulmonary oedema, n (%)	1 (1.3)	2 (2.3)	1.000
Acute lung injury/ARDS, n (%)	1 (1.3)	1 (1.2)	1.000
Duration of mechanical ventilation (hr), median (IQR)*	17	38 (4-318)	ND
Duration of stay in HDU or ICU (days), median (IQR)	1.7 (0.9-2.9)	1.2 (0.9-5.1)	0.823
Duration of hospital stay (days), median (IQR)	4.4 (2.6-7.6)	5.6 (3.4-8.6)	0.167
Death, n (%)			
At 90 days	0	0	
At 12 months	3 (4.1)	2 (2.3)	0.663
Outcome	**Low Fluid (<5000ml) (N=81)**	**High Fluid (>5000ml) (N=79)**	**P**
Primary outcome			
Disability-free survival at 1yr, n (%)	66/77 (86)	55/76 (72)	0.049
Death or persistent disability, n	15	24	
Death	2	3	
Persistent disability	13	21	
Secondary outcomes			
Pneumonia, n (%)	5 (6.2)	7 (8.9)	0.562
Acute kidney injury, n (%)	8 (10.0)	14 (18.9)	0.166
Pulmonary oedema, n (%)	2 (2.5)	1 (1.3)	1.000
Acute lung injury/ARDS, n (%)	1 (1.2)	1 (1.3)	1.000
Duration of mechanical ventilation (hr), median (IQR)#	29	8	0.700
Duration of stay in HDU or ICU (days), median (IQR)	1.1 (0.9-3.5)	1.7 (0.9-3.0)	0.696
Duration of hospital stay (days), median (IQR)	4.4 (2.5-6.6)	5.6 (3.5-11.3)	0.002
Death, n (%)			
At 90 days	0	0	
At 12 months	2 (2.5)	3 (3.8)	0.681

HDU high dependency unit, *ICU* intensive care unit, *IQR* interquartile range.

*Mechanical ventilation – Restrictive Fluid group n=2, Liberal Fluid group n=4. Mann-Whitney U Test.
Mechanical ventilation – Restrictive Fluid group n=3, Liberal Fluid group n=3. Mann-Whitney U Test.
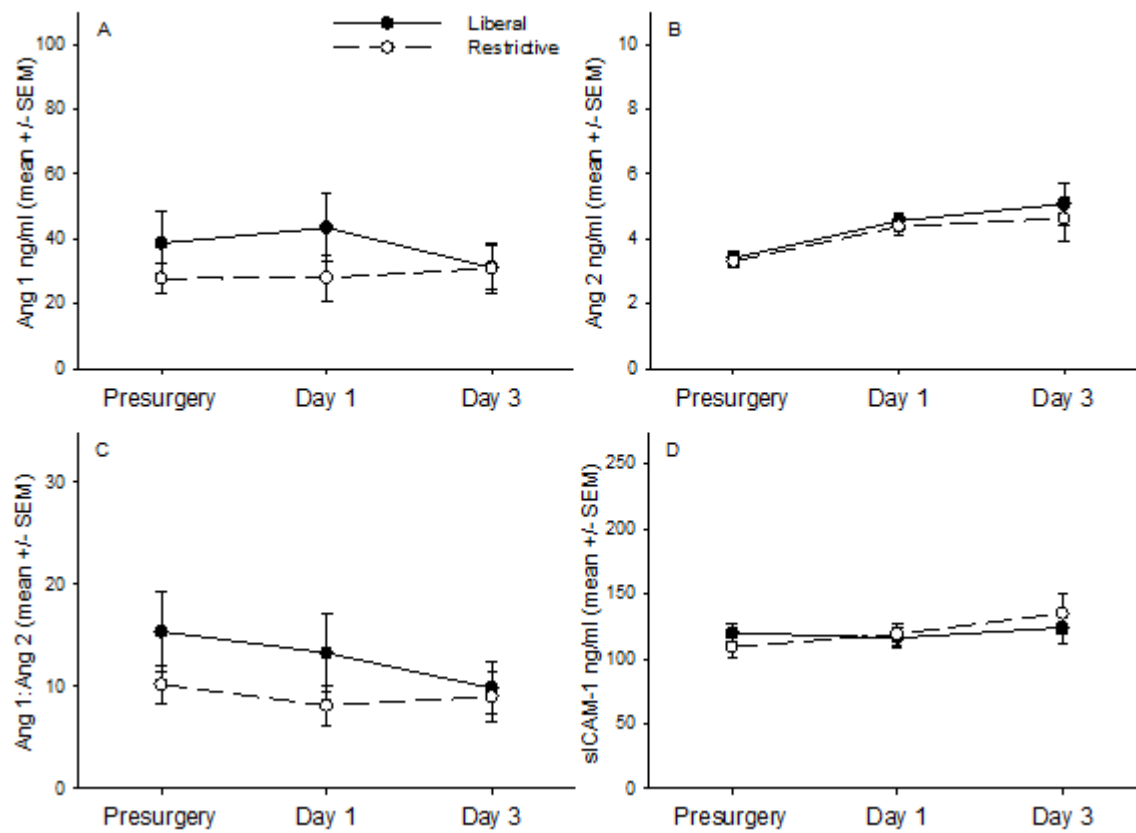
Figure S3

Fig. S3 Plasma biomarkers expressed per ml of plasma, by treatment groups during the first three days from surgery. *Ang*, angiopoietin, *sICAM,* soluble Intracellular adhesion molecule, *SEM,* standard error of the mean.
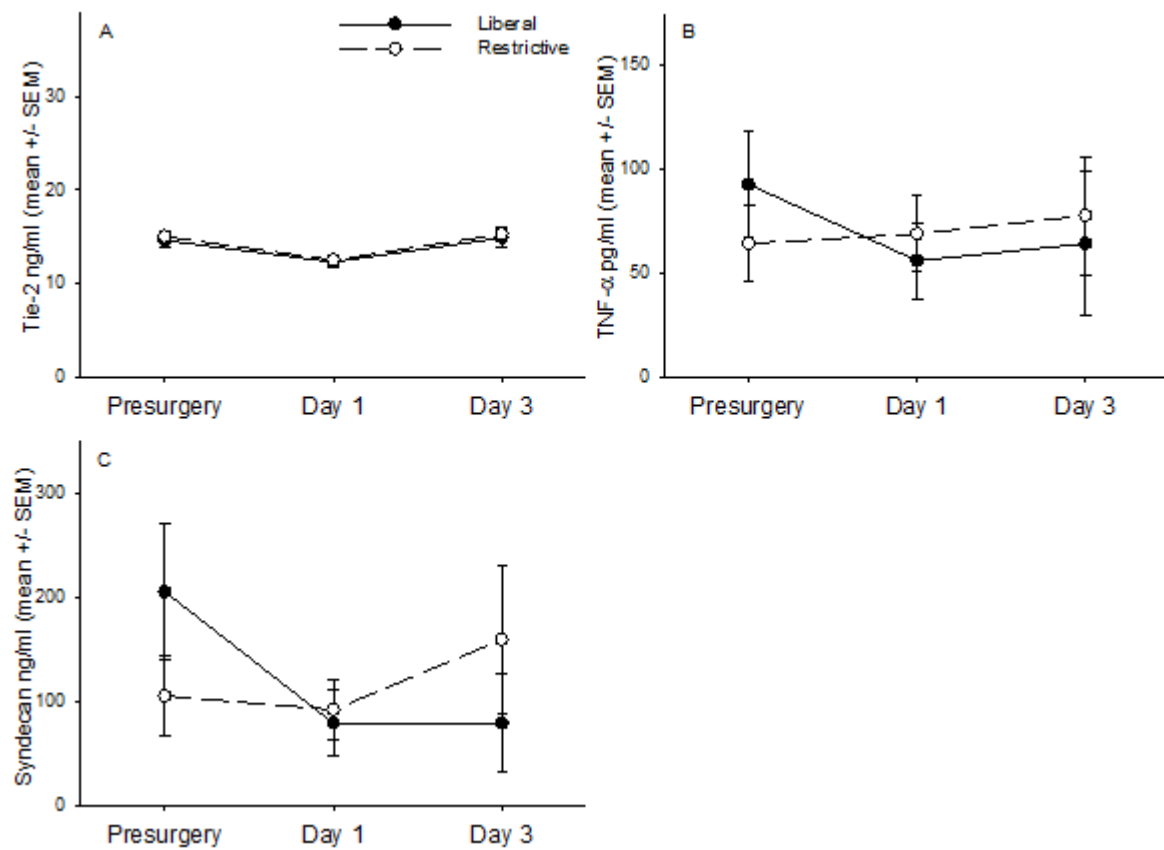
Figure S4

Fig. S4 Plasma biomarkers expressed per ml of plasma, by treatment groups during the first three days from surgery. *SEM,* standard error of the mean; *sTie-2,* soluble Angiopoietin-1 receptor; *TNF-a,* tumor necrosis factor alpha.
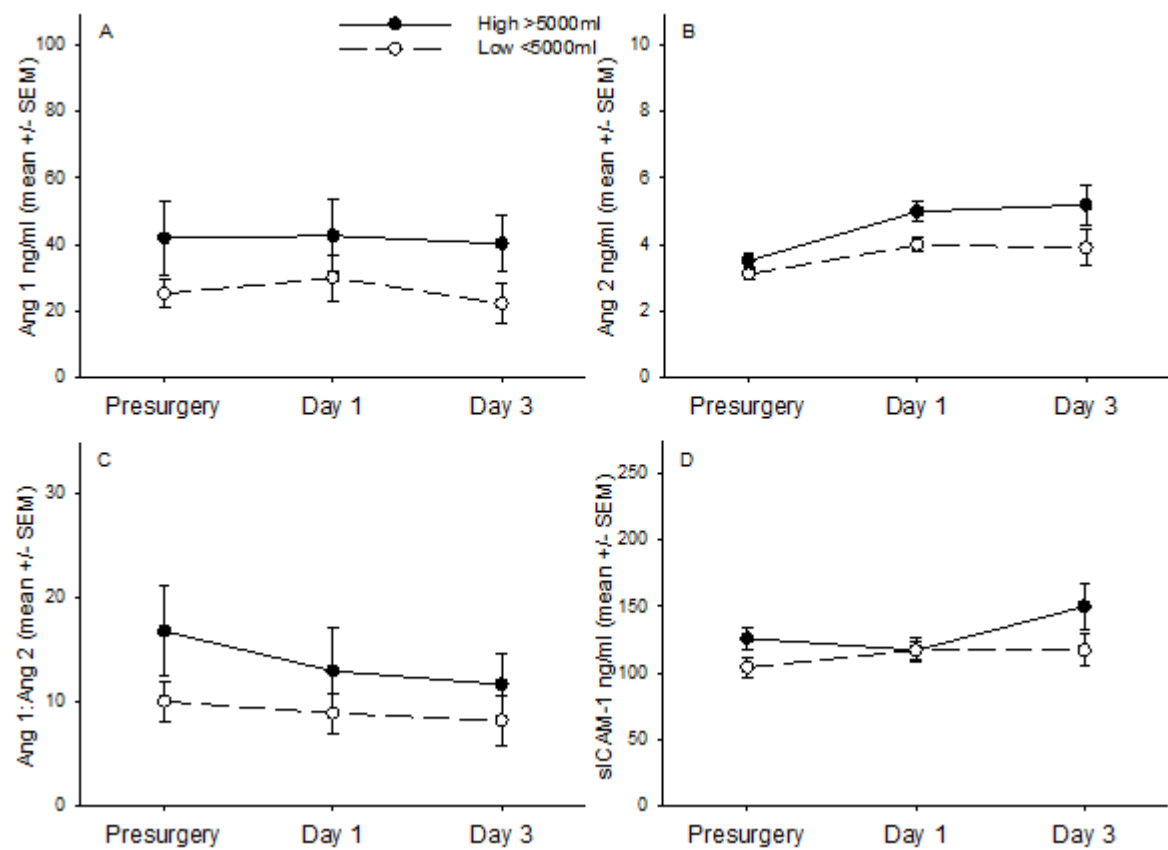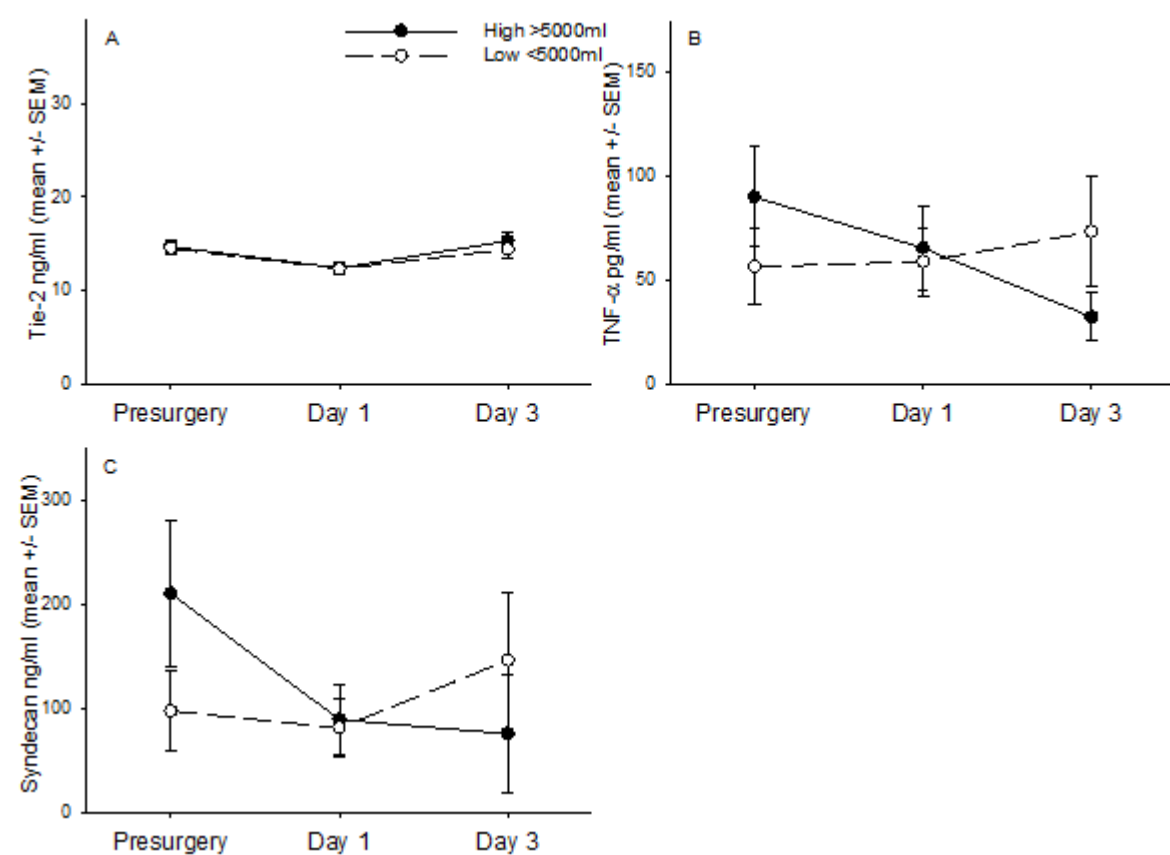
Figure S5

Fig. S5 Plasma biomarkers expressed per ml of plasma, by total intravenous fluid administered, dichotomised into High >5000ml and Low <5000ml groups, during the first three days from surgery. *Ang*, angiopoietin, *sICAM,* soluble Intracellular adhesion molecule, *SEM,* standard error of the mean.

Figure S6

Fig. S6 Plasma biomarkers expressed per ml of plasma, by total intravenous fluid administered, dichotomised into High >5000ml and Low <5000ml groups, during the first three days from surgery. *SEM,* standard error of the mean; *sTie-2,* soluble Angiopoietin-1 receptor; *TNF-a*, tumor necrosis factor alpha.
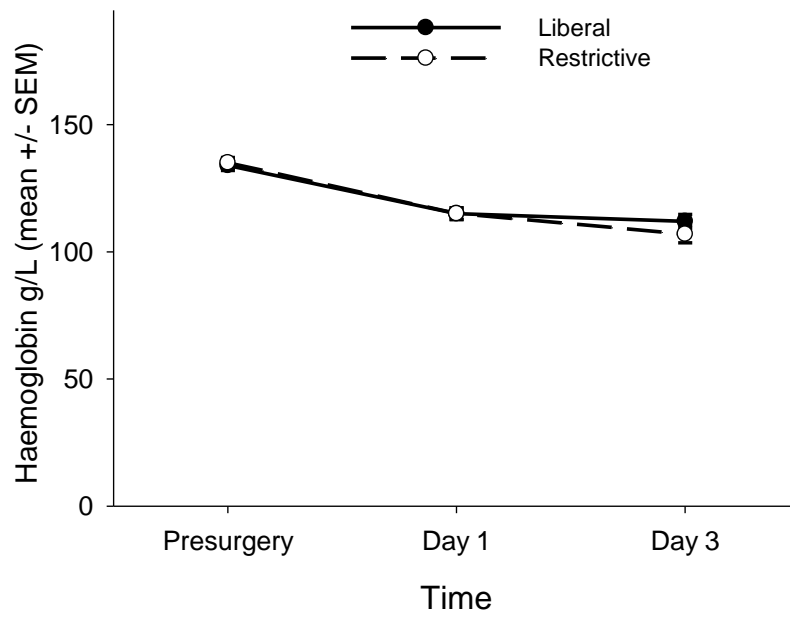
Figure S7

Figure S7: Change in haemoglobin in liberal and restrictive groups. There was no statistical difference between the liberal and restrictive groups, p=0.45.
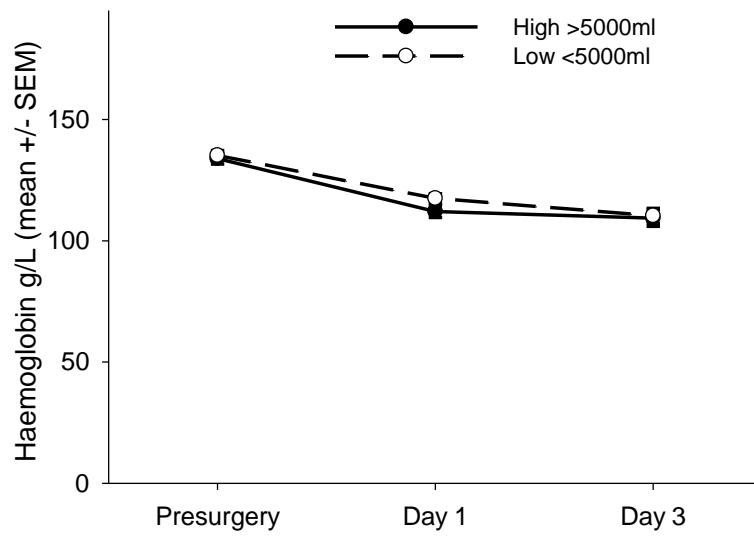
Figure S8

Figure S8: Change in haemoglobin in high and low fluid groups. There was no statistical difference between the high and low fluid groups, p=0.23.
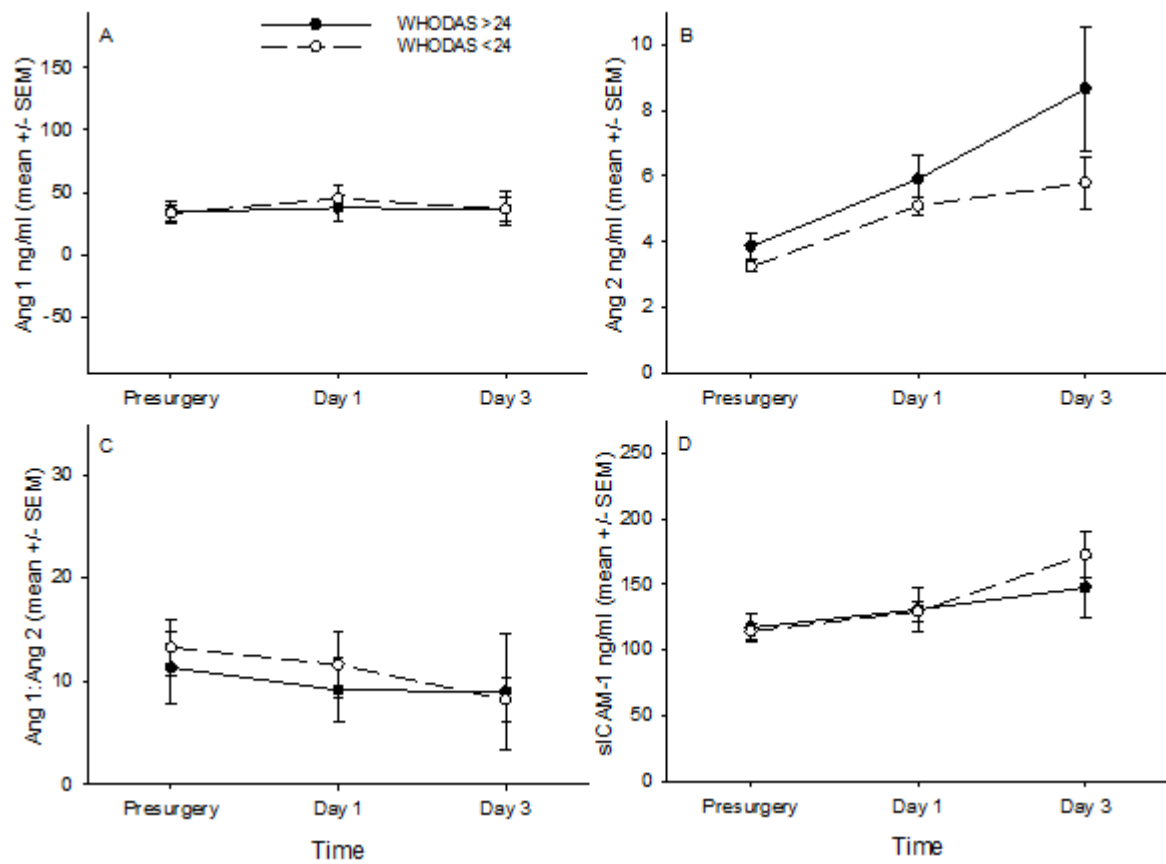
Figure S9

Fig. S9 Plasma biomarkers, normalised for change in plasma volume, by disability free survival at 12 months, defined as WHODAS score <24, during the first three days from surgery. *Ang*, angiopoietin, *sICAM*, soluble Intracellular adhesion molecule, *SEM*, standard error of the mean.
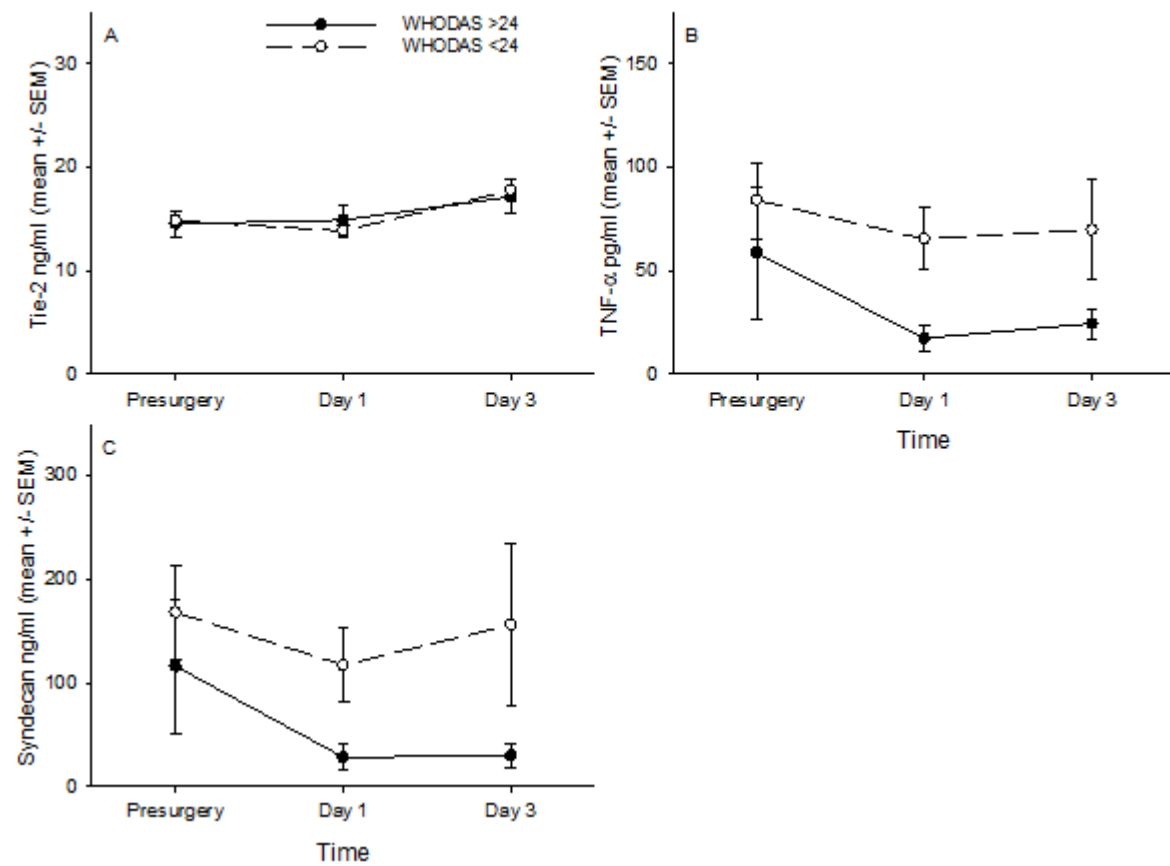
Figure S10

Fig. S10 Plasma biomarkers, normalised for change in plasma volume, by disability free survival at 12 months, defined as WHODAS score <24, during the first three days from surgery. *SEM,* standard error of the mean; *sTie-2,* soluble Angiopoietin-1 receptor; *TNF-a*, tumor necrosis factor alpha.