Additional file B Appendix on patient management in each cohort.

Cohort 1:

Routine fluid input at the ICU was started at a total of 3 liters of fluid per 24 hours as per the local SAH management protocol. This included all oral fluids plus, if necessary, 0.9% saline intravenously. Additional fluids were given (6% hydroxyethyl starch 130/0.4 or 0.9% saline), when fluid balance became less than +500 ml daily or when body temperature exceeded 38°C (0.5 liters of 0.9% saline for every degree Celsius per 24 hours). All patients were treated with oral nimodipine 6 x 60 mg for 21 days. When endovascular coiling of the ruptured aneurysm was feasible this was done as soon as possible. Surgical treatment was scheduled when coiling was technically not feasible and as soon as the patient had a World Federation of Neurosurgical Societies (WFNS) grade I or II. Otherwise, surgery was postponed until day 12 after the initial bleed. Immediate treatment of the ruptured aneurysm was postponed when the patient had an admission WFNS grade V and treatment was scheduled as soon as WFNS grade improved.

Cohort 2:

Cohort 2 consisted of patients managed according to a fluid management protocol guided by cardiac output monitoring with transpulmonary thermodilution (Additional file A). Briefly, the inclusion criteria for cohort 2 were equal to the entry characteristics for the protocol and were GCS < 15 and at least one of the following characteristics: hypotension (systolic blood pressure < 100 mmHg or MAP < 65 mmHg), not responsive to fluid administration; (neurogenic) pulmonary edema or clinically relevant cardiac dysfunction (as judged by attending ICU physician); negative fluid balance (-1L/day); DCI as judged by attending neurologist and either a persisting negative fluid balance (-500 mL/day) or progressive neurological deterioration despite extra fluid loading (aimed at mean arterial pressure of at least 80 mmHg and positive fluid balance). If cardiac index was < 4.0 L/min/m2, a fluid bolus of 250 mL 6% hydroxyethyl starch 130/0.4 (Voluven) was infused and repeated until cardiac index increased to > 4.0 L/min/m2 or did not further increase. If cardiac index did not increase after a fluid bolus, dobutamine was started and titrated until cardiac index increased to target or dosage reached 5 µg/kg/min. If a patient had an indication for dobutamine but a heart rate of > 100 beats per minute, enoximone was started and titrated similarly to a maximum dosage of 2 µg/kg/min (Additional file A).

Additional file C Imputation assumptions and formula used in the Aregimpute function in R

[(1) the number of missing values for each variable or the number of complete vs incomplete cases

In total, 119 observations (18%) of fluid input data, 119 observations (18%) of fluid loss data, 8 (3.6%) Hijdra cistern sum scores, and 12 (5.4%) of Hijdra ventricle sum scores were missing and imputed. There were 146 complete cases prior to imputation (65%).

(2) The outcome was available for all patients and the missing number of key exposure variables have already been mentioned. Below is a comparison table between the fluid volumes of the measured values and the imputed values.

	No DCI		**DCI**	
	Complete cases (n)	**Imputed cases (n)**	**Complete cases (n)**	**Imputed cases (n)**
Fluid input				
day 1	4.4 ± 0.13 (110)	4.4 ± 0.13 (132)	5.0 ± 0.20 (82)	4.9 ± 0.19 (91)
day 2	4.2 ± 0.12 (107)	4.2 ± 0.12 (132)	4.8 ± 0.22 (82)	5.0 ± 0.21 (91)
day 3	4.5 ± 0.17 (92)	4.6 ± 0.15 (132)	4.7 ± 0.18 (77)	4.8 ± 0.17 (90)*
Fluid loss				
day 1	2.8 ± 0.13 (110)	2.9 ± 0.13 (132)	3.3 ± 0.19 (82)	3.3 ± 0.17 (91)
day 2	3.2 ± 0.16 (107)	3.2 ± 0.14 (132)	3.5 ± 0.22 (82)	3.6 ± 0.23 (91)
day 3	3.9 ± 0.18 (92)	3.9 ± 0.15 (132)	3.9 ± 0.21 (77)	3.8 ± 0.19 (90)*
Hijdra sum score				
Cistern	16 (9 - 20) (127)	16 (9 - 20) (132)	20 (14 - 23) (88)	20 (14 - 23) (91)
Ventricular	2 (0 - 4) (124)	2 (0 - 4) (132)	3 (0 - 6) (87)	3 (0 - 6) (91)

Fluid in liters ± standard error. Score with interquartile range. DCI: delayed cerebral ischemia. *One patient died at day 3 and data for this patient was therefore not imputed.

(3) The main reason contributing to occurrence of missing data in cohort 1 is due to the transferral of patients for endovascular interventions, see the methods section. Transferals were at random, based on in which hospital the on-call intervention neuroradiologist was based in.

(4) The data are assumed to be missing at random to allow statistical imputation.

(5) The imputation was performed with the AregImpute function in R statistical software using the following variables in the model: sex, age, admission GCS, aneurysm location, treatment mode, GOS, death within 6 months, Hijdra cistern score, Hijdra ventricle score, intracranial hemorrhage,

diastolic/systolic/mean blood pressure at admission, fluid input on day 1 to 3 and fluid loss day 1 to 3. The specific formula used in the Aregimpute function is shown below.

Formula:

sex + age + admissionGCS + as.factor(aneurloc*.m)* + *as.factor(treatment_mode.m)* + *I(GOS.m)* + *death_within_6months.m* + *HIJDRA_CIST_SUMSCORE.m* + *HIJDRA_VENTR_SUMSCORE.m* + *ICH.m* + *DBPadmission.r* + *SBPadmission.r* + *MAPadmission.r* + *I(TEMPadmission.m)* + *FL_INTAKE_D1.m* + *FL_INTAKE_D2.m* + *FL_INTAKE_D3.m* + *FL_EXCRETION_D1.m* + *FL_EXCRETION_D2.m* + *FL_EXCRETION_D3.m*

Additional file D Multivariable logistic regression models (cohort 1) with fluid input, in the first 24 to 72 hours, dichotomized at various cutpoints, as predictors for delayed cerebral ischemia.

Variable	OR	95% CI	OR	95% CI	OR	95% CI
Fluid input cutoff		**3 L**		**4 L**		**5 L**
Age (year)	1.01	0.99 – 1.03	1.01	0.99 – 1.03	1.01	0.99 – 1.04
Gender (female)	1.25	0.69 – 2.26	1.26	0.70 – 2.27	1.32	0.72 – 2.41
Admission WFNS (> 3)	2.54	1.38 – 4.67	2.50	1.36 – 4.61	2.40	1.30 – 4.44
Hijdra Cistern score (≥ 17)	2.15	1.21 – 3.80	2.13	1.20 – 3.76	2.05	1.15 – 3.66
Hijdra Ventricular score (≥ 2)	1.17	0.64 – 2.14	1.16	0.63 – 2.12	1.13	0.61 – 2.09
Fluid input 0 – 24h (L)	1.40	0.56 – 3.52	1.29	0.71 – 2.35	2.18	1.17 – 4.04
Fluid input cutoff		**6 L**		**8 L**		**10 L**
Age (year)	1.01	0.99 – 1.03	1.01	0.99 – 1.04	1.01	0.99 – 1.03
Gender (female)	1.26	0.70 – 2.28	1.26	0.69 – 2.30	1.28	0.70 – 2.32
Admission WFNS (> 3)	2.51	1.37 – 4.61	2.48	1.34 – 4.58	2.51	1.37 – 4.63
Hijdra Cistern score (≥ 17)	2.19	1.23 – 3.89	2.15	1.20 – 3.85	2.13	1.20 – 3.79
Hijdra Ventricular score (≥ 2)	1.17	0.64 – 2.13	1.13	0.61 – 2.09	1.20	0.65 – 2.20
Fluid input 0 – 48h (L)	2.00	0.60 – 6.70	2.30	1.22 – 4.32	2.01	1.10 – 3.69
Fluid input cutoff		**9 L**		**12 L**		**15 L**
Age (year)	1.01	0.99 – 1.04	1.02	0.99 – 1.04	1.01	0.99 – 1.03
Gender (female)	1.23	0.68 – 2.23	1.27	0.70 – 2.31	1.27	0.69 – 2.32
Admission WFNS (> 3)	2.53	1.38 – 4.64	2.55	1.38 – 4.71	2.45	1.32 – 4.54
Hijdra Cistern score (≥ 17)	2.24	1.26 – 3.98	2.21	1.24 – 3.95	2.27	1.26 – 4.09
Hijdra Ventricular score (≥ 2)	1.12	0.61 – 2.05	1.13	0.61 – 2.08	1.24	0.67 – 2.31
Fluid input 0 – 72h (L)	3.89	0.42 – 36.1	1.93	1.02 – 3.65	2.60	1.39 – 4.89

Each set of variables shows the multivariate regression model for the specified cutoff value for cumulative fluid input.

WFNS: World Federation of Neurosurgical Societies grading score; OR: odds ratio; CI: confidence interval.

Additional file E Univariable logistic regression models for data from cohort 1 with DCI as outcome

Variabele	**OR**	**95% CI**
Age (year)	1.01	0.99 – 1.03
Gender (female)	1.24	0.71 – 2.17
Admission WFNS score	2.81	1.59 – 4.96
Hijdra Cistern score	1.06	1.02 – 1.10
Hijdra Ventricular score	1.13	1.04 – 1.23
Fluid input 0–24h (L)	1.25	1.05 – 1.49
Fluid input 0–48h (L)	1.28	1.12 – 1.45
Fluid input 0–72h (L)	1.17	1.06 – 1.29
Fluid balance 0–24h (L)	1.08	0.91 – 1.29
Fluid balance 0–48h (L)	1.10	0.98 – 1.24
Fluid balance 0–72h (L)	1.08	0.99 – 1.18

WFNS: World Federation of Neurosurgical Societies grading score

Additional file F Multivariable logistic regression models for cumulative fluid input and balance data with DCI infarction as outcome from cohort 1.

	Fluid input			Fluid balance	
Variable	**OR**	**95% CI**	**Variable**	**OR**	**95% CI**
Age (year)	0.97	0.95 – 1.00	Age (year)	0.97	0.95 – 1.00
Gender (female)	0.98	0.51 – 1.91	Gender (female)	0.91	0.47 – 1.74
Admission WFNS (> 3)	3.25	1.66 – 6.35	Admission WFNS (>3)	3.81	1.97 – 7.39
Hijdra Cistern score (≥ 17)	1.60	0.83 – 3.07	Hijdra Cistern score (≥ 17)	1.57	0.82 – 3.00
Hijdra Ventricular score (≥ 2)	1.12	0.56 – 2.24	Hijdra Ventricular score (≥ 2)	1.10	0.55 – 2.20
Fluid input 0 – 24h (L)	1.24	1.02 – 1.51	Fluid balance 0 – 24h (L)	1.16	0.94 – 1.45
Age (year)	0.97	0.95 – 1.00	Age (year)	0.97	0.95 – 1.00
Gender (female)	0.98	0.50 – 1.91	Gender (female)	0.89	0.46 – 1.72
Admission WFNS (> 3)	3.26	1.66 – 6.40	Admission WFNS (> 3)	3.63	1.87 – 7.05
Hijdra Cistern score (≥ 17)	1.52	0.79 – 2.94	Hijdra Cistern score (≥ 17)	1.57	0.82 – 3.00
Hijdra Ventricular score (≥ 2)	1.14	0.56 – 2.29	Hijdra Ventricular score (≥ 2)	1.09	0.54 – 2.19
Fluid input 0 – 48h (L)	1.26	1.08 – 1.47	Fluid balance 0 – 48h (L)	1.15	1.00 – 1.33
Age (year)	0.97	0.95 – 1.00	Age (year)	0.97	0.95 – 1.00
Gender (female)	1.02	0.52 – 1.99	Gender (female)	0.92	0.47 – 1.78
Admission WFNS (> 3)	3.58	1.83 – 7.01	Admission WFNS (> 3)	3.62	1.86 – 7.05
Hijdra Cistern score (≥ 17)	1.55	0.80 – 2.99	Hijdra Cistern score (≥ 17)	1.61	0.84 – 3.09
Hijdra Ventricular score (≥ 2)	1.16	0.58 – 2.33	Hijdra Ventricular score (≥ 2)	1.06	0.53 – 2.13
Fluid input 0 – 72h (L)	1.18	1.05 – 1.32	Fluid balance 0 – 72h (L)	1.12	1.01 – 1.25

WFNS: World Federation of Neurosurgical Societies grading score

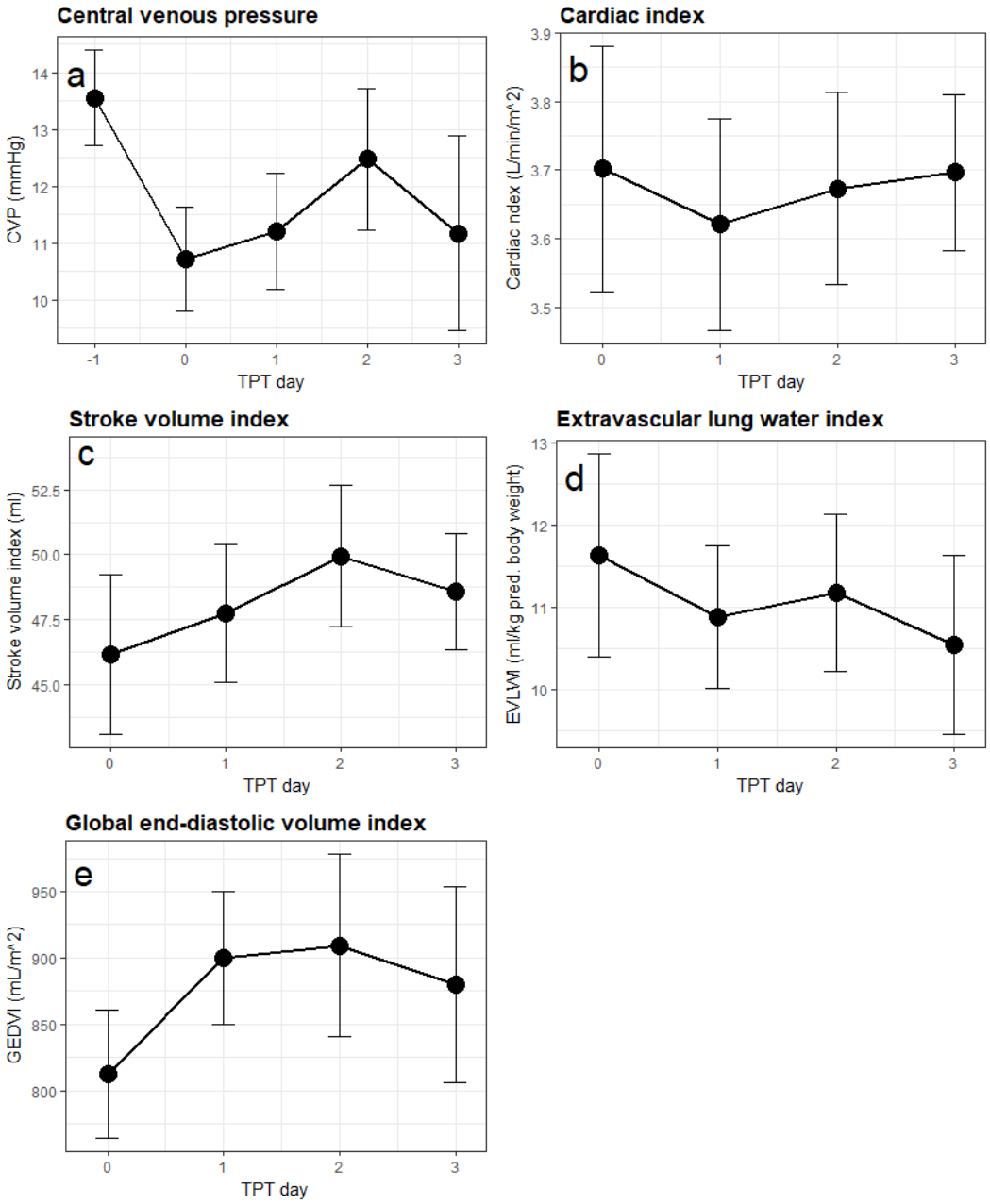
Additional file G Multivariate logistic regression models for cumulative fluid input and balance data from cohort 1 with Glasgow Outcome Score as outcome.

	Fluid input			Fluid balance	
Variable	**OR**	**95% CI**	**Variable**	**OR**	**95% CI**
Age (year)	1.04	1.01 – 1.07	Age (year)	1.04	1.01 – 1.07
Gender (female)	1.24	0.62 – 2.47	Gender (female)	1.16	0.59 – 2.29
Admission WFNS (> 3)	3.55	1.78 – 7.10	Admission WFNS (> 3)	4.05	2.06 – 7.95
Hijdra Cistern score (≥ 17)	1.51	0.77 – 2.94	Hijdra Cistern score (≥ 17)	1.43	0.74 – 2.77
Hijdra Ventricular score (≥ 2)	1.07	0.53 – 2.17	Hijdra Ventricular score (≥ 2)	1.16	0.58 – 2.33
Fluid input 0 – 24h L	1.22	1.00 – 1.49	Fluid balance 0 – 24h (L)	0.96	0.77 – 1.19
Age (year)	1.04	1.01 – 1.07	Age (year)	1.04	1.01 – 1.07
Gender (female)	1.18	0.59 – 2.35	Gender (female)	1.16	0.59 – 2.29
Admission WFNS (> 3)	3.67	1.84 – 7.30	Admission WFNS (> 3)	4.04	2.05 – 7.95
Hijdra Cistern score (≥ 17)	1.46	0.75 – 2.84	Hijdra Cistern score (≥ 17)	1.44	0.74 – 2.79
Hijdra Ventricular score (≥ 2)	1.12	0.55 – 2.26	Hijdra Ventricular score (≥ 2)	1.14	0.57 – 2.29
Fluid input 0 – 48h (L)	1.14	1.01 – 1.29	Fluid balance 0 – 48h (L)	1.00	0.87 – 1.15
Age (year)	1.05	1.02 – 1.08	Age (year)	1.04	1.02 – 1.07
Gender (female)	1.22	0.61 – 2.46	Gender (female)	1.12	0.56 – 2.23
Admission WFNS (> 3)	3.86	1.94 – 7.67	Admission WFNS (> 3)	3.96	1.99 – 7.84
Hijdra Cistern score (≥ 17)	1.47	0.75 – 2.89	Hijdra Cistern score (≥ 17)	1.50	0.77 – 2.92
Hijdra Ventricular score (≥ 2)	1.12	0.55 – 2.27	Hijdra Ventricular score (≥ 2)	1.07	0.53 – 2.16
Fluid input 0 – 72h (L)	1.12	1.00 – 1.25	Fluid balance 0 – 72h (L)	1.00	0.89 – 1.11

WFNS: World Federation of Neurosurgical Societies grading score

N=207, for 16 patients the outcome could not be retrieved.

Additional file H Hemodynamic data in cohort 2.



Data is represented as mean with standard error as two-sided error bar. TPT day 3 is used as the reference value (R) for the comparisons: there were no significant differences over time. Because the placement of a jugular or subclavian central venous catheter at admission for aSAH is not standard practice in our institution, data for central venous pressure is only available from at least TPT day -1 until TPT day 3. TPT: transpulmonary thermodilution.