Supplemental Online Content

Hernández G, Ospina-Tascón GA, Petri Damiani L, et al; ANDROMEDA-SHOCK Investigators and the Latin America Intensive Care Network (LIVEN). Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: the ANDROMEDA-SHOCK ransomized clinical trial. *JAMA*. doi:10.1001/jama.2019.0071

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Exclusion Criteria

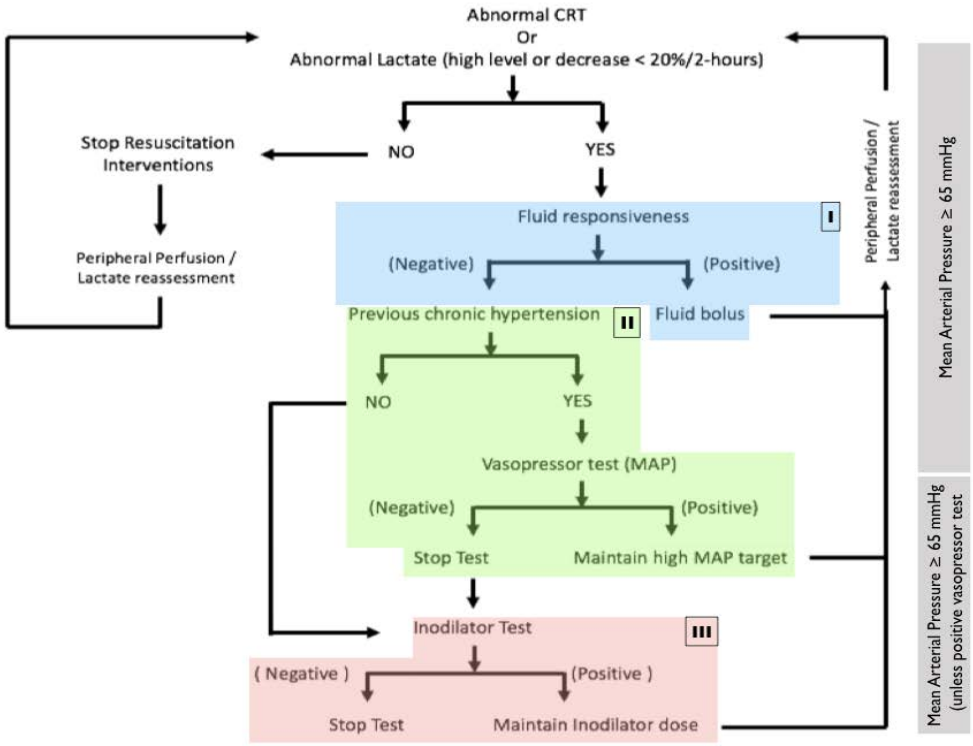
1. Pregnancy
2. Anticipated surgery or dialysis procedure during the first 8h after septic shock diagnosis
3. Do-not-resuscitate status
4. Child B or C liver cirrhosis
5. Active bleeding
6. Acute hematological malignancy
7. Severe concomitant acute respiratory distress syndrome
8. More than 4h after officially meeting septic shock criteria

Additional post-hoc sensitivity analyses

- Intention-to-treat unadjusted Cox proportional hazards model
- Intention-to-treat Cox proportional hazards model adjusted by APACHE II, SOFA, lactate level, CRT, infection source, and intravenous fluid loading per weight before randomization
- Per protocol (8h protocol completed) Cox proportional hazards model, adjusted by APACHE II, SOFA, lactate level, CRT and infection source.
- Per protocol (8h protocol completed) unadjusted Cox proportional hazards model
- Intention-to-treat unadjusted analysis frailty Cox model
- Per protocol (8h protocol completed) frailty Cox model adjusted by APACHE II, SOFA, lactate level, CRT and Infection source.

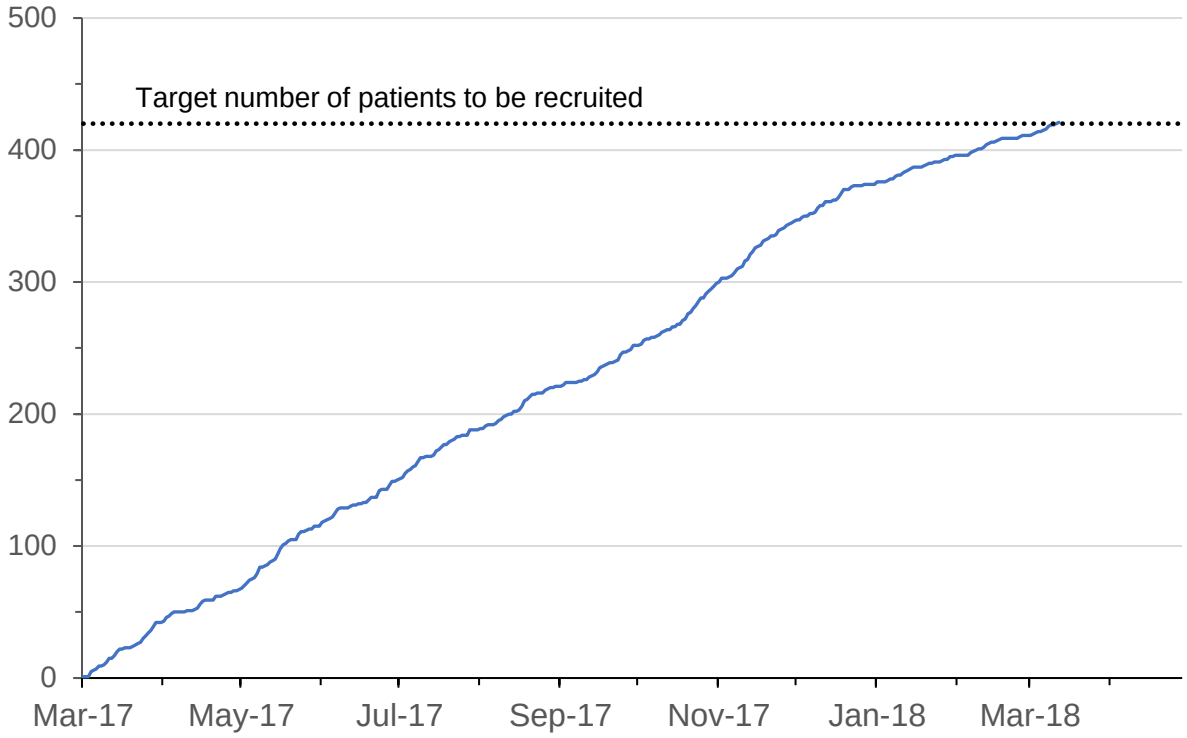
eFigures

eFigure 1. Resuscitation Protocol During the Intervention Period



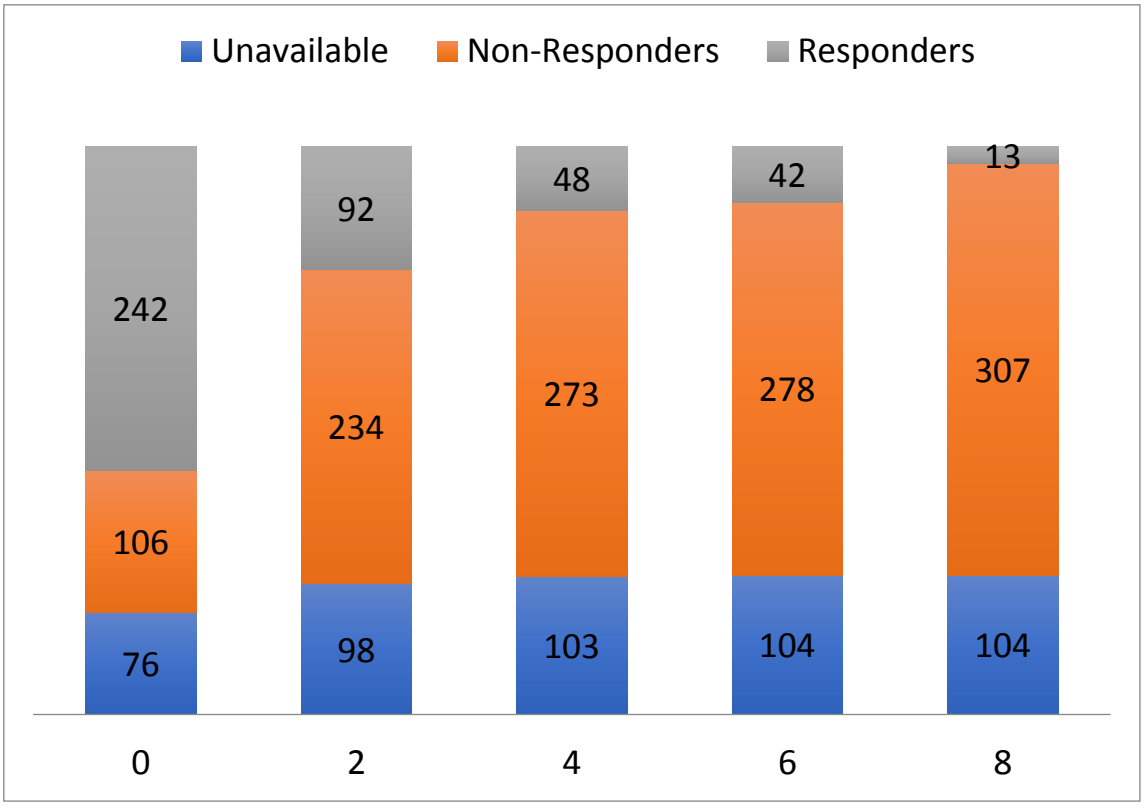
The figure describes the sequential approach to resuscitation. The process starts with fluid loading according to the status of fluid responsiveness (first step). If the goal is not obtained, the second step is a vasopressor test, and then an inodilator test (third step). CRT denotes capillary refill time.

eFigure 2. Cumulative Recruitment per Month

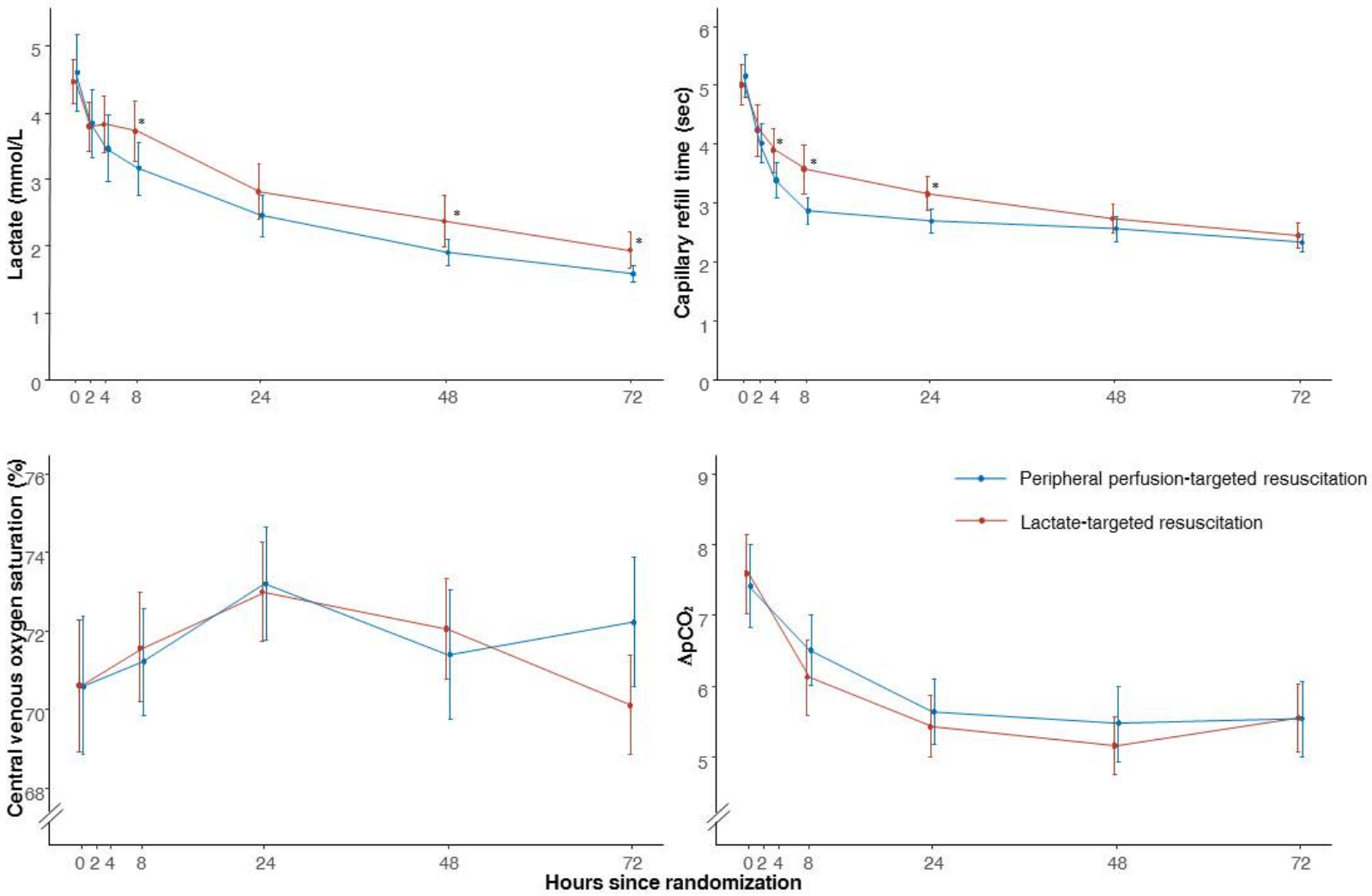


eFigure 3. Evolution of Fluid Responsiveness State During the 8h Intervention Period

Fluid responsiveness was determined periodically during the intervention period as commanded by the clinical report form and the management algorithm. At baseline, fluid responsiveness was unavailable in 76 patients. The group of patients categorized as with unavailable fluid responsiveness status over-time (0 to 8 hours) was the sum of early deaths and patients in whom it could be not determined mainly because of technical reasons.

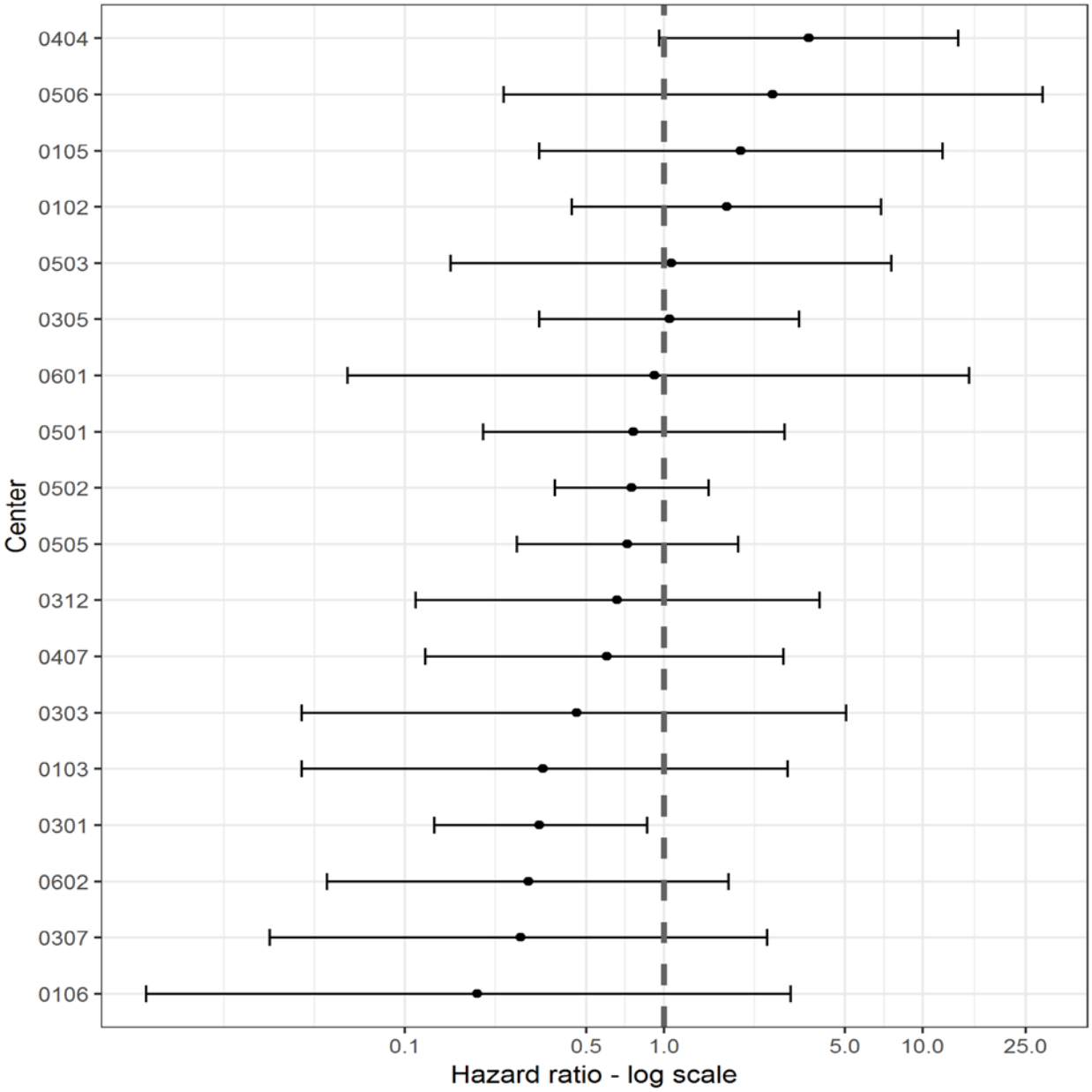


eFigure 4. Perfusion Variables From Baseline to 72 Hours in the Peripheral Perfusion and Lactate Groups



Results presented as mean and 95% confidence interval using generalized linear mixed models with different distributions: Gaussian distribution was used for central venous oxygen saturation and Gamma distribution was used for lactate, capillary refill time and central venous-arterial pCO_2 gradient. P values < 5% comparing groups in each time point are indicated with a ***** sign.

eFigure 5. Treatment Effect on 28-Day Mortality Across Sites



P value=0.33 for homogeneity of effect across sites, calculated with a Cox proportional-hazards model with a center-treatment interaction term and adjustment for 5 pre-specified baseline covariates: Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ-Failure Assessment (SOFA) score, lactate level, CRT, and source of infection.

eTables

eTable 1. Characteristics of Participant Centers, Number of Patients Enrolled and Rate of Enrolment

Country	Participating site	Hospital type	Nº hospital beds	Nº ICU beds	Annual nº ICU presentations	Screened patients	Total nº patients recruited	Patients assigned to lactate-targeted resuscitation	Patients assigned to peripheral perfusion-targeted resuscitation	Patients randomized per month
Argentina	Clínica La Pequeña Familia	private	100	20	809	42	5	3	2	0.4
Argentina	Sanatorio Otamendi y Miroli	Private	206	28	374	77	21	10	11	1.8
Argentina	Hospital Provincial del Centenario	public	190	16	515	36	9	6	3	0.7
Argentina	Sanatorio Parque	private	90	15	1057	38	12	7	5	0.9
Argentina	Hospital Interzonal San Martín	public	278	14	353	18	3	1	2	0.3
Argentina	Sanatorio Allende	private	262	23	1189	21	3	2	1	0.3
Chile	Hospital Barros-Luco Trudeau	Public	900	21	865	124	55	27	28	5.5
Chile	Hospital del Salvador	Public	400	12	602	44	4	2	2	0.3
Chile	Hospital Dr. Sótero del Río	Public	800	18	750	81	5	3	2	0.4
Chile	Hospital Guillermo Grant Benavente	Public	977	36	760	49	35	15	20	2.7
Chile	Hospital San Juan de Dios de Curicó	Public	285	10	362	17	1	1	0	0.1
Chile	Hospital San Juan de Dios de Santiago	Public	600	17	424	43	11	7	4	0.9
Chile	Hospital Clínico Universidad de Chile	private	500	12	419	40	4	2	2	0.3
Chile	Pontificia Universidad Católica de Chile	private	480	32	10176	99	27	15	12	2.1
Chile	Hospital Herminda Martinez	Public	466	12	313	28	4	1	3	0.4
Colombia	Hospital San Vicente de Paul	public	651	14	388	18	1	1	0	0.1
Colombia	Hospital de Santa Clara	private	250	32	1150	15	5	0	5	0.6
Colombia	Hospital Universitario de Ñarino	public	380	20	1630	46	16	9	7	2.0
Colombia	Fundación Valle del Lili	private	512	90	4294	72	27	18	9	3.0

Colombia	Hospital Universitario del Río	private	40	8	157	29	15	10	5	1.2
Ecuador	Hospital Eugenio Espejo	public	400	23	817	154	55	27	28	4.2
Ecuador	Hospital San Francisco de Quito	public	128	8	517	59	23	11	12	1.8
Ecuador	Hospital Enrique Garcés	public	370	7	456	23	2	1	1	0.7
Ecuador	Hospital General Docente Calderón	public	150	12	586	91	48	18	30	3.7
Ecuador	Hospital Carlos Andrade Marín	public	600	35	1869	19	13	7	6	1.0
Ecuador	Hospital IESS Ibarra	public	146	6	202	21	7	3	4	0.7
Uruguay	Hospital de Clínicas	public	359	11	414	4	2	1	1	0.7
Uruguay	Hospital Español Juan J Crottogini	public	120	24	627	19	11	4	7	1.0

Two of the 28 sites (Hospital Enrique Garcés of Quito, and Hospital de Clínicas, Montevideo) left the study after 3 months because of organizational problems, and thus 26 centers participated until the end of the trial.

eTable 2. Hemodynamic and Perfusion Variables From Baseline to 72 hours in the Peripheral Perfusion and Lactate Groups

Variable	Group	Baseline	2h	4h	8h	24h	48h	72h
Number of patients	PP	212	191	189	183	163	151	144
	L	212	187	186	184	170	153	146
Heart rate – beats / minute	PP	103 ± 23	101 ± 21	101 ± 24	100 ± 23	93 ± 21	85 ± 16	85 ± 16
	L	103 ± 23	102 ± 22	102 ± 22	99 ± 21	96 ± 22	90 ± 19	87 ± 19
	P value	-	0.68	0.89	0.38	0.54	0.15	0.81
Systolic arterial blood pressure – mmHg	PP	102 ± 22	110 ± 19	110 ± 18	111 ± 19	114 ± 18	118 ± 17	118 ± 19
	L	99 ± 21	108 ± 19	110 ± 19	108 ± 21	112 ± 20	118 ± 21	121 ± 20
	P value	-	0.33	0.67	0.28	0.52	0.97	0.16
Diastolic arterial blood pressure – mmHg	PP	53 ± 13	56 ± 11	56 ± 10	57 ± 11	58 ± 10	63 ± 12	63 ± 11
	L	53 ± 12	57 ± 11	58 ± 11	56 ± 9	59 ± 11	63 ± 13	65 ± 11
	P value	-	0.40	0.02	0.58	0.33	0.99	0.06
Mean arterial blood pressure – mmHg	PP	69 ± 14	74 ± 10	74 ± 11	74 ± 11	75 ± 10	81 ± 12	80 ± 12
	L	68 ± 13	73 ± 11	75 ± 10	73 ± 11	76 ± 13	81 ± 15	85 ± 13
	P value	-	0.79	0.29	0.49	0.46	0.63	**<0.01**
Median norepinephrine dose (IQR) – mcg/Kg/min	PP	0.24 [0.11 - 0.40]	0.24 [0.10 - 0.40]	0.21 [0.08 - 0.41]	0.20 [0.09 - 0.40]	0.17 [0.08 - 0.40]	0.11 [0.05 - 0.22]	0.10 [0.03 - 0.18
	LT	0.20 [0.10 - 0.35]	0.20 [0.10 - 0.39]	0.22 [0.10 - 0.42]	0.23 [0.09 - 0.44]	0.22 [0.10 - 0.46]	0.12 [0.07 - 0.35]	0.10 [0.06 - 0.21
	P value	-	0.58	0.13	0.17	0.81	**<0.01**	**<0.01**
Norepinephrine use – no. (%)	PP	208 (100)	186 (90.3)	179 (87.7)	162 (80.6)	120 (60.9)	78 (40.2)	48 (24.7)
	L	208 (100)	184 (88.0)	180 (86.5)	169 (81.6)	122 (58.9)	84 (40.6)	59 (28.6)
	P value	-	0.90	0.95	0.80	0.69	0.93	0.61
Median diuresis (IQR) – total ml / kg / hour in previous period	PP	-	0.6 [0.2 - 1.3]	0.8 [0.3 - 1.5]	0.8 [0.3 - 1.5]	0.9 [0.3 - 1.8]	1.0 [0.5 - 1.6]	1.1 [0.5 - 1.7]
	L	-	0.5 [0.2 - 1.4]	0.7 [0.3 - 1.4]	0.8 [0.4 - 1.6]	0.6 [0.1 - 1.3]	0.8 [0.2 - 1.4]	0.8 [0.3 - 1.5]
	P-value	-	0.49	0.56	0.62	**0.03**	0.21	0.24
Lactate – mmol/l	PP	4.6 ± 4.3	3.8 ± 2.6	3.5 ± 2.4	3.2 ± 2.6	2.5 ± 2.0	1.9 ± 1.2	1.6 ± 0.7
	L	4.5 ± 2.5	3.8 ± 2.7	3.8 ± 3.1	3.7 ± 3.3	2.8 ± 2.8	2.4 ± 2.5	1.9 ± 1.7
	P-value	-	0.72	0.30	**0.05**	0.09	**0.01**	**<0.01**
Median capillary refill time (IQR) – sec	PP	5 [4 - 6]	3.1 [2.5 - 5]	3 [2 - 4]	2.3 [2 - 3]	2 [2 - 3]	2 [2 - 3]	2 [2 - 3]
	L	4 [3 - 6]	3.6 [2.9 - 5]	3 [2.5 - 4.9]	3 [2 - 4]	3 [2 - 3.5]	2 [2 - 3]	2 [2 - 3]
	P-value	-	0.52	**0.01**	**<0.01**	**<0.01**	0.08	0.56
Central venous oxygen saturation – %	PP	70.6 ± 12.8	-	-	71.2 ± 9.4	73.2 ± 9.5	71.4 ± 9.9	72.2 ± 9.6
	L	70.6 ± 12.0	-	-	71.6 ± 9.8	73.0 ± 8.4	72.1 ± 8.0	70.1 ± 7.6
	P-value	-	-	-	0.54	0.83	0.44	0.12
Median central venous-arterial pCO2 gradient (IQR) – mmHg	PP	7 [5 - 10]	-	-	6 [5 - 8]	5 [4 - 7]	5 [3 - 7]	5 [3 - 7]
	L	7 [5 - 10]	-	-	6 [4 - 8]	5 [4 - 7]	5 [3 - 7]	5 [4 - 7]
	P-value	-	-	-	0.16	0.57	0.70	0.56

* Plus–minus values are means ± SD. PP denotes peripheral perfusion group, L, lactate group, and pCO_2, partial pressure of carbon dioxide. Comparisons were done using generalized linear mixed models with different distributions: Gaussian distribution was used for heart rate, central venous oxygen saturation, systolic, diastolic and mean arterial blood pressures; gamma distribution was used for norepinephrine dose, diuresis, lactate, capillary refill time and central venous-arterial pCO_2 gradient; binomial (logistic model) was used for norepinephrine.

eTable 3. Protocol Violations and Deviations*

Type of violation or deviation	Peripheral Perfusion-Targeted Resuscitation Group (N = 212)	Lactate-Targeted Resuscitation Group (N = 212)
Eligibility criteria violation†	**2**	**3**
Inclusion criteria	1	2
No need of vasopressor	1	1
Normal lactate	0	1
Exclusion criteria	1	1
Age less than 18 years-old	1	0
Advanced cirrhosis	0	1
Treatment protocol violation	**3**	**3**
Did not receive assigned treatment	5	3
Lack of personnel to deliver intervention	4	2
Malfunction of lactate point-of-care device	0	1
Urgent surgery	1	0
Treatment protocol deviation	**26**	**20**
Treatment protocol mismanagement	16	16
Administering fluid bolus when not indicated	5	4
Not administering fluid bolus when indicated	4	4
Mismanagement of vasopressor test	4	5
Mismanagement of inodilator test	3	3
Early termination of assigned treatment	10	4
Refractory shock	8	4
Urgent surgery	1	0
Gastrointestinal bleeding	1	0

* All patients were analyzed according to the treatment group they were randomly assigned, irrespective of violations or deviations.
† Cases that were randomized but did not meet eligibility criteria were treated according to randomly assigned treatment group.

eTable 4. Use of Vasopressor Test, Inodilator Test and Adjunctive Drugs for Shock

Treatment	Peripheral Perfusion Group (n=212)	Lactate Group (n=212)	P Value*
Vasopressor test – no. (%)	61 (28.8)	85 (40.1)	0.02
Inodilator test – no. (%)	30 (14.2)	36 (17.0)	0.60
Any adjunctive therapy – no. (%)	45 (21.2)	62 (29.2)	0.07
Steroids	32 (15.1)	49 (23.1)	0.06
Epinephrine	21 (9.9)	35 (16.5)	0.01
Vasopressin	2 (0.9)	12 (5.7)	0.42
High Volume Hemofiltration	5 (2.4)	9 (4.2)	0.05

* P values calculated with Fisher exact test.

eTable 5. Capillary Refill Time and Lactate Levels at Each Time Point of the Intervention Period in Fluid Unresponsive Patients

Peripheral Perfusion Group

		CRT	Lactate
	n	Median [IQR 25-75] (sec)	Mean ± SD (mmol/l)
T0	49	4.0 [3.0-6.0]	4.3 ± 2.3
T2	119	3.0 [2.2-4.0]	3.8 ± 2.8
T4	141	3.0 [2.0-4.0]	3.5 ± 2.6
T8	156	2.2 [2.0-3.0]	3.2 ± 2.9

Lactate Group

		CRT	Lactate
	n	Median [IQR 25-75] (sec)	Mean ± SD (mmol/l)
T0	57	4.0 [2.0-6.0]	4.4 ± 2.3
T2	115	3.0 [2.8-4.5]	3.5 ± 2.6
T4	132	3.0 [2.2-4.9]	3.5 ± 2.9
T8	151	3.0 [2.0-4.0]	3.5 ± 2.9

eTable 6. Sensitivity Analyses of the Treatment Effect on the Primary Outcome

Type of analysis	Cox Proportional hazards or Frailty Cox Model*	Hazard ratio (95% CI)	P Value
Pre-specified sensitivity analyses†			
Intention to treat analysis, adjusted by APACHE II, SOFA, Infection source, CRT and lactate	Frailty Cox model	0.75 (0.57 to 0.98)	0.04
***Post hoc* sensitivity analyses**			
Intention-to-treat unadjusted analysis	Cox proportional hazards model	0.79 (0.58 to 1.07)	0.13
Intention-to-treat analysis, adjusted by APACHE II, SOFA, infection source, CRT, lactate and intravenous fluid loading per weight before randomization	Cox proportional hazards model	0.75 (0.55 to 1.02)	0.07
Per protocol (8h protocol completed) analysis, adjusted by APACHE II, SOFA, infection source, CRT and lactate.	Cox proportional hazards model	0.72 (0.52 to 0.99)	0.04
P*er protocol* (8h protocol completed) unadjusted analysis	Cox proportional hazards model	0.76 (0.55 to 1.04)	0.09
Intention-to-treat unadjusted analysis	Frailty Cox model	0.79 (0.59 to 1.05)	0.11
Per protocol 8h protocol completed) analysis, adjusted by APACHE, SOFA, Infection source, CRT and lactate.	Frailty Cox model	0.72 (0.56 to 0.93)	0.01

* Frailty models with trial center as random effects. Reported Hazard ratio is the marginal effect (e.g., average effect over the distribution of the center random effects).
† Sensitivity analysis pre-specified in our statistical analysis plan elaborated and submitted for publication before the database was locked and analyses were started.