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Persistence of central venous oxygen desaturation during early sepsis is associated with higher mortality: a retrospective analysis of the ALBIOS trial

Running head: Prognosis of $ScvO_2$ <70% during early sepsis

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Abstract

Background: Relevance of low (<70%) central venous oxygen saturation ($ScvO_2$) during early sepsis has been recently questioned by three negative trials (ProCESS, ARISE and ProMISe) on early goal-directed therapy (EGDT). However, subjects included in those trials had $ScvO_2$ at enrolment as high as 71±13%, 73±11% and 70±12%. Herein we assessed the association between persistence of central venous oxygen desaturation ($ScvO_2$ <70%) and 90-day mortality in subjects enrolled in the ALBIOS trial, focusing on those with initial $ScvO_2$ <70%.

Methods: Irrespectively from treatment assignment (to receive albumin or not), all subjects enrolled in the trial received EGDT aiming for $ScvO_2$ ≥70% at six hours. Using multivariable logistic regression analysis, we tested the association between $ScvO_2$ <70% at six hours and 90-day mortality in those with initial $ScvO_2$ <70% (n=514) or ≥70% (n=961).

Results: $ScvO_2$ <70% at six hours was independently associated with higher 90-day mortality in subjects with initial $ScvO_2$ <70% (OR 1·84, 95%-CI 1·19-2·85; p=0·007) but not in those with initial $ScvO_2$ ≥70% (OR 1·25, 95%-CI 0·79-1·95; p=0·357). Among subjects with initial $ScvO_2$ <70%, persistence of central venous oxygen desaturation was associated with history of cardiac disease and higher plasma levels of biomarkers of cardiac injury but not with greater severity of disease or more aggressive resuscitation (required per protocol).

Conclusions: In the ALBIOS trial, persistence of central venous oxygen desaturation predicted higher 90-mortality, possibly because it reflected untreated cardiac dysfunction. Subjects with $ScvO_2$ <70% may benefit most from personalised EGDT.

Trial Registry: ClinicalTrials.gov; NCT00707122.

Introduction

During severe sepsis or septic shock, hypoxemia, anaemia, and low or mal-distributed cardiac output can decrease oxygen supply,[1] mitochondrial dysfunction can limit oxygen use,[2] and overt inflammation can increase oxygen demand. If severe or prolonged, the resulting imbalance between oxygen delivery and consumption will lead to cellular dysfunction or death.[3] Central venous oxygen desaturation (that is, central venous oxygen saturation [$ScvO_2$] <70%) signals a mismatch between oxygen supply and demand in the upper, and possibly even in the lower, part of the human body.[4]

Approximately 15 years ago, one single centre randomized controlled trial showed that (*early goal-directed*) therapy aiming for prompt reversal of central venous oxygen desaturation can reduce in-hospital mortality of subjects with systemic inflammatory response to infection and either a systolic blood pressure ≤90 mm Hg after a crystalloid-fluid challenge (20-30 ml/kg of body weight) or a blood lactate concentration of ≥4 mmol/L.[5] Since then, targeting $ScvO_2$ ≥70% during initial resuscitation from severe sepsis or septic shock has been strongly encouraged.[6] Subsequent large retrospective and prospective studies further supported this recommendation.[7,8]

More recently, three multicentre randomized controlled trials did not confirm those previous findings:[9–11] assignment of subjects with severe sepsis or septic shock to early goal-directed therapy did not reduce 60-day or 90-day mortality, but significantly increased costs of hospitalization.[12] Based on these results, most recent Surviving Sepsis Campaign Guidelines no longer recommend targeting, and even monitoring, $ScvO_2$ during early management of sepsis.[13]

One reason for this inconsistency may rely on the marked difference in $ScvO_2$ at enrolment between the first positive trial (49±11%)[5] and the other three negative trials (71±13%,[9] 73±11%,[10] and 70±12%)[11]. Harms of central venous oxygen desaturation and benefits of its early correction may become clear only if initial $ScvO_2$ is <70%.

Based on this hypothesis, we investigated the incidence, risk factors, and association with 90-day mortality of central venous oxygen desaturation during the first six hours of treatment of severe sepsis or septic shock in subjects included in the Albumin Italian Outcome Sepsis (ALBIOS) trial,[14] specifically focusing on those who presented with $ScvO_2$ <70%.

Methods

This is a retrospective analysis of the ALBIOS trial, a multicentre randomized controlled pragmatic study on the efficacy of albumin replacement during the first 28 days of treatment of severe sepsis or septic shock. The ALBIOS trial complied with the 1975 Declaration of Helsinki as revised in 2008 and was approved by the institutional review boards of participating centres. Written informed (deferred) consent was obtained from each subject enrolled, according to the Italian legislation.

Details on the study protocol and main results of the original trial have been reported elsewhere.[14] Briefly, the trial enrolled 1818 adults with a clinical diagnosis of severe sepsis or septic shock from less than 24 hours, at any time during their stay in 100 Italian Intensive Care Units (ICU). Severe sepsis was defined as proven or suspected infection; two or more signs of the systemic inflammatory response syndrome; and at least one acute, sepsis-related, organ dysfunction as measured with the Sequential Organ Failure Assessment (SOFA) score (please refer to legend of Table 1 for details).[15–18] Septic shock was defined as a score ≥3 for the cardiovascular component of the SOFA score, that is need of dopamine (>5 μg/kg/min), epinephrine or norepinephrine.[16] Subjects fulfilling these criteria were randomly assigned to receive either 20% albumin and crystalloid solutions (study group) or crystalloid solutions alone (control group) for fluid resuscitation, from randomization until day 28 or ICU discharge, whichever came first.

Irrespectively from treatment assignment, all subjects had to receive fluids, catecholamine(s), red blood cells, sedation and/or mechanical ventilation according to a standardized protocol, to reach the following targets within the first six hours: mean arterial pressure 65-90 mm Hg; central venous pressure 8-12 mm Hg; and $ScvO_2$ ≥70% (early goal-directed therapy).[5]

In the present analysis, we included only subjects with $ScvO_2$ recorded both at enrolment and at six hours (Fig. 1). Some of these subjects also had their plasma levels of biomarkers of cardiac injury

N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) measured at day one, as part of a predefined and previously reported sub-study.[19]

- Statistical analysis

Continuous variables are reported as mean (SD) or median (IQR), while categorical variables are reported as proportion. Groups were compared with Student's *t* or Mann-Whitney rank sum test, Chi-square or Fisher's exact test, as appropriate.

Multivariable logistic regression analyses were applied to identify risk factors for 90-day mortality. Variables recorded at enrolment or at six hours associated with 90-day mortality at univariable analyses ($p<0.05$), were included in multivariable models. For multivariable analyses only, missing data of potential predictors of outcome were handled depending on their frequency:[20] if <5% they were imputed with median (by subgroup) values; if 5-10% (as for serum albumin at enrolment) then subjects were excluded from the analysis. This rule did not apply to the variable "with adequate antibiotic therapy at day one" (yes or no), as it reasonably affected outcome.[21] This variable was always included in multivariable models, and missing values (culture-negative samples) were replaced with a dummy indicator. Backward selection was used to define final models. Results are reported as odds ratio (OR) and 95% confidence interval (95%-CI).

Statistical analyses were performed with SAS software 9.3 (SAS Institute; Cary, NC, USA) and Sigma Plot software 11.0 (Jandel Scientific Software; San Jose, CA, USA).

Results

- Incidence, risk factors, and association with 90-day mortality of initial central venous oxygen desaturation

Eight subjects enrolled in the ALBIOS trial were excluded from the original analysis owing to withdrawal of consent (n=2) or randomization error (n=6); 335 other subjects were excluded from this present analysis because of missing $ScvO_2$ at enrolment (n=218) and/or at six hours (n=268). Among the remaining 1475 subjects, 514 (35%) had an initial $ScvO_2$ <70% (61±8%; range 28-69%) (Fig. 1).

As reported in Table 1, subjects with initial $ScvO_2$ <70% differed in several aspects from those with initial $ScvO_2$ ≥70%. More commonly, they had undergone elective surgery, had a history of cardiac disease and were enrolled early after fulfilment of inclusion criteria. Less commonly, they had undergone emergency surgery, suffered from septic shock, were treated with mechanical ventilation, and had received albumin in the previous 24 hours. On average, they were older, had higher Simplified Acute Physiology Score (SAPS) II and lower, but quite normal, arterial oxygenation, mean arterial pressure, urine output and haemoglobin concentration. Initial central venous oxygen desaturation was also associated with higher plasma levels of biomarkers of cardiac injury at day one.

As for 90-day mortality, it was higher in subjects with initially low, compared to normal, $ScvO_2$ (44% *vs*. 38%; p=0·033) (Fig. 2). However, at multivariable analysis, initial $ScvO_2$ <70% did not emerge as a significant risk factor for death (OR 0·98, 95% CI 0·75-1·28; p=0·877) (e-Table 1 and 2).

- Incidence, risk factors, and association with 90-day mortality of central venous oxygen desaturation at six hours

Among 514 subjects with initial $ScvO_2$ <70%, 277 (54%) had $ScvO_2$ <70% even at six hours ("persistent" central venous oxygen desaturation) (Fig. 1). As shown in Table 2, these latter subjects more commonly had undergone elective, but not emergency, surgery and more frequently had pre-existing congestive or ischemic cardiac disease than those with $ScvO_2$ <70% at enrolment but not at six hours ("transient" central venous oxygen desaturation). On average, they also had lower initial $ScvO_2$ at enrolment, lower arterial oxygenation, mean arterial pressure and haemoglobin concentration at six hours, and higher plasma levels of bio-markers of cardiac injury at day one, than the others.

Mortality at 90 days was significantly higher in subjects with persistent, compared to transient, central venous oxygen desaturation (50% *vs*. 37%; p=0·005) in spite of similar scores of severity of disease (SAPS II) and organ dysfunction (SOFA score). When this analysis was adjusted for possible confounders in multivariable models, persistence of central venous oxygen desaturation appeared to increase the risk of death (Fig. 3) (e-Table 1, 3-5).

Among 961 subjects with initial $ScvO_2$ ≥70%, 122 (13%) had $ScvO_2$ <70% at six hours whereas 839 (87%) had $ScvO_2$ ≥70% at six hours (Fig. 1). Mortality at 90 days significantly differed between these two groups at univariable (48% *vs*. 37%; p=0·023) but not at multivariable analyses (Fig. 3; e-Table 1, 3-5).

Finally, when we extended the multivariable analyses to the entire study population (514 subjects with initial $ScvO_2$ <70% and 961 subjects with initial $ScvO_2$ ≥70%; n=1475), central venous oxygen desaturation at six hours emerged as an independent risk factor for death (Fig. 3; e-Table 1, 3-5).

- Clinical characteristics and interventions associated with persistence, compared to resolution, of initial central venous oxygen desaturation

Among 514 subjects with initial $ScvO_2$ <70%, those with or without $ScvO_2$ <70% even at six hours were similar for age, SAPS II, SOFA score, initial arterial lactate concentration (2·4 [1·6-4·7] *vs.* 2·8 [1·6-4·6] mmol/L; p=0·666) and prevalence of shock (Table 2). As for the first six hours of treatment, subjects with persistent central venous oxygen desaturation received significantly less crystalloids and fluids in general, no more blood transfusions, no more catecholamine(s), and no more mechanical ventilation than those with transient central venous oxygen desaturation (Table 2). This in spite of the fact that the $ScvO_2$ was remaining below the target and the study protocol advocated more aggressive therapy for these exact cases.

- Biomarkers of cardiac stress and injury

Circulating levels of NT-proBNP and hs-cTnT were measured in 772 subjects at day one (Table 3). Among subjects with initial $ScvO_2$ <70%, these biomarkers were higher in those with persistent, compared to transient, central venous oxygen desaturation. According to multivariable analyses reported above, these were the subjects with an increased risk of death. By contrast, among subjects with initial $ScvO_2$ ≥70%, circulating levels of NT-proBNP and hs-cTnT did not significantly differ between those with $ScvO_2$ <70% or ≥70% at six hours. According to multivariable analyses, these two groups also had similar risk of dying.

Discussion

In this retrospective analysis of a multicentre randomized trial, non-resolution of initial central venous oxygen desaturation ($ScvO_2$ <70%) increased 90-day mortality of severe sepsis or septic shock, independently from other risk factors for death.

Initial central venous oxygen desaturation was associated with higher 90-day mortality at univariable, but not at multivariable, analysis. By contrast, central venous oxygen desaturation at six hours remained associated with higher mortality even after adjusting for possible confounders in multivariable models. According to subgroup analysis, this result was valid only for subjects with initial $ScvO_2$ <70% (and $ScvO_2$ <70% at six hours), that is, those with *persistent* central venous oxygen desaturation. Although detailed data on regional oxygen delivery and consumption were not available, we suspect that these were the subjects with an oxygen deficit profound enough and/or prolonged enough to trigger cellular dysfunction and death.[22,23] Final outcome probably depended more on *degree* and *duration* than on mere occurrence of low $ScvO_2$.

There are several reasons why persistence of central venous oxygen desaturation, in face of (intended) early goal-directed therapy, can have affected outcome.

First, it may have merely identified subjects who were most critically ill. However, at univariable analysis, subjects with $ScvO_2$ <70% even at six hours (higher mortality) did not really differ from those with $ScvO_2$ <70% only at enrolment (lower mortality) for several well-validated markers of severity of disease including age, SAPS II, SOFA score, initial arterial lactate concentration, and prevalence of shock. In accordance with these findings, persistence of central venous oxygen desaturation was an independent predictor of death even at multivariable analysis.

Second, it may have indicated low compliance with early goal-directed therapy. In fact, among subjects with initial $ScvO_2$ <70%, those with $ScvO_2$ <70% even at six hours did not receive higher

intensity of treatment than the others, as required per-protocol in case of non-normalization of $ScvO_2$. In other words, benefits of early resolution of central venous oxygen desaturation may have at least partly depended on stricter adherence to resuscitation "rules".

Third, and possibly even more importantly, it can have reflected acute(-on-chronic) cardiac dysfunction, as it was linked to highest prevalence of congestive or ischemic heart disease and highest circulating biomarkers of myocardial stress and injury (NT-proBNP and hs-cTnT).[24] On one side, this cardiac dysfunction reasonably contributed at lowering $ScvO_2$ by limiting cardiac output and oxygen delivery. On the other side, it possibly directly affected outcome, even more strongly than central venous oxygen desaturation at six hours did. In fact, according to multivariable analyses, $ScvO_2$ <70% at six hours was associated with an increased risk of death only among subjects with initial central venous oxygen desaturation. Plasma levels of NT-proBNP and hs-cTnT at day one somehow paralleled this finding: they significantly differed between subjects with $ScvO_2$ <70% or ≥70% at six hours only among those with initial $ScvO_2$ <70%. Persistence of central venous oxygen desaturation could have primarily reflected more severe, and perhaps inadequately treated, cardiac dysfunction; this condition, and not low $ScvO_2$ at six hours per se, may have directly contributed at increasing the risk of death.

The first, positive, trial on early-goal directed therapy was quite small and with unexpectedly high mortality among controls.[5] Trials published more recently, that were consistently negative, addressed most of these issues. However, they all enrolled subjects with less frequent and/or less severe central venous oxygen desaturation.[9–11] These subjects could have hardly benefited from early goal-directed therapy, as they lacked the condition that was meant to be treated. Our own results were positive when referred to subjects with initial $ScvO_2$ <70%: persistence of central venous desaturation was associated with 13% absolute (and 35% relative) increase of 90-day mortality, just as in the very first and positive trial. At the same time, they were negative (no better

outcome) when referred to subjects with initial $ScvO_2$ ≥70%, just as in the subsequent three negative trials.[9–11]

Our study has some limitations. First, it is a retrospective analysis of a trial that was not designed to investigate benefits or harms of targeting $ScvO_2$ during the early phase of sepsis. Nonetheless, the original study protocol advocated such an approach for both the study and the control groups.[5] The ALBIOS trial enrolled more than 500 subjects with initial $ScvO_2$ <70%. In the three most recent trials, $ScvO_2$ was not recorded in the control group.[9–11] Therefore, neither of these latter studies nor their combined patient-level meta-analysis,[12] can provide any conclusive evidence for or against early-goal directed therapy in subjects presenting with central venous oxygen desaturation. Second, in accordance with the original study protocol, arterial lactate was not measured at six hours. Therefore, we cannot establish whether normalization (or decrease) of lactate is a better initial endpoint than normalization of $ScvO_2$.[25] Third, circulating biomarkers of cardiac dysfunction were measured only in a predefined subgroup of subjects. Nonetheless, this subgroup was highly representative of the entire study population of the ALBIOS trial.[26]

Conclusions

This retrospective analysis suggests that persistence of initial central venous oxygen desaturation is associated with increased 90-day mortality in subjects with severe sepsis or septic shock, likely due undertreated cardiac dysfunction. Subjects with $ScvO_2$ <70% may benefit most from personalised early goal-directed therapy.

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A.Pr. conceived the present work, run the analysis and wrote the manuscript. S.M., R.L., R.F., M.R., G.T., A.Pe., L.G. and P.C. were members of the steering Committee of the original ALBIOS trial. C.P. and G.P. collected data. P.C. coordinated the original ALBIOS trial, conceived the present work, run the analysis and wrote the manuscript; he had full access to all the data in the study and had final responsibility for the decision to submit the paper for publication. All authors reviewed the final version of the manuscript for important intellectual content and approved it.

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Table 1. Comparison of baseline characteristics, physiological variables and laboratory variables at enrolment between subjects with or without initial central venous desaturation.

	Entire study population	**With initial $ScvO_2$ <70%**	**With initial $ScvO_2$ ≥70%**	**p**
N (%)	1475 (100)	514 (35)	961 (65)	
$ScvO_2$ at enrolment (%)	72±10	61±8	78±5	
Age – years	66±14	68±14	65±15	<0·001
Female sex – n (%)	583 (40)	201 (39)	382 (40)	0·809
Body mass index – kg/m^2	27±6	26±5	27±6	0·713
Reason for admission to ICU – n (%)				<0·001
Medical	830 (56)	288 (56)	542 (56)	
Elective surgery	105 (7)	55 (11)	50 (5)	
Emergency surgery	540 (37)	171 (33)	369 (38)	
Pre-existing conditions – n (%)				
Liver disease	20 (2)	2 (0)	18 (2)	0·019
Chronic obstructive pulmonary disease	172 (12)	57 (11)	115 (12)	0·617
Chronic renal failure	55 (4)	25 (5)	30 (3)	0·093
Immunodeficiency	192 (13)	62 (12)	130 (14)	0·426
Congestive or ischemic heart disease	259 (18)	129 (25)	130 (14)	<0·001
SAPS II	48 [37-59]	50 [38-61]	47 [36-58]	0·002
SOFA score	8·00 [6·00-10·00]	8·00 [6·00-10·00]	8·00 [6·00-10·00]	0·193
Physiological variables at enrolment				
Arterial oxygen saturation (%)	97 [95-98]	96 [93-98]	97 [96-99]	<0·001
Heart rate – beats/min	106±21	106±22	106±20	0·965
Mean arterial pressure – mm Hg	73±15	71±16	74±15	<0·001
Central venous pressure – mm Hg	10±5	10±5	10±5	0·125
Urine output – ml/h	50 [25-100]	50 [20-100]	60 [30-100]	0·003
Laboratory variables at enrolment				
Leukocytes – $10^3/mm^3$	11·8 [5·2-18·3]	12·2 [4·8-18·8]	11·4 [5·4-17·9]	0·907
Haemoglobin – g/dl	11·0±2·0	10·8±2·0	11·1±2·0	<0·001
Lactate – mmol/L	2·5 [1·5-4·2]	2·5 [1·6-4·7]	2·5 [1·5-4·0]	0·128
Serum albumin – g/L	24±6	24±6	24±6	0·064
N-terminal pro-B-type natriuretic peptide on	4393 [1271-13444]	6464 [2521-21777]	3467 [1036-9607]	<0·001

day 1 (ng/L)				
High-sensitivity cardiac troponin T on day 1 (ng/L)	51 [21-133]	68 [33-206]	43 [18-116]	<0·001
Organ(s) dysfunction – n (%)				0·444
One organ	304 (21)	93 (18)	211 (22)	
Two organs	553 (37)	200 (39)	353 (37)	
Three organs	404 (27)	144 (28)	260 (27)	
Four organs	160 (11)	60 (12)	100 (10)	
Five organs	54 (4)	17 (3)	37 (4)	
Septic shock – n (%)	943 (64)	311 (61)	632 (66)	0·045
With mechanical ventilation at enrolment – n (%)	1173 (80)	369 (72)	804 (84)	<0·001
Albumin in previous 24 h – n (%)	259 (18)	73 (14)	186 (19)	0·013
Synthetic colloids in previous 24 h – n (%)	799 (54)	269 (52)	530 (55)	0·301
With two or more catecholamines at enrolment – n (%)	402 (27)	128 (25)	274 (29)	0·138
With antibiotic(s) – n (%)	1379 (93)	475 (92)	904 (94)	0·219
With adequate antibiotic(s) on day 1 – n (%)	647 (77)	238 (79)	409 (76)	0·294
Enrolled within 6 h – n (%)	485 (33)	194 (38)	291 (30)	0·004

Variables were defined as in the original study protocol.[14] Body mass index was the ratio between body weight and the square of body height. Liver disease denoted the presence of cirrhosis, portal hypertension, or previous episodes of liver insufficiency. Immunodeficiency denoted the presence of immunosuppressive diseases or receipt of immunosuppressive therapies. Congestive or ischemic heart disease was defined as New York Heart Association class II (class III and class IV were original exclusion criteria). The Simplified Acute Physiology Score (SAPS) II was used to assess the severity of systemic illness at baseline. Scores range from 0 to 163, with higher scores indicating more severe illness.[17] The Sequential Organ Failure Assessment (SOFA) score includes sub-scores ranging from 0 to 4 for each of six components (neurological, respiration, coagulation, liver, cardiovascular and renal components), with higher scores indicating more severe acute organ dysfunction.[15] In the original ALBIOS trial, and herein, this scoring system was slightly modified by excluding the assessment of the neurological component (with the Glasgow Coma Scale), which

was not performed in these subjects, and by decreasing to 65 mm Hg the mean arterial pressure threshold for a cardiovascular sub-score of 1, for consistency with the target of early goal-directed therapy. Organ dysfunctions were defined as a SOFA score ≥2 for the respiratory component; ≥2 for the coagulation component; ≥2 for the liver component; 1, 3 or 4 for the cardiovascular component; and ≥2 for the renal component. Shock was defined as a SOFA score ≥3 for the cardiovascular component.[16] Antibiotic(s) were considered appropriate if all pathogenic microorganisms isolated at the site of infection were susceptible to at least one of the drugs administered by day one, as judged by a local microbiologist.[18]

Data on SOFA score were available for 1434 subjects; data on arterial oxygen saturation for 1461; data on central venous pressure for 1450; data on leukocytes for 1468; data on haemoglobin for 1458; data on lactate for 1419; data on albumin for 1349; data on N-terminal pro-B-type natriuretic peptide for 771; data on high-sensitivity cardiac troponin T on 772; and data on adequacy of antibiotic(s) on day one for 837.

Table 2. Comparison of baseline characteristics, physiological and laboratory variables at six hours, and treatments administered during the first six hours between subjects with $ScvO_2$ <70% at enrolment and at six hours (as for non-successful early goal-directed therapy), and subjects with $ScvO_2$ <70% at enrolment but not at six hours (as for successful early goal-directed therapy).

	$ScvO_2$ <70% at 6 h	**$ScvO_2$ ≥70% at 6 h**	**p**
N (%)	277 (54)	237 (46)	
$ScvO_2$ at 6 h (%)	60±9	76±5	
$ScvO_2$ at enrolment (%)	59±8	63±7	<0·001
Age – years	68±13	68±14	0·998
Female sex – n (%)	113 (41)	86 (37)	0·396
Body mass index – kg/m^2	26±5	26±5	0·726
Reason for admission to ICU – n (%)			0·022
Medical	153 (55)	135 (57)	
Elective surgery	39 (14)	16 (7)	
Emergency surgery	85 (31)	86 (36)	
Pre-existing conditions – n (%)			
Liver disease	1 (0)	1 (0)	0·912
Chronic obstructive pulmonary disease	29 (10)	28 (12)	0·628
Chronic renal failure	16 (6)	9 (4)	0·299
Immunodeficiency	35 (13)	27 (11)	0·666
Congestive or ischemic heart disease	82 (30)	47 (20)	0·011
SAPS II	49 [38-63]	50 [38-60]	0·757
SOFA score	8 [6-10]	8 [6-10]	0·752
Physiological variables at 6 h			
Arterial oxygen saturation (%)	97 [94-98]	98 [96-99]	<0·001
Heart rate – beats/min	100±21	98±21	0·482
Mean arterial pressure – mm Hg	75±13	80±14	<0·001
Central venous pressure – mm Hg	11±5	11±5	0·763
Urine output – ml/h	83 [33-150]	85 [42-167]	0·442
Laboratory variables at 6 h			
Leukocytes – $10^3/mm^3$	NA	NA	-
Haemoglobin – g/dl	10·3±1·6	10·7±1·7	0·028
Lactate – mmol/L	NA	NA	-
Serum albumin – g/L	NA	NA	-
N-terminal pro-B-type natriuretic peptide on day 1 (ng/L)	6463 [2167-19341]	5230 [2340-15265]	0·024
High-sensitivity cardiac troponin T on day 1 (ng/L)	80 [37-269]	56 [28-134]	<0·001
Organ(s) dysfunction – n (%)			0·790
One organ	53 (19)	40 (17)	

Two organs	102 (37)	98 (41)	
Three organs	81 (29)	63 (27)	
Four organs	33 (12)	27 (11)	
Five organs	8 (3)	9 (4)	
Septic shock – n (%)	165 (60)	146 (62)	0·638
With mechanical ventilation at 6 h – n (%)	190 (69)	179 (76)	0·082
Albumin in previous 24 h – n (%)	37 (13)	36 (15)	0·553
Synthetic colloids in previous 24 h – n (%)	139 (50)	130 (55)	0·291
With two or more catecholamines at 6 h – n (%)	71 (26)	57 (24)	0·680
With antibiotic(s) – n (%)	255 (92)	220 (93)	0·743
With adequate antibiotic(s) on day 1 – n (%)	131 (80)	107 (78)	0·629
Enrolled within 6 h – n (%)	102 (37)	92 (39)	0·642
Randomized to albumin – n (%)	144 (52)	130 (55)	0·516
Fluids administered from enrolment to 6 h			
20% Albumin (ml)	0 [0-300]	100 [0-300]	0·295
Red blood cell units (n)	0 [0-0]	0 [0-0]	0·589
Fresh frozen plasma (ml)	0 [0-0]	0 [0-0]	0·819
Platelets (ml)	0 [0-0]	0 [0-0]	0·565
Crystalloids (ml)	1000 [600-2000]	1500 [725-2120]	0·028
Other fluids (ml)	200 [0-500]	100 [0-500]	0·118
Total (ml)	1860 [1250-2750]	2080 [1490-2900]	0·039

These data refer to 514 subjects with initial $ScvO_2$ <70% (see also figure 1). Variables were defined as in Table 1. NA: not available.

Data on SOFA score were available for 500 subjects; data on arterial oxygen saturation for 510; data on central venous pressure for 504; data on haemoglobin for 510; data on N-terminal pro-B-type natriuretic peptide for 250; data on high-sensitivity cardiac troponin T on 251; and data on adequacy of antibiotic(s) on day one for 300.

Table 3. Biomarkers of cardiac (dys)function in 772 subjects enrolled in the ALBIOS trial, divided in groups based on their $ScvO_2$ at enrolment and at six hours.

	$ScvO_2$ at 6 h <70%	**$ScvO_2$ at 6 h ≥70%**	**p**
Initial $ScvO_2$ <70%	NT-proBNP: 8485 [2902-23405] hs-cTnT: 80 [37-269]	NT-proBNP: 5230 [2340-15265] hs-cTnT: 56 [28-134]	0·024 0·024
Initial $ScvO_2$ ≥70%	NT-proBNP: 3467 [1021-9603] hs-cTnT: 43 [18-116]	NT-proBNP: 3324 [1036-11057] hs-cTnT: 42 [21-127]	0·842 0·567

NT-proBNP: plasma level of N-terminal pro-B-type natriuretic peptide (in ng/L) at day one. hs-cTnT: plasma level of high-sensitivity cardiac troponin T (in ng/L) at day one. Please refer to reference 19 for details on methods.

Figure 1. Study design of the present analysis and crude 90-day mortality rates in the identified subgroups.

Figure 2. 90-day mortality of subjects enrolled in the ALBIOS trial, stratified according to their initial $ScvO_2$.

Error bars indicate 95%-CI.

Figure 3. Association between baseline characteristics, physiological and laboratory variables, $ScvO_2$ at six hours and 90-day mortality in subjects enrolled in the ALBIOS trial.

Herein we show the results of multivariable analyses applied to identify predictors of 90-day mortality, including presence or absence of central venous oxygen desaturation ($ScvO_2$ <70%) at six hours. The upper panel displays results adjusted for baseline characteristics, physiological variables recorded at enrolment and laboratory variables recorded at enrolment (Table 1). The lower panel displays results adjusted for baseline characteristics, physiological variables recorded at six hours and laboratory variables recorded at six hours (Table 2). Dots area reflects sample size. Error bars indicate 95%-CI.