The impact of organ failure on outcome of patients after cardiac arrest

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Abstract

Objectives: To assess the incidence and impact of extra-cerebral organ dysfunction on prognosis of patients admitted after cardiac arrest (CA).

Design: Analysis of the Intensive Care Over Nations (ICON) database.

Setting: Seven hundred and thirty intensive care units (ICUs) in 84 countries.

Patients: All adult patients admitted to a participating center between May 8 and 18, 2012 except admissions for routine postoperative surveillance. For this analysis, patients admitted after CA (defined as those with "post-anoxic coma" or "cardiac arrest" as the reason for ICU admission) were included.

Measurements and main results: Data were collected daily for a maximum of 28 days; patients were followed up for outcome data until death or hospital discharge. Favorable neurological outcome was defined as alive at hospital discharge and with a last available neurological SOFA subscore of 0-2. Among the 469 patients admitted after CA, 250 (53%) had had out-of-hospital CA and therapeutic hypothermia was used in 126 (27%) cases; 210 (45%) patients died during the ICU stay and 357 (76%) had an unfavorable outcome. Non-survivors had a significantly higher incidence of renal (43 vs. 16%) cardiovascular (56 vs. 45%) and respiratory (62 vs. 48%) failure on admission (all $p<0.05$) and during the ICU stay (all $p<0.05$) than survivors. Similar results were found for patients with unfavorable vs. favorable neurological outcomes. In multivariable analysis, renal failure on admission, admission SAPS II score, maximum lactate levels within the first 24 hours after ICU admission and development of severe sepsis were independent predictors of ICU mortality. Mechanical ventilation on admission, high admission SAPS II score and neurological dysfunction on admission were independent predictors of unfavorable neurological outcome.

Conclusions: In this multicenter cohort, extra-cerebral organ dysfunction was common in CA patients. Renal failure on admission was the only extra-cerebral organ dysfunction independently associated with higher ICU mortality in our population.

Keywords: cardiac arrest, organ failure, outcome, prognosis

Introduction

Rates of sudden cardiac arrest (CA) vary greatly around the globe, but it is estimated that the incidence is around 55 per 100,000 person-years [1]. Overall outcomes remain poor, with less than 10% of patients leaving the hospital alive with good neurological recovery [1]. Brain damage, exacerbated by the global ischemia-reperfusion (I/R) injury, is the leading cause of death. Therapeutic hypothermia (TH) has been employed following return of spontaneous circulation (ROSC) to limit the extent of brain damage, although some concerns remain, including optimal temperature levels, target population and duration of cooling [2, 3]. Poor cardiac function may itself be responsible for altered organ function. The so-called "post-cardiac arrest syndrome" links I/R injury with brain damage, myocardial dysfunction and a systemic inflammatory response that has remarkable similarities to that of sepsis and may result in the development of multi-organ failure (MOF), regardless of whether or not TH is used [4].

There are very limited data available on the extent and prognostic value of extra-cerebral organ dysfunction after CA. Roberts et al. [5] recently reported that almost all (96%) patients from a cohort of 203 patients resuscitated after CA had some degree of organ dysfunction, in particular cardiovascular and respiratory impairments; two-thirds of these patients had at least two extra-cerebral organ dysfunctions. Only alterations in the cardiovascular and respiratory systems, as assessed by Sequential Organ Failure Assessment (SOFA) subscores, were independently associated with in-hospital mortality. More recently, renal dysfunction has also been reported as an independent prognostic factor of mortality among CA survivors [6], although conflicting data have been reported [7]. Almost no data on hepatic and coagulation dysfunction are available in this setting. Information on whether extra-cerebral organ dysfunction may influence the outcome of patients after CA could open new lines of research, in particular related to the clinical management and potential prevention of such complications.

The objectives of this study were, therefore, to assess the incidence of extra-cerebral organ failure in patients resuscitated from CA and its impact on prognosis. For this purpose, we analyzed data from a contemporary, international database of

patients admitted to the intensive care unit (ICU), the Intensive Care Over Nations (ICON) audit [8].

Methods

Full details of the methodology have been provided previously [8] and a list of participating ICUs is given in the Supplemental Digital Content (Appendix 1).

Participating centers

Participating centers were recruited by open invitation, through national scientific societies, international meetings and/or individual contacts. Participation was voluntary and no financial reimbursement was provided. The participating institutions obtained local ethical approval.

Inclusion criteria

Each participating center (Appendix 1) prospectively collected data on all adult patients (>16 years of age) who were admitted to their ICU between May 8 and May 18, 2012; patients who remained in the ICU for less than 24 hours (i.e., for routine post-operative surveillance) or who were readmitted were not included. Data were collected daily during the ICU stay for a maximum of 28 days, using electronic case report forms through a secured web-based platform. Patients were followed up for outcome data until death or hospital discharge, whichever came first.

Data collection

Demographics and comorbid diseases (including chronic obstructive pulmonary disease [COPD], solid or hematologic cancer [with metastasis or receiving chemotherapy or radiotherapy in the 6 months before ICU admission], liver cirrhosis, heart failure [New York Heart Association classification III/IV], acquired immunodeficiency syndrome, chronic renal failure, immunosuppression, severe malnutrition and insulin-dependent diabetes mellitus) were collected on admission. Clinical and laboratory data to calculate the simplified acute physiology score (SAPS) II [9] and the acute physiology and chronic health evaluation (APACHE) II score [10] were reported as the worst values within the first 24 hours since ICU admission. Microbiological and clinical infections were reported daily as well as the antibiotics

given. A daily assessment of organ function was performed using the SOFA score [11].

Definitions

Most of the definitions have been provided elsewhere [8]. Briefly, infection was defined in accordance with the International Sepsis Forum definitions [12]. Sepsis was defined as the presence of infection with the concomitant occurrence of at least one organ failure (i.e. a SOFA subscore > 2 for each organ) [13]. Septic shock was defined as sepsis complicated by cardiovascular failure (i.e., cardiovascular SOFA subscore >2). For the purposes of this substudy, patients with "post-anoxic coma" or "cardiac arrest" listed as the reason for ICU admission were considered as having been admitted after CA. CA was considered to have occurred out-of-hospital (OHCA) if patients were admitted through the emergency department and/or by ambulance; all other patients were considered to have had an in-hospital CA (IHCA). Patients were considered to have received TH after CA if the lowest body temperature during the first day after ICU admission was < 34°C. At the time of the ICON audit, the TTM study [2], which suggested similar effects on outcome for a cooling strategy using 33°C or 36°C, had not yet been published and routine practice was to target a temperature of 32-34°C [14].

Patients were considered as "comatose" (neurological SOFA > 2) or "non-comatose" (neurological SOFA 0-2) on admission. ICU mortality rates and overall neurological outcomes were collected: patients who were alive at hospital discharge and in whom the last recorded neurological SOFA (central nervous system [CNS]-SOFA) subscore was between 0 and 2 (corresponding to a Glasgow Coma Scale [GCS] score of 10-15) were defined as having a "favorable neurological outcome"; other patients (non-survivors and survivors with CNS-SOFA of 3-4, i.e., GCS <10) were defined as having an unfavorable neurological outcome.

Statistical analysis

Data are expressed as mean ± standard deviation (SD), median [interquartile range (IQR)] or count (percentage), as appropriate. For continuous variables, normality assumption checking was performed by inspection of residual and normal plots. Differences between groups were assessed using the analysis of variance (ANOVA), Kruskal-Wallis test, Student's T test, Mann-Whitney test, χ^2 test, or Fisher's exact test,

as appropriate. The time-courses of each SOFA subscore in survivors and non-survivors or in patients with favorable or unfavorable neurological outcome were analyzed using generalized estimating equation (GEE) models. Multivariable logistic regression was used to identify independent predictors of ICU death and of unfavorable neurological outcome; only variables with a p value < 0.2 in the univariate analysis were consideredin the multivariable analyses. All reported p-values are two-sided and a p value of less than 0.05 was considered to indicate statistical significance. Data were analyzed using IBM® SPSS® Statistics software, version 22 for Windows (IBM, Armonk, NY).

Results

Among the 10,069 patients included in the ICON registry, 469 were admitted to the ICU with post-anoxic coma or CA as the reason for admission and thus considered to have had a CA. The mean patient age was 66 years, 282 (61%) patients were male and 209 (44%) had no comorbidities (Table 1). The CA occurred out-of-hospital in 250 (53%) patients. On admission, the median SAPS II score was 60 [46-75] and the SOFA score 10 [7-13]; 337 (72%) patients were comatose and TH was used in 126 patients. A total of 210 (45%) patients died during their ICU stay and 357 (76%) had an unfavorable neurological outcome; decisions were made to limit therapy in 170 (36%) patients.

Mean arterial pressure (MAP), pH and PaO_2/FiO_2 ratio on the first day were lower, and maximal lactate level on the first day was higher in non-survivors than in survivors (Table 1). Non-survivors also had higher SAPS II and SOFA scores on admission and were more frequently treated with vasopressors; they were also more likely to have a decision to limit therapy than were survivors. Similar differences were found when patients with favorable and unfavorable neurological outcomes were compared (Table 1).

The non-survivors had a significantly greater incidence of renal, respiratory and cardiovascular failure than the survivors on admission (43 vs. 16%, 56 vs. 45%, 62 vs. 48%, respectively – all p values < 0.05; Figure 1A) and during the ICU stay (71% vs. 50%, 71 vs. 54%, 75 vs. 57%, respectively – all p values < 0.05; Figure 2A). Similar differences were found in patients with unfavorable and favorable neurological outcomes (Figures 1B and 2B).

The time-course of several organ SOFA subscores differed in survivors and non-survivors. In particular, the hepatic SOFA increased over time in the non-survivors but not in the survivors ($p=0.015$; Figure 3A), whereas CNS and cardiovascular SOFA scores decreased over time in the survivors but not in the non-survivors (both $p<0.001$; Figures 3B and 3C). The renal SOFA subscore remained unchanged over time in the survivors and was higher, although it progressively decreased over time, in the non-survivors ($p< 0.001$; Figure 3D). The time-course of respiratory and hematologic SOFA subscores was similar in survivors and non-survivors (Supplemental Material; Figures 1 and 2). Renal SOFA subscores decreased over time in patients with a favorable neurological outcome but not in those with an unfavorable outcome ($p = 0.02$; Figure 4). Similar results were found for the CNS-SOFA subscore (Supplemental Material; Figure 3). The analysis of other SOFA subscores showed a similar temporal trend between patients with FO and PO (Supplemental Material; Figures 4-7).

Among the ICU survivors, 150 (57%) patients had an unfavorable neurological outcome. Thirty-three (16%) of the non-survivors had good neurological function (CNS-SOFA score of 0-2) before death (Figure 5); however, the CNS-SOFA score on admission was also 0-2 in all these patients (0 in 19 patients, 1 in 3 patients and 2 in 11 patients); no patient who was comatose on admission and eventually died had improved neurological function during the ICU stay. These non-survivors with good neurological function more frequently had renal failure than did survivors, regardless of their neurological function ($p < 0.001$ versus survivors with good neurological function and versus survivors with poor neurological function); they also more frequently had circulatory failure ($p=0.026$) and respiratory failure ($p=0.094$) than the ICU survivors with good neurological function (Figure 6).

In the multivariable analysis, renal failure on admission, high SAPS II score and high lactate levels within the first 24 hours after ICU admission and the development of sepsis were independent predictors of ICU mortality (Table 2). Mechanical ventilation on admission, high SAPS II score and increasing neurological SOFA score on admission were independent predictors of unfavorable neurological outcome (Table 2). None of the extra-cerebral organ failures occurring during the ICU stay was independently associated with ICU mortality or neurological outcome.

Discussion

This large observational study showed that patients with a poor outcome after CA had a higher incidence of renal, cardiovascular and respiratory failure on admission or during the ICU stay compared to patients with good outcomes. Renal failure on admission was an independent predictor of ICU death together with the severity of disease, high lactate levels and the development of sepsis. However, extra-cerebral organ failure occurring later during the ICU stay did not significantly influence ICU mortality or neurological outcome.

Previous studies have reported renal dysfunction in nearly 50% of patients after CA, in particular in patients with pre-existing renal dysfunction, older age, a longer duration of resuscitation and the presence of shock [7, 15-17]. Severe acute kidney injury (AKI) was also associated with a significantly higher mortality at 30 days after CA in one study [16], but AKI was not an independent predictor of mortality or poor neurological outcome in two others [7, 17]. It is difficult to compare these findings as different confounders, including the measured outcomes (e.g., hospital survival vs. neurological outcome), the use of TH and the proportion of patients with OHCA, may have significantly influenced the results. Importantly, as limitation of life-sustaining therapies is initiated in a number of patients with extensive brain injury, regardless of the development of AKI, it is not always possible to assess the impact of AKI on outcome. In our study, renal failure was a more significant determinant of outcome than cardiovascular or respiratory dysfunction. Our data differ from those of the study by Roberts et al. [5], who also reported that extra-cerebral organ dysfunction was common after CA but found that only cardiovascular dysfunction and altered gas exchange were primarily associated with outcome. However, Roberts et al. [5] conducted their study in a single US academic hospital over several years, whereas we collected data from a multicenter international database from consecutive patients over a short time period. Moreover, in the study by Roberts et al. [5], blood lactate levels were not recorded and we observed that increased lactate concentrations after CA were significantly associated with ICU mortality. As high lactate concentrations are primarily a consequence of prolonged CA and/or severe subsequent hemodynamic impairment [18-20], lactate can be considered as an extracerebral variable that can strongly predict poor outcome in these patients. Abnormalities in tissue perfusion occurring after CA may also potentially contribute to brain hypoperfusion and the development of multiple organ failure [4]. Thus, monitoring of lactate in this setting may be of more value than just blood

pressure or cardiac output, to assess the severity of tissue hypoxia. Other studies have also shown the prognostic value of admission blood lactate levels after CA and of changes in lactate levels in the hours after CA [18-21].

In this large database, patients admitted after CA represented around 5% of the entire ICU population, similar to values reported in other studies [22]. The SAPS II score was higher in patients with poor neurological outcome or those who died during their ICU stay than in the other patients; however, the SAPS and APACHE scores are not good prognostic tools in patients with CA [23, 24]. Conversely, the highest extra-cerebral SOFA score at 72 hours after CA was independently associated with in-hospital mortality [5]. Admission factors that were correlated with an increased SOFA score after CA were non-shockable rhythm, the amount of epinephrine used, the use of TH and elevated levels of stress hormones [25]. In particular, the cardiovascular component of the SOFA score has been shown to accurately predict outcomes of patients with CA when combined with neurological examination [26]; our results suggest that the renal component should perhaps also be considered in prediction models.

Mechanical ventilation was one of the independent predictors of poor neurological outcome. Sutherasan et al. showed that high tidal volume and plateau pressure with lower positive end-expiratory pressure (PEEP) were associated with the occurrence of severe pulmonary complications during the ICU stay in CA patients [27], suggesting a potential role of ventilator settings on the outcome of such patients. Moreover, patients receiving mechanical ventilation are more exposed to high oxygen levels or abnormal carbon dioxide concentrations, which have been shown to have a significant negative impact on brain recovery after a post-anoxic injury [28, 29].

Not surprisingly, the severity of brain dysfunction on admission also predicted an unfavorable outcome. The initial GCS motor score was significantly associated with neurological outcome, together with age, bystander cardiopulmonary resuscitation, the time from collapse to return of spontaneous circulation and pupil size in a large cohort of CA patients in Japan [30]. Initial coma was also found to be one of the most important determinants of outcome in another large database including both IHCA and OHCA [31].

Another interesting finding was that 16% of non-survivors had relatively preserved cerebral function during their ICU stay. In the last few years, various studies have focused their interest on identifying markers of poor neurological

outcome as if mortality after resuscitated CA is exclusively associated with lack of neurological recovery [32-34]. Neurological recovery was often assessed 3 to 6 months after CA and all non-survivors were considered to have a poor neurological outcome. However, a significant proportion of CA patients die from protracted shock and multiple organ failure [34], but this often occurs early after CA, before any possible neurological outcome assessment. In our study, patients with good neurological function after CA died from other reasons, in particular other organ failures. This finding highlights the importance of repeated neurological assessment of CA patients during the ICU stay because a single long-term assessment may underestimate the potential for neurological recovery in some patients.

This study has some limitations. First, we did not have data available on CA characteristics, such as initial rhythm, time to ROSC, quality of CPR, which are main outcome determinants after CA. Second, our cohort included patients with "post-anoxic coma" and "cardiac arrest" as the reason for ICU admission, with no information on the time from arrest to ICU admission. Third, we focused on ICU and hospital mortality, but not longer-term (e.g., 6 to 12 months) neurological evaluation. Fourth, management of patients with CA may have been different among centers and this may have influenced the occurrence of extra-cerebral organ failure and its impact on patient outcome; however, this is also a strength of the study, allowing greater generalizability of our findings. Fifth, data on the duration of hypothermia and the potential complications associated with this therapy were not available. Finally, we arbitrarily identified patients with good and poor neurological outcome according to the GCS, and could not assess the ability to follow commands or evaluate cognitive function, which may be better indications of subtle post-anoxic injury.

Conclusions

In this multicenter cohort, extra-cerebral organ dysfunction was common in CA patients. Renal failure on admission was the only extra-cerebral organ dysfunction independently associated with higher ICU mortality in our population.

Declaration of interests

No competing interests to declare.

Acknowledgments

We would like to thank Hassane NJIMI for his help with the statistical analyses.

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Table 1. Characteristics of the study population, according to ICU survival or neurological outcome at hospital discharge.

	All patients (n=469)	**Survivors (n=247)**	**Non-Survivors (n=210)**	**Favorable neurological outcome (n=97)**	**Unfavorable neurological outcome (n=357)**
Age, years	66 [52-77]	65 [52-75]	68 [52-78]	67 [53-75]	66 [52-77]
Male, n (%)	282 (61)	149 (61)	126 (61)	60 (62)	222 (60)
Weight, kgs	75 [65-87]	75 [66-90]	71 [61-83]	75 [65-90]	74 [65-85]
OHCA	250 (53)	120 (49)	124 (59)	34 (35)	216 (58)
IHCA	219 (47)	127 (51)	86 (41)	63 (65)	156 (42)
No Co-morbidities, n (%)	209 (44)	101 (41)	108 (51)	49 (51)	163 (44)
COPD / asthma, n (%)	65 (14)	39 (16)	26 (12)	17 (17)	51 (14)
Heart failure, n (%)	72 (15)	30 (12)	42 (20)	10 (10)	62 (17)
Diabetes, n (%)	45 (10)	20 (8)	25 (12)	12 (12)	33 (9)
Cancer, n (%)	38 (8)	18 (7)	20 (10)	10 (10)	28 (8)
Chemotherapy, n (%)	9 (2)	4 (2)	5 (2)	1 (1)	8 (2)
Liver cirrhosis, n (%)	14 (3)	1 (1)	13 (6)	1 (1)	13 (3)
Chronic renal failure, n (%)	50 (11)	21 (9)	29 (14)	10 (10)	40 (11)
HIV, n (%)	1 (0)	-	1 (1)	-	1 (1)
Corticosteroids, n (%)	14 (3)	6 (2)	8 (4)	1 (1)	13 (3)
Medical admission, n (%)	373 (83)	189 (91)	184 (89)	70 (74)	303 (84)
SAPS II score on admission	60 [46-75]	53 [39-64]	71 [57-81] *	38 [29-49]	65[54-79] *
SOFA score on admission	10 [7-13]	8 [6-11]	12 [9-14] *	6 [3-8]	11[8-13] *
Infections					
Infection on admission, n (%)	112 (24)	60 (24)	52 (25)	20 (21)	92 (25)
Infection any time, n (%)	200 (43)	120 (49)	80 (38)	41 (41)	159 (43)
Septic Shock on admission, n (%)	75 (16)	40 (16)	35 (17)	11 (11)	64 (17)
Septic Shock any time, n (%)	133 (28)	74 (30)	59 (28)	20 (21)	113 (30)
Vasopressors on admission, n (%)	262 (57)	124 (50)	138 (66)*	42 (43)	220 (62)*

Mechanical ventilation on admission, n (%)	408 (87)	205 (83)	203 (97)	67 (69)	341 (92)*
Mechanical ventilation any time, n (%)	425 (91)	211 (85)	204 (97)	71 (73)	354 (95)*
Hemodialysis/CRRT on admission, n (%)	38 (8)	19 (8)	19 (9)	4 (4)	34 (9)
Hemodialysis/CRRT any time, n (%)	103 (23)	59 (24)	44 (21)	17 (17)	86 (23)
MAP max on first day, mmHg	99 [87-112]	100 [89-113]	97 [85-111]	100 [88-113]	98 [87-112]
MAP min on first day, mmHg	61 [50-70]	63 [55-71]	56 [45-68]	63 [55-79]	60 [49-70]*
pH max on first day, mmHg	7.40 [7.30-7.45]	7.41 [7.35-7.46]	7.37 [7.23-7.44]*	7.42 [7.36-7.47]	7.39 [7.28-7.45]*
pH min on first day, mmHg	7.25 [7.11-7.35]	7.29 [7.19-7.36]	7.18 [7.05-7.29]*	7.32 [7.23-7.38]	7.23 [7.10-7.33]*
$PaCO_2$ max on first day, mmHg	45 [37-57]	44 [36-55]	46 [37-60]	45 [37-53]	45 [36-60]
$PaCO_2$ min on first day, mmHg	34 [28-40]	34 [28-40]	33 [27-39]	35 [29-40]	33 [28-40]
PaO_2 max on first day, mmHg	144 [98-229]	135 [94-197]	149 [101-265]	141 [95-190]	145 [99-234]
PaO_2 min on first day, mmHg	77 [61-98]	77 [64-94]	75 [57-105]	78 [66-90]	76 [60-100]
PaO_2/FiO_2 max on first day	232 [144-344]	232 [151-337]	233 [132-361]	270 [161-374]	227 [143-343]*
PaO_2/FiO_2 min on first day	195 [132-288]	200 [149-294]	186 [120-285]*	218 [165-300]	192 [124-285]*
Lactate max on first day, mmol/L	3.6 [2.0-7.6]	2.6 [1.5-5.5]	5.8 [2.5-10.5]*	2.1 [1.2-5.5]	4.30 [2.3-8]*
ICU stay, days	4 [2-8]	5 [3-10]	3 [1-6] *	4 [2-6]	4 [1-8]
Hospital stay, days	8 [2-20]	17 [8-31]	3 [1-6] *	15 [8-22]	5 [2-16] *
Limitation of care, n (%)	170 (36)	40 (16)	126 (61) *	11 (11)	159 (44)*
ICU mortality, n (%)	210 (45)	-	210 (100) *	-	210 (59)
Hospital mortality, n (%)	247 (54)	37 (15)	210 (100) *	11 (11)	236 (67)*

Missing values: 12 for mortality; 5 for sex; 36 for weight; 23 for source of admission; 15 for vasopressors on admission; 15 for ICU stay, 16 for hospital stay;
* $p < 0.05$ survivors versus non-survivors; favorable outcome versus unfavorable outcome
OHCA= out of hospital cardiac arrest; IHCA= in hospital cardiac arrest; COPD = chronic obstructive pulmonary disease; SAPS = simplified acute physiology score; SOFA = Sequential Organ Failure Assessment; PAC = pulmonary artery catheter; CRRT= continuous renal replacement therapy; MAP = mean arterial pressure; ICU = intensive care unit; HIV: human immunodeficiency virus

Table 2. Multivariable analysis to identify the independent predictors of ICU mortality and unfavorable outcome.

Variable	p value	OR	95% CI for OR	
			Lower	Upper
Predictors of ICU mortality				
SAPS II score on admission	< 0.001	1.047	1.025	1.069
Lactate max, mEq/L	0.004	1.093	1.029	1.161
Renal failure on admission	0.011	2.413	1.220	4.774
Severe sepsis during ICU stay	0.022	0.537	0.316	0.912
Predictors of unfavorable outcome				
SAPS II on admission	<0.001	1.107	1.077	1.138
MV on admission	0.020	3.787	1.234	11.628
CNS-SOFA on admission	<0.001	4.237	3.097	5.796

SAPS= Simplified Acute Physiological Score; ICU = intensive care unit; Lactate max = maximal lactate levels within the first 24 hours since ICU admission

Figure legends

Fig. 1. Occurrence of extra-cerebral organ failure on ICU admission in (A) survivors and non-survivors and (B) patients with favorable and unfavorable neurological outcomes. *$p<0.05$

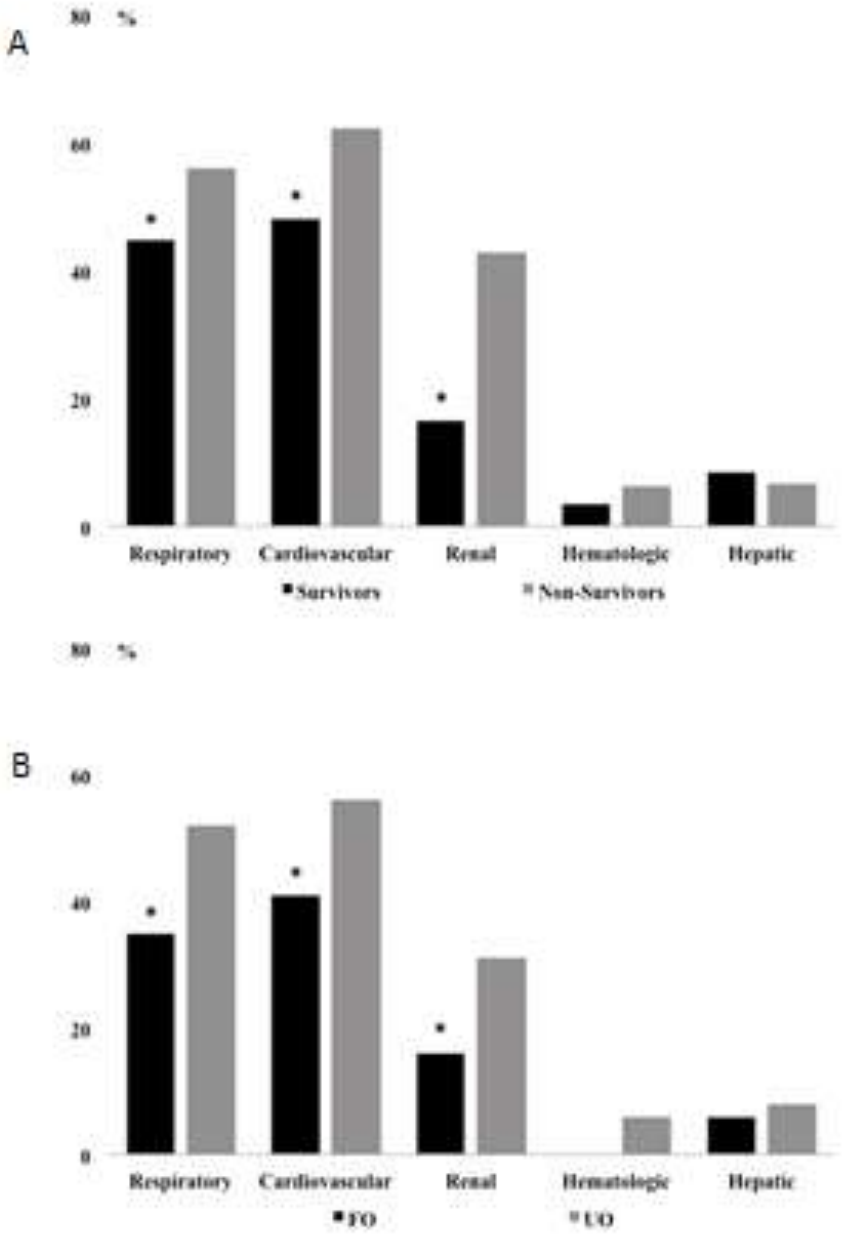
Fig. 2. Occurrence of extra-cerebral organ failure during the ICU stay in (A) survivors and non-survivors and (B) patients with favorable and unfavorable neurological outcomes. *$p<0.05$

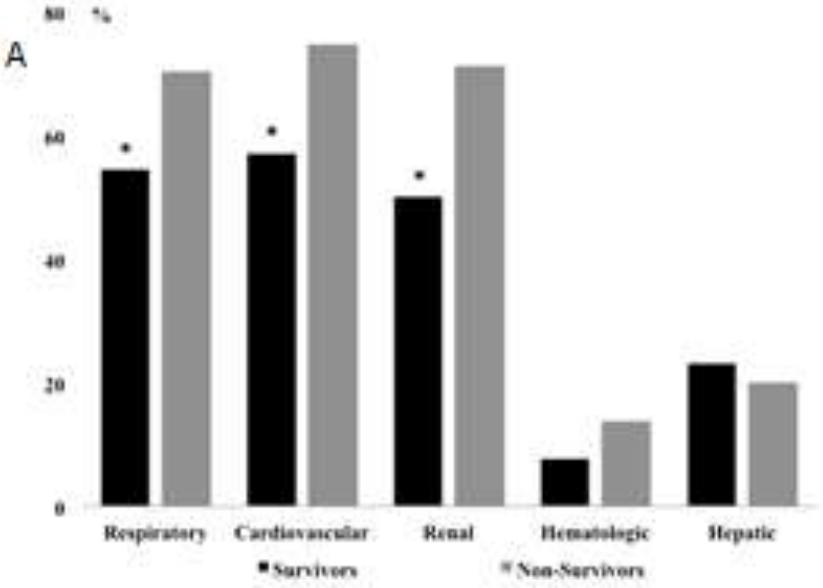
Fig. 3. Time course of SOFA subscores in survivors and non-survivors. A: hepatic; B: neurologic; C: cardiovascular; D: renal

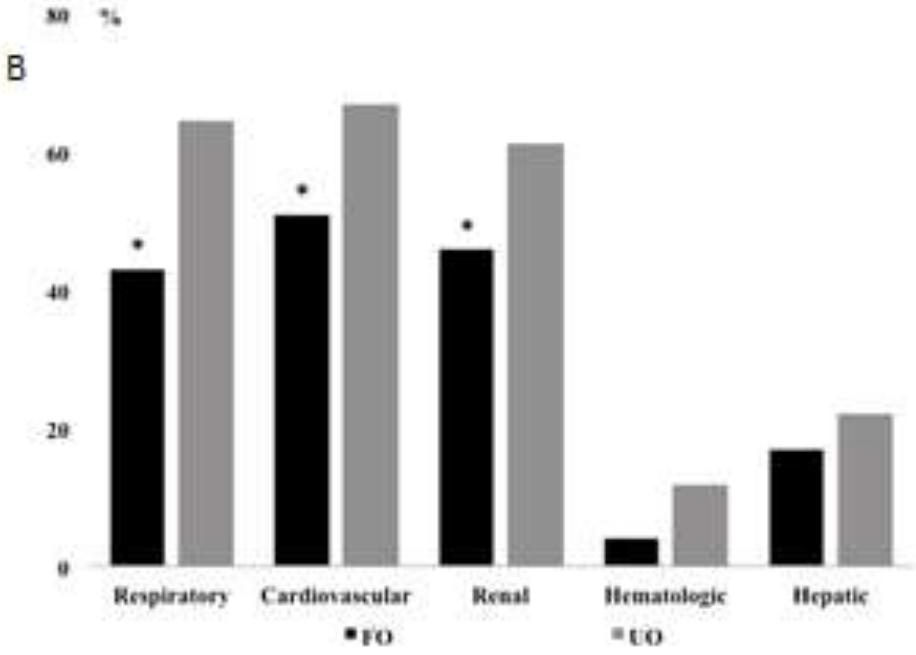
Fig. 4. Time-course of renal SOFA in patients with favorable (left panel) and unfavorable (right panel) neurological outcome.

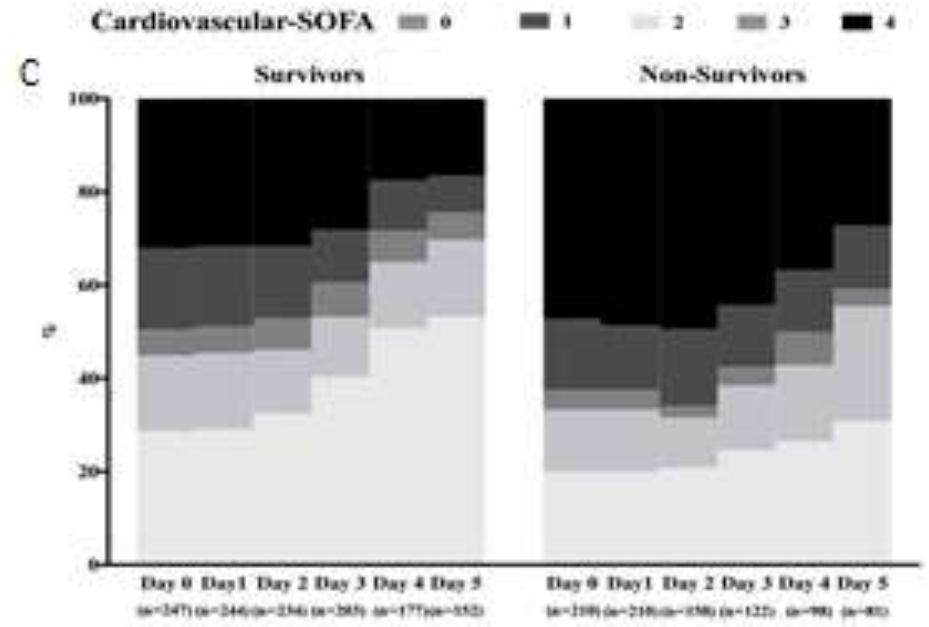
Fig. 5. Differences in the last available SOFA subscores in survivors (S) and non-survivors (NS).

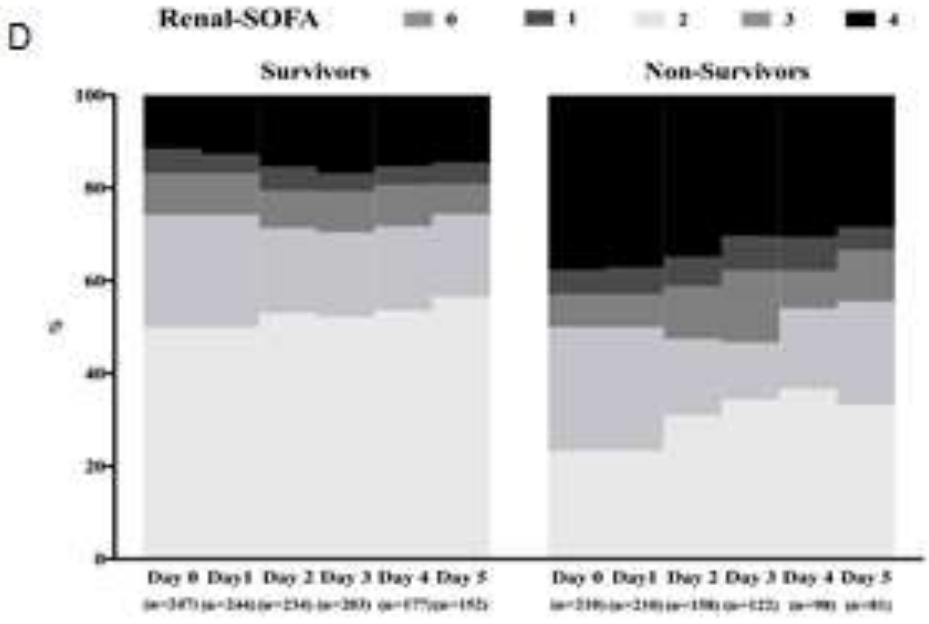
Fig. 6. Occurrence of circulatory, respiratory and renal failure in patients according to their outcome (alive OR dead with neurological recovery [CNS+] or persistent neurological impairment [CNS-]).

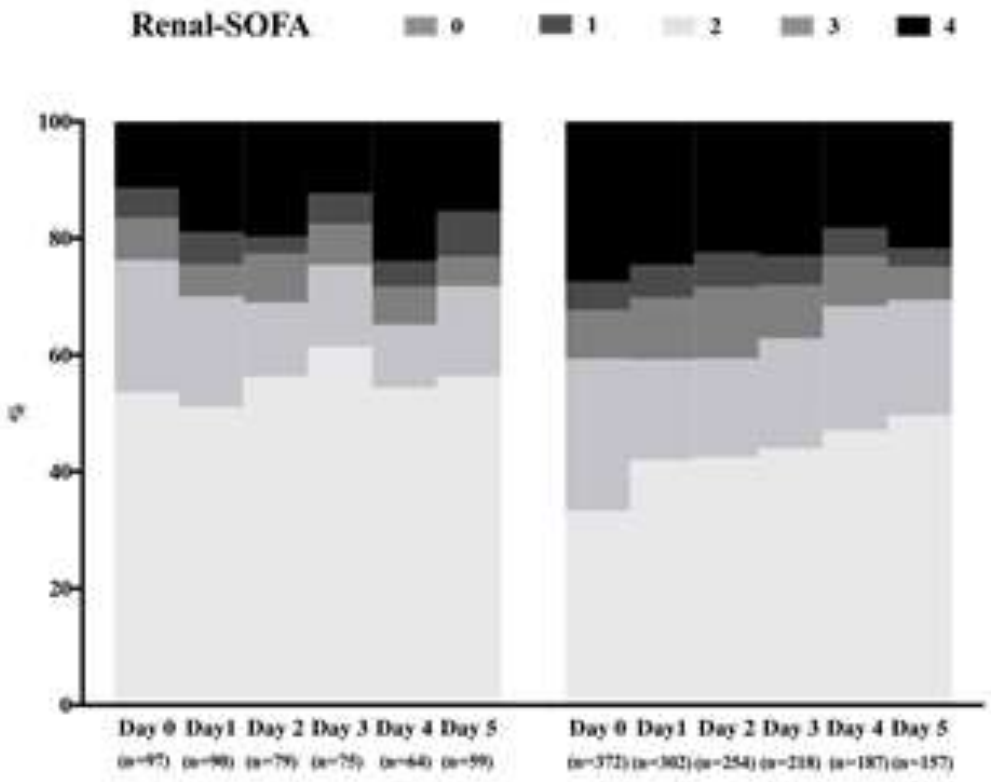

A
80 %
60
40
20
0
Respiratory
Cardiovascular
Renal
Hematologic
Hepatic
Survivors
Non-Survivors
B
80 %
60
40
20
0
Respiratory
Cardiovascular
Renal
Hematologic
Hepatic
FO
UO

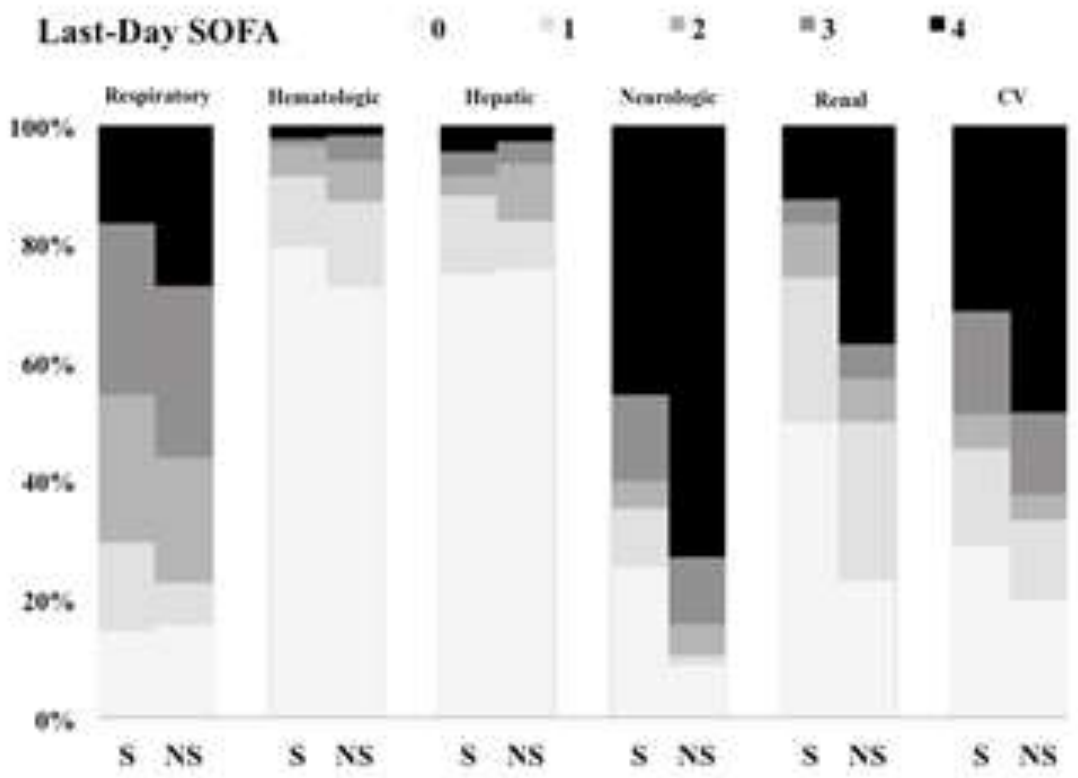

A
80
%
60
40
20
0
*
*
*
Respiratory
Cardiovascular
Renal
Hematologic
Hepatic
Survivors
Non-Survivors

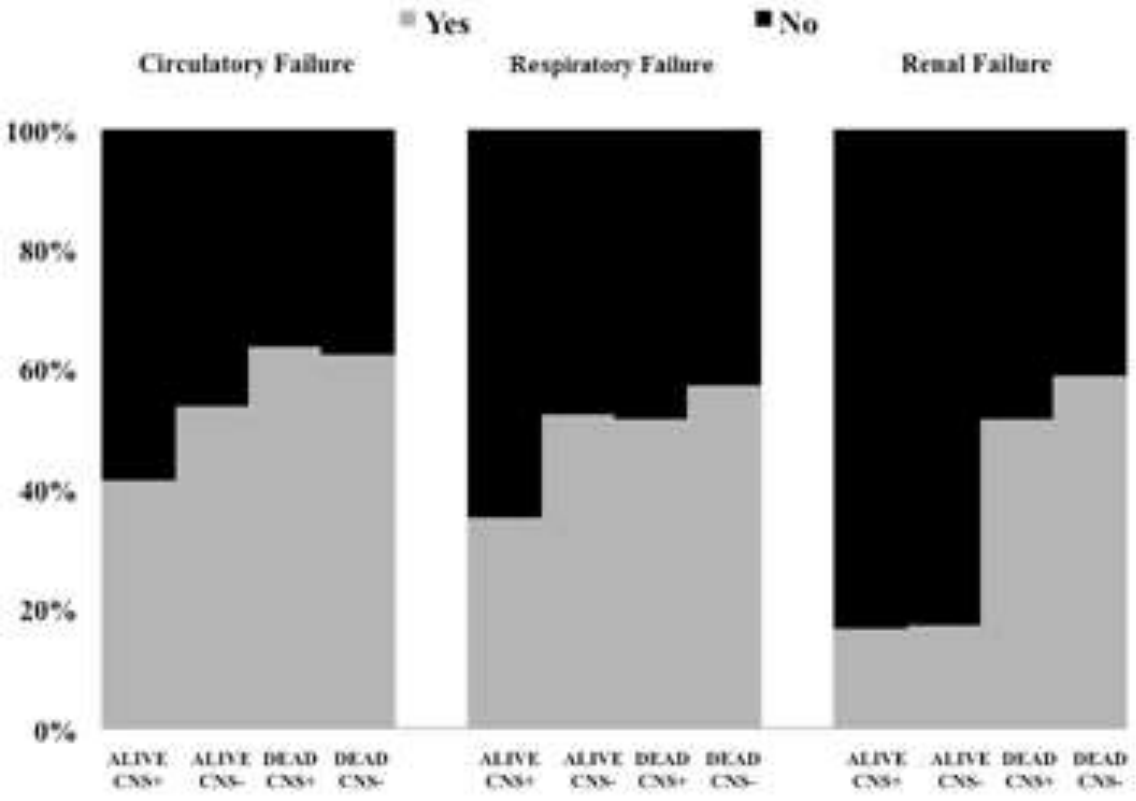

B
80
%
60
40
20
0
*
*
*
Respiratory
Cardiovascular
Renal
Hematologic
Hepatic
FO
UO


C
Cardiovascular-SOFA
0
1
2
3
4
Survivors
Non-Survivors
100
80
60
40
20
0
Day 0 Day1 Day 2 Day 3 Day 4 Day 5
Day 0 Day1 Day 2 Day 3 Day 4 Day 5


D
Renal-SOFA
0
1
2
3
4
Survivors
Non-Survivors
100
80
60
40
20
0
Day 0 Day1 Day 2 Day 3 Day 4 Day 5
Day 0 Day1 Day 2 Day 3 Day 4 Day 5


Renal-SOFA
0
1
2
3
4
100
80
60
40
20
0
%
Day 0 Day1 Day 2 Day 3 Day 4 Day 5
(n=97) (n=90) (n=79) (n=75) (n=64) (n=59)
Day 0 Day1 Day 2 Day 3 Day 4 Day 5
(n=372) (n=302) (n=254) (n=218) (n=187) (n=157)


Last-Day SOFA
0
1
2
3
4
Respiratory
Hematologic
Hepatic
Neurologic
Renal
CV
100%
80%
60%
40%
20%
0%
S NS
S NS
S NS
S NS
S NS
S NS


Yes
No
Circulatory Failure
Respiratory Failure
Renal Failure
100%
80%
60%
40%
20%
0%
ALIVE CNS+
ALIVE CNS-
DEAD CNS+
DEAD CNS-
ALIVE CNS+
ALIVE CNS-
DEAD CNS+
DEAD CNS-
ALIVE CNS+
ALIVE CNS-
DEAD CNS+
DEAD CNS-

Appendix 1. Alphabetical list of participating centers by region and country

Africa
Angola: Clinica Sagrada Esperança (E Tomas)
Democratic Republic of Congo: Cliniques Universitaires De Kinshasa (E Amisi Bibonge)
Morocco: Chu Ibn Rochd Casablanca (B Charra); Ibn Sina Hospital (M Faroudy)
South Africa: Chris Hani Baragwanath Academic Hospital (L Doedens); Grey's Hospital (Z Farina); Sandton Medi Clinic (D Adler); Tygerberg Hospital (C Balkema); Union hospital Alberton (A Kok)
Tunisia: Bizerte Hospital (S Alaya); Military Hospital of Tunis (H Gharsallah)

East Europe
Albania: National Trauma Centre and Military Hospital, Tirana (D Muzha)
Bulgaria: Alexandrovska University Hospital (A Temelkov); Emergency University Hospital 'Pirogov' (G Georgiev); Tokuda Hospital Sofia (G Simeonov); Uh St Ekaterina Sofia (G Tsaryanski); University Hospital for Obstetrics and Gynaecology (S Georgiev); University Hospital Sveta Marina - Varna (A Seliman)
Croatia: General Hosp. Sibenik (S Vrankovic); University Hospital Centre "Sestre Milosrdnice" (Z Vucicevic); University Hospital Centre Zagreb (I Gornik); University Hospital for Infectious Diseases (B Barsic); University Hospital Dubrava (I Husedzinovic)
Czech Republic: Centre of Cardiovascular and Transplant Surgery (P Pavlik); Charles University Hospital (J Manak); IKEM, Prague (E Kieslichova); KNTB Zlín A.S. (R Turek); Krajska Nemocnice Liberec (M Fischer); Masarykova Nemocnice V Usti Nad Labem (R Valkova); St. Anne's University Hospital Brno (L Dadak); University Hospital Haradec Králové (P Dostal); University Hospital Brno (J Malaska); University Hospital Olomouc (R Hajek); University Hospital Plzen (A Židková); Charles University Hospital Plzen (P Lavicka)
Estonia: Tartu University Hospital (J Starkopf)
Georgia: Critical Care Medicine Institute (Z Kheladze); Jo Ann Medical Centre (M Chkhaidze); Kipshidze Central University Hospital (V Kaloiani)
Hungary: Dr. Kenessey Albert Hospital (L Medve); Fejér County St George Teaching Hospital (A Sarkany); Flor Ferenc County Hospital (I Kremer); Jávorszky Ödön Hospital (Z Marjanek); Peterfy Hospital Budapest (P Tamasi)
Latvia: Infectology Centre of Latvia (I Krupnova); Paul Stradins Clinical University Hospital (I Vanags); Riga East Clinical University Hospital (V Liguts)
Lithuania: Hospital of Lithuanian University of Health Sciences Kauno Klinikos (V Pilvinis); Vilnius University Hospital (S Vosylius); Vilnius University Hospital "Santariskiu Clinics", HSICU (G Kekstas); Vilnius University Hospital Santariskiu Clinics, CICU (M Balciunas)
Poland: Csk Mswia (J Kolbusz); Medical University (A Kübler); Medical University Of Wroclaw (B Mielczarek); Medical University Warsaw (M Mikaszewska-Sokolewicz); Pomeranian Medical University (K Kotfis); Regional Hospital in Poznan (B Tamowicz); Szpital Powiatowy W Ostrowi Mazowieckiej (W Sulkowski); University Hospital, Poznam (P Smuszkiewicz); Wojewódzki Szpital Zakazny (A Pihowicz); Wojewódzkie Centrum Medyczne (E Trejnowska)
Romania: Emergency County Hospital Cluj (N Hagau); Emergency Institute for Cardiovascular Diseases (D Filipescu); Fundeni Clinical Institute (G Droc); Galati Hospital

(M Lupu); Inbi "Prof. Dr. Matei Bals" (A Nica); Institute of Pulmonology Marius Nasta (R Stoica); Institutul Clinic Fundeni (D Tomescu); Sfantul Pantelimon Hospital (D Constantinescu); Spitalul Cf 2 Bucuresti (G Valcoreanu Zbaganu); University of Medicine and Pharmacy Iuliu Hatieganu Cluj-Napoca (S Adriana)
Russia: City Clinical Hospital No 40 (V Bagin); City Hospital No 40 (D Belsky); Clinical Hospital N.A. N.V.Solovyev (S Palyutin); Emergency Research Institute N.A. Djanelidze (S Shlyapnikov); Federal Research Centre Paediatric Haematology, Oncology and Immunology (D Bikkulova); Krasnoyarsk State Medical University, Krasnoyarsk Regional Hospital (A Gritsan); Medical Association "Novaya Bolnitsa" (G Natalia); Military Medical Academy (E Makarenko); Novosibirsk Medical University (V Kokhno); Omsk Regional Clinical Hospital (A Tolkach); Railway Hospital of Khabarovsk (E Kokarev); St Alexy Hospital (B Belotserkovskiy); State District Hospital (K Zolotukhin); Vishnevsky Institute of Surgery (V Kulabukhov)
Serbia: Clinic for Cardiac Surgery, Clinical Centre of Serbia (L Soskic); Clinic for Digestive Surgery, Clinical Centre Serbia (I Palibrk); Clinic for Vascular Surgery, Clinical Centre Nis (R Jankovic); Clinical Centre of Serbia (B Jovanovic); Clinical Centre of Serbia (M Pandurovic); Emergency Centre, Clinical Centre of Belgrade (V Bumbasirevic); General University Hospital (B Uljarevic); Military Medical Academy (M Surbatovic); Urology Hospital (N Ladjevic)
Slovakia: District Hospital (G Slobodianiuk); Faculty Hospital (V Sobona); University Hospital Bratislava-Hospital Ruzinov ICU (A Cikova); University Hospital Ruzinov Bratislava (A Gebhardtova)

East & Southeast Asia
China: A Tertiary Hospital (C Jun); Affiliated Hospital of Medical College Qingdao Universty (S Yunbo); Beijing Cancer Hospital ,Beijing Institute for Cancer Research (J Dong); Beijing Chaoyang Hospital (S Feng); Beijing Friendship Hospital (M Duan); Beijing Tongren Hospital Affiliate of Capital Medical University (Y Xu); Beijing University People's Hospital (X Xue); Beijing Luhe Hospital (T Gao); Cancer Hospital, Chinese Academy of Medical Sciences (X Xing); China Academy of Chinese Medical Sciences Guang 'An Men Hospital (X Zhao); Chuxiong, Yunnan Province, People's Hospital (C Li); Donge County People's Hospital of Shandong Province (G Gengxihua); Fu Wai Hospital, Chinese Academy of Medical Sciences (H Tan); Fujian Provincial Hospital (J Xu); Fuxing Hospital, Capital Medicine University (L Jiang); Guangdong General Hospital (Q Tiehe); Henan Provincial People's Hospital (Q Bingyu); Xian Jiaotong University College of Medicine (Q Shi); Kunming Third People's Hospital (Z Lv); Lanzhou University Second Hospital (L Zhang); No 309th Hospital (L Jingtao); No.1 Hospital of China Medical University (Z Zhen); Peking University Shougang Hospital (Z Wang); Peking University Third Hospital (T Wang); Pla Navy General Hospital (L Yuhong); Qilu Hospital Shandong University (Q Zhai); Ruijin Hospital Affiliated Medical School of Jiaotong University, Shanghai (Y Chen); Shandong Provincial Hospital (C Wang); Shanghai 10th People's Hospital (W Jiang); Shanghai First People's Hospital (W Ruilan); Sichuan Provincial People's Hospital (Y Chen); Sichuan Provincial People's Hospital (H Xiaobo); Sir Run Run Shaw Hospital (H Ge); The Affiliated of Guiyang Medical College (T Yan); The Fifth People's Hospital of Shanghai, Fudan University (C Yuhui); The First Affiliated Hospital of Dalian Medical University (J Zhang); The First Affiliated Hospital of Suzhou University (F Jian-Hong); The First Affiliated Hospital of Xinjiang Medical University

(H Zhu); The First Hospital of Jilin University (F Huo); The First Hospital of Jilin University (Y Wang); The First People's Hospital of Kunming (C Li); The General Hospital of Shenyang Military Region ,China (M Zhuang); The People's Hospital of Cangzhou (Z Ma); The Second Hospital of Jilin University (J Sun); The Second People's Hospital of Liaocheng City Shandong Province (L Liuqingyue); The Third Xiangya Hospital (M Yang); Tongde Hospital of Zhejiang Province (J Meng); Tongji University Shanghai East Hospital (S Ma); United Christian Hospital of Hong Kong Sar (K Lee); West China Hospital, Scu (Y Kang); Wuhan Centre Hospital (L Yu); Xiangya Hospital, Changsha, Hunan Province, China (Q Peng); Yantai Yuhuangding Hospital (Y Wei); Yantaishan Hospital, Shandong Province (W Zhang); Zhejiang Provincial People's Hospital (R Sun)
Hong Kong (China): Pamela Youde Nethersole Eastern Hospital (A Yeung); Princess Margaret Hospital (W Wan); Queen Elizabeth Hospital (K Sin)
Indonesia: Anestesi (M Wijanti); Pku Muhammadiyah Bantul, Yogyakarta, Indonesia (U Widodo); Rd Mattaher Hospital Jambi (H Samsirun); Rumah Sakit Pantai Indah Kapuk (T Sugiman); Sardjito Hospital (C Wisudarti); School of Medicine Unpad - Hasan Sadikin Hospital (T Maskoen)
Japan: Chiba Hokusoh Hospital, Nippon Medical School (N Hata); Chiba University Hospital (Y Kobe); Fujita Health University School of Medicine (Y Shimomura); Japanese Red Cross Maebashi Hospital (D Miyazaki); Jichi Medical University Hospital (S Nunomiya); Jikei University School of Medicine (S Uchino); Kimitsu Chuo Hospital (N Kitamura); Kochi Medical School (K Yamashita); Kyoto Prefectural University of Medicine (S Hashimoto); Nara Medical University Hospital (H Fukushima)
Malaysia: Hospital Sultanah Nur Zahirah, Kuala Terengganu, Terengganu, (N Nik Adib); Kuala Lumpur Hospital (L Tai); Queen Elizabeth Hospital 2 (B Tony)
Philippines: Cebu Velez General Hospital (R Bigornia); Chong Hua Hospital (R Bigornia); Perpetual Succour Hospital (R Bigornia); The Medical City (J Palo)
Singapore: Alexandra Hospital (S Chatterjee); National University Health System (B Tan); Singapore General Hospital (A Kong); Tan Tock Seng Hospital (S Goh)
Taiwan: National Taiwan University Hospital (C Lee)
Thailand: Maharaj Nakorn Chiangmai Hospital,Chiaingmai University (C Pothirat); Prince of Songkla University (B Khwannimit); Ramathibodi Hospital (P Theerawit); Ramathibodi Hospital, Somdech Phra Debaratana Medical Centre (P Pornsuriyasak); Siriraj Hospital, Mahidol University (A Piriyapatsom)

Middle East
Egypt: Cairo University (A Mukhtar); Demerdash Surgical Intensive Care Unit (Dsicu); Ain Shams Faculty of Medicine (A Nabil Hamdy); Zaitoun Specialized Hospital (H Hosny)
Iran: Gums (A Ashraf); Imam Hossein Hospital, Sbums (M Mokhtari); Imamreza Hospital (S Nowruzinia); Laleh Hospital (A Lotfi); Shiraz University of Medical Sciences (F Zand); Shiraz University of Medical Sciences (R Nikandish); Tehran Medical Sciences University (O Moradi Moghaddam)
Israel: Rabin Medical Centre (J Cohen); Sourasky Tel Aviv Medical Centre (O Sold)
Lebanon: Centre Hospitalier Du Nord (T Sfeir)
Oman: Sohar Hospital (A Hasan)
Palestinian Territories: Specialized Arab Hospital (D Abugaber)
Saudi Arabia: Almana General Hospital (H Ahmad); KFSHRC, Riyadh (T Tantawy); King

Abdulaziz Medical City Riyadh (S Baharoom); King Abdulaziz University (H Algethamy); King Saud Medical City (A Amr); Riyadh Military Hospital (G Almekhlafi)
Turkey: Erciyes University Medical Faculty (R Coskun); Erciyes University Medical School (M Sungur); Gülhane Military Medical Academy (A Cosar); International Hospital, Istanbul (B Güçyetmez); Istanbul University Cerrahpasa Medical School Hospital (O Demirkiran); Istanbul University Istanbul Medical Faculty (E Senturk); Karadeniz Technical University, Medical Faculty (H Ulusoy); Memorial Atasehir Hospital (H Atalan); Pamukkale Universty (S Serin); Yuzuncu Yil Universitesy Medical Faculty (I Kati)
United Arab Emirates: Dubai Hospital (Z Alnassrawi); Mafraq Hospital (A Almemari); Sheikh Khalifa Medical City (K Krishnareddy); Tawam Hospital (S Kashef); The City Hospital (A Alsabbah)

North America
Canada: Hôpital Charles Lemoyne (G Poirier); St. Michael's Hospital (J Marshall); Toronto General Hospital (M Herridge); Toronto Western Hospital (M Herridge)
Puerto Rico: San Juan Hospital (R Fernandez)
United States: Christiana Care Health System (G Fulda); Cincinnati Children's Hospital Medical Centre (S Banschbach); El Camino Hospital (J Quintero); George Washington Hospital (E Schroeder); Hospital of The University of Pennsylvania (C Sicoutris); John H Stroger Hospital of Cook County (R Gueret); Mayo Clinic, CCM (R Kashyap); Mayo Clinic, PCC (P Bauer); Medical College of Wisconsin (R Nanchal); Northwestern Memorial Hospital (R Wunderink); Orlando Regional Medical Centre (E Jimenez); Washington Hospital Centre (A Ryan); Washington Hospital Centre,2H (A Ryan); Washington Hospital Centre, 2G (A Ryan); Washington Hospital Centre, 3H (A Ryan); Washington Hospital Centre, 3G (A Ryan); Washington Hospital Centre, 4H (A Ryan); Washington Hospital Centre, CVRR (A Ryan)

Oceania
Australia: Armadale Health Service (D Prince); Bendigo Hospital (J Edington); Canberra Hospital (F Van Haren); Flinders Medical Centre (A Bersten); Joondalup Health Campus (B Richards); Lismore Base Hospital (M Kilminster); Mater Adult Hospital (D Sturgess); Prince Charles Hospital, Brisbane (M Ziegenfuss); Royal Adelaide Hospital (S O' Connor); Royal Brisbane and Womens' Hospital (J Lipman); Royal Darwin Hospital (L Campbell); Royal Hobart Hospital (R Mcallister); Sir Charles Gairdner Hospital (B Roberts); The Queen Elizabeth Hospital (P Williams)
New Zealand: Auckland District Health Board (R Parke); Christchurch Hospital (P Seigne); Hawke's Bay Hospital (R Freebairn); Midcentral Health, Palmerston North Hospital (D Nistor); Middlemore Hospital (C Oxley); Wellington Hospital (P Young)

South America
Argentina: Cemic (Centro De Educación Médica E Investigaciones Clínicas) (R Valentini); Fleni (N Wainsztein); Hospital Aleman (P Comignani); Hospital Central San Isidro (M Casaretto); Hospital Fernandez (G Sutton); Hospital Francisco Lopez Lima Area Programa General Roca (P Villegas); Sanatorio Allende (C Galletti); Sanatorio De La Trinidad Palermo (J Neira); Sanatorio Julio Corzo Rosario (D Rovira)
Belize: Karl Heusner Memorial Hospital and Belize Healthcare Partner (J Hidalgo)
Bolivia: Hospital Obrero No1 (F Sandi)

Brazil: Cias -Unimed Vitória (E Caser); Evangelical Hospital of Cachoeiro De Itapemirim (M Thompson); Hospital 9 De Julho (M D'agostino Dias); Hospital Alcides Carneiro (L Fontes); Hospital Das Clínicas Luzia De Pinho Melo (M Lunardi); Hospital Das Nações De Curitiba (N Youssef); Hospital De Base Famerp (S Lobo); Hospital De Clínicas De Niterói (R Silva); Hospital De Clínicas Padre Miguel (J Sales Jr); Hospital De Terapia Intensiva (L Madeira Campos Melo); Hospital Do Trabalhador (M Oliveira); Hospital Esperanca (M Fonte); Hospital Evangelico De Londrina (C Grion); Hospital Geral De Fortaleza (C Feijo); Hospital Geral De Roraima (V Rezende); Hospital Israelita Albert Einstein (M Assuncao); Hospital Mater Dei (A Neves); Hospital Meridional (P Gusman); Hospital Meridional (D Dalcomune); Hospital Moinhos De Vento (C Teixeira); Hospital Municipal Ruth Cardoso (K Kaefer); Hospital Nereu Ramos (I Maia); Hospital Pasteur (V Souza Dantas); Hospital Pro Cardiaco (R Costa Filho); Hospital Regional De Samambaia (F Amorim); Hospital Regional Hans Dieter Schmidt (M Assef); Hospital Santa Casa - Campo Mourão (P Schiavetto); Hospital Santa Paula (J Houly); Hospital Santapaula (J Houly); Hospital São José Do Avaí (F Bianchi); Hospital São Lucas Da Pucrs (F Dias); Hospital Sao Vicente De Paula (C Avila); Hospital São Vicente De Paulo (J Gomez); Hospital Saude Da Mulher (L Rego); Hospital Tacchini (P Castro); Hospital Unimed Costa Do Sol-Macae-Rj (J Passos); Hospital Universitário - Ufpb - João Pessoa (C Mendes); Hospital Universitário De Londrina (C Grion); Hospital Universitário São Francisco (G Colozza Mecatti); Santa Casa De Caridade De Diamantina (M Ferrreira); Santa Casa De Misericordia De Tatui (V Irineu); São Francisco De Paula Hospital (M Guerreiro)
Chile: Clinica Indisa (S Ugarte); Clinica Las Lilas (V Tomicic); Hospital Carlos Van Buren (C Godoy); Hospital Del Trabajador De Santiago (W Samaniego); Hospital El Pino (I Escamilla); Hospital Mutual De Seguridad (I Escamilla)
Colombia: Centro Medico Imbanaco (L Castro Castro); Clinica Colombia Cali (G Libreros Duque); Clínica Del Café (D Diaz-Guio); Clínica La Estancia S.A. (F Benítez); Clinica Medellin (A Guerra Urrego); Fundacion Clinica Shaio (R Buitrago); Hospital Santa Clara (G Ortiz); Hospital Universitario Fundación Santa Fe De Bogota (M Villalba Gaviria)
Costa Rica: Calderón Guardia Hospital (D Salas); Hospital Dr Rafael Angel Varlderon Guardia Ccss (J Ramirez-Arce)
Ecuador: Clinica La Merced (E Salgado); Hospital Eugenio Espejo (D Morocho); Hospital Luis Vernaza (J Vergara); Shdug Sistema Hospitalario Docente De La Universidad De Guayaquil (M Chung Sang)
El Salvador: General Hospital (C Orellana-Jimenez)
Guatemala: Hospital Centro Medico (L Garrido)
Honduras: Instituto Hondureño Del Seguro Social (O Diaz)
Martinique: Centre Hospitalier Universitaire De Fort-De-France (D Resiere)
Mexico: Centro Estatal De Cuidados Críticos (C Osorio); Centro Médico Nacional "20 De Noviembre" Issste (A De La Vega); Fundacion Clinica Medica Sur (R Carrillo); Has-Tec (V Sanchez); Hospital 1o De Octubre, Issste (A Villagomez); Hospital Español De Mexico (R Martinez Zubieta); Hospital General Ajusco Medio (M Sandia); Hospital General Guadalupe Victoria (M Zalatiel); Hospital Juarez De Mexico (M Poblano); Hospitalcivil De Guadalajara, Hspitaljuan I Menchaca (D Rodriguez Gonzalez); Instituto Mexicano Del Seguro Social (F Arrazola); Instituto Mexicano Del Seguro Social (L Juan Francisco); Instituto Nacional De Cancerología, Mexíco (SA Ñamendys-Silva); ISSSTE Guerra Moya); Medical Centre ISSEMYM Toluca (M Hernandez); Mixta (D Rodriguez Cadena); Secretaria De Salud Del Distrito

Federal (I Lopez Islas)
Panama: Hospital Santo Tomás (C Ballesteros Zarzavilla); Social Security Hospital (A Matos)
Peru: Clinica Anglo Americana (I Oyanguren); Essalud (J Cerna); Hospital Nacional Dos De Mayo (R Quispe Sierra); Hospital Rebagliati (R Jimenez); Instituto Nacional De Enfermedades Neoplasicas (L Castillo)
Turks And Caicos Islands: Gulhane Medical Faculty (R Ocal); Izmir Atatürk Educational And Research Hosp. (A Sencan)
Uruguay: CAMS (S Mareque Gianoni); CASMU (A Deicas); Hospital Español Asse (J Hurtado); Hospital Maciel (G Burghi)
Venezuela: Centro Medico De Caracas (A Martinelli); Hospital Miguel Perez Carreño (I Von Der Osten)

South Asia
Afghanistan: MSF Trauma Hospital Kunduz (C Du Maine)
India: Amri Hospitals (M Bhattacharyya); Amri Hospitals Salt Lake (S Bandyopadhyay); Apollo Hospital (S Yanamala); Apollo Hospitals (P Gopal); Apollo Hospitals, Bhubaneswar (S Sahu); Apollo Speciality Hospital (M Ibrahim); Asian Heart Institute (D Rathod); Baby Memorial Hospital Ltd, Calicut, Kerala (N Mukundan); Batra Hospital & Mrc, New Delhi 110062 (A Dewan); Bombay Hospital Institute of Medical Sciences (P Amin); Care Hospital (S Samavedam); Cims Hospital (B Shah); Columbiaasia Hospital, Mysore (D Gurupal); Dispur Hospitals (B Lahkar); Fortis Hospital (A Mandal); Fortis Hospital (Noida) (M Sircar); Fortis-Escorts Hospital, Faridabad, India (S Ghosh); Ganga Medical Centre & Hospital P Ltd. (V Balasubramani); Hinduja Hospital (F Kapadia); KDAH (S Vadi); Kerala Institute of Medical Sciences (Kims, RMCC) (K Nair); Kerala Institute of Medical Sciences (Kims, DTEM) (S Tripathy); Kovai Medical Centre and Hospital (S Nandakumar); Medanta The Medicity, Gurgaon (J Sharma); Medica Superspecialty Hospitals (A Kar); Metro Heart Institute with Multispeciality (S Jha); Ruby Hall Pune (K Zirpe/Gurav); Saifee Hospital (M Patel); Spandan Multispeciality Hospital (A Bhavsar); Tata Main Hospital (D Samaddar); Tata Memorial Hospital (A Kulkarni)
Pakistan: Aga Khan University (M Hashmi); Hearts International Hospital (W Ali); Liaquat National Hospital (S Nadeem)
Sri Lanka: Sri Jayewardenepura General Hospital (K Indraratna)

West Europe
Andorra: Hospital Nostra Senyora De Meritxell (A Margarit)
Austria: Akh Wien (P Urbanek); Allgemeines Und Orthopädisches Landeskrankenhaus Stolzalpe (J Schlieber); Barmherzige Schwestern Linz (J Reisinger); General Hospital Braunau (J Auer); Krankenhaus D. Barmherzigen Schwestern Ried I.I. (A Hartjes); Krankenhaus Floridsdorf (A Lerche); LK Gmünd-Waidhofen/Thaya-Zwettl, Standort Zwettl (T Janous); LKH Hörgas-Enzenbach (E Kink); LKH West (W Krahulec); University Hospital (K Smolle)
Belgium: AZ Groeninge Kortrijk (M Van Der Schueren); AZ Jan Palfijn Gent (P Thibo); AZ Turnhout (M Vanhoof); Bracops Anderlecht (I Ahmet); Centre Hospitalier Mouscron (G Philippe); CH Peltzer La Tourelle (P Dufaye); Chirec Edith Cavell (O Jacobs); CHR Citadelle (V Fraipont); CHU Charleroi (P Biston); Chu Mont-Godinne (A Dive); CHU Tivoli (Y Bouckaert); Chwapi (E Gilbert); Clinique Saint-Pierre Ottignies (B Gressens); Clinique-

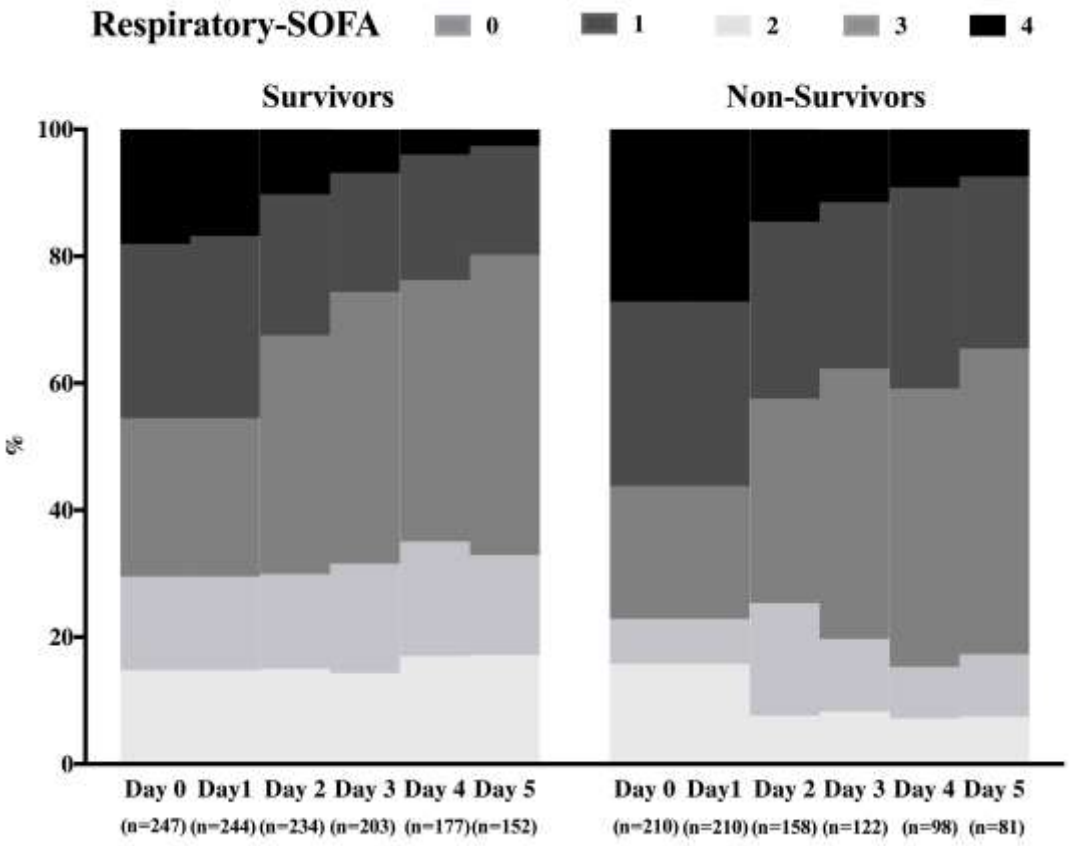
Maternité Sainte Elisabeth (E Pinck); Cliniques De L'Europe - St-Michel (V Collin); Erasme University Hospital (JL Vincent); Ghent University Hospital (J De Waele); Moliere Hospital (R Rimachi); Notre Dame (D Gusu); Onze Lieve Vrouw Ziekenhuis, Aalst (K De Decker); Ixelles Hospital (K Mandianga); Sint-Augustinus (L Heytens); St Luc University Hospital (UCL) (X Wittebole); UZ Brussel (S Herbert); Vivalia Site De Libramont (V Olivier); VZW Gezondheidszorg Oostkust Knokke-Heist (W Vandenheede); ZNA Middelheim (P Rogiers)
Denmark: Herning Hospital (P Kolodzeike); Hjoerring Hospital (M Kruse); Vejle Hospital (T Andersen)
Finland: Helsinki University Central Hospital (V Harjola); Seinäjoki Central Hospital (K Saarinen)
France: Aix Marseille Univ, Hôpital Nord (M Leone); Calmette Hospital, Lille (A Durocher); Centre Hospitalier de Dunkerque (S Moulront); Centre Hospitalier Lyon Sud (A Lepape); Centre Hospitalo-Universitaire Nancy-Brabois (M Losser); CH Saint Philibert, Ghicl, Lille (P Cabaret); CHR De Dax (E Kalaitzis); CHU Amiens (E Zogheib); CHU Dijon (P Charve); CHU Dupuytren (B Francois); CHU Nîmes (J Lefrant); Centre Hospitalier De Troyes (B Beilouny); Groupe Hospitalier Est Francilien-Centre Hospitalier De Meaux (X Forceville); Groupe Hospitalier Paris Saint Joseph (B Misset); Hopital Antoine Béclère (F Jacobs); Hopital Edouard Herriot (F Bernard); Hôpital Lariboisère, APHP, Paris France (D Payen); Hopital Maison Blanche, Reims (A Wynckel); Hopitaux Universitaires de Strasbourg (V Castelain); Hospices Civils de Lyon (A Faure); CHU-Grenoble (P Lavagne); CHU-Nantes (L Thierry); Réanimation Chirurgical Cardiovasculaire, CHRU Lille (M Moussa); University Hospital Ambroise Paré (A Vieillard-Baron); University Hospital Grenoble (M Durand); University Hospital of Marseille (M Gainnier); University of Nice (C Ichai)
Germany: Alexianer Krefeld Gmbh (S Arens); Charite Hochschulmedizin Berlin (C Hoffmann); Charite-University-Hospital, Berlin (M Kaffarnik); Diakoniekrankenhaus Henriettenstiftung Gmbh (C Scharnofske); Elisabeth-Krankenhaus Essen (I Voigt); Harlaching Hospital, Munich Municipal Hospital Group (C Peckelsen); Helios St. Johannes Klinik (M Weber); Hospital St. Georg Leipzig (J Gille); Klinik Hennigsdorf Der Oberhavel Kliniken Gmbh (A Lange); Klinik Tettnang (G Schoser); Klinikum "St. Georg" Leipzig (A Sablotzki); Klinikum Augsburg (U Jaschinski); Klinikum Augsburg (A Bluethgen); Klinikum Bremen-Mitte (F Vogel); Klinikum Bremen-Ost (A Tscheu); Klinikum Heidenheim (T Fuchs); Klinikum Links Der Weser Gmbh (M Wattenberg); Klinikum Luedenscheid (T Helmes); Krankenhaus Neuwerk (S Scieszka); Marienkrankenhaus Schwerte (M Heintz); Medical Centre Cologne Merheim (S Sakka); Schwarzwald-Baar Klinikum Villingen-Schwenningen (J Kohler); St. Elisabeth Krankenhaus Köln-Hohenlind (F Fiedler); St. Martinus Hospital Olpe (M Danz); Uniklinikum Jena (Y Sakr); Universitätsklinikum Tübingen (R Riessen); Universitätsmedizin Mainz (T Kerz); University Hospital Aachen, CPACC (A Kersten); University Hospital Aachen, DMIII (F Tacke); University Hospital Aachen, OIC (G Marx); University Hospital Muenster (T Volkert); University Medical Centre Freiburg (A Schmutz); University Medical Centre Hamburg-Eppendorf (A Nierhaus); University Medical Centre Hamburg-Eppendorf (S Kluge); University Medicine Greifswald (P Abel); University of Duisburg-Essen (R Janosi); University of Freiburg (S Utzolino); University clinic Ulm (H Bracht); Vivantes Klinikum Neukoelln (S Toussaint)
Greece: Ahepa University Hospital (M Giannakou Peftoulidou); Athens University (P Myrianthefs); Athens University Medical School (A Armaganidis); Evangelismos Hospital (C Routsi); General Hospital of Chania, Crete (A Xini); Hippokration General Hospital,

Thessaloniki (E Mouloudi); General hospital of Velos (I Kokoris); Lamia General Hospital (G Kyriazopoulos); Naval and Veterans Hospital (S Vlachos); Papanikolaou General Hospital (A Lavrentieva); University Hospital Alexandroupolis (P Partala); University of Ioannina (G Nakos)
Iceland: Landspitali University Hospital (A Moller); Landspitali University Hospital Fossvogur (S Stefansson)
Ireland: Cork University Hospital (J Barry); Mercy University Hospital (R O'Leary); Mid Western Regional Hospital Complex (C Motherway); Midland Regional Hospital Mullingar, Co Westmeath (M Faheem); St. Vincent's University Hospital (E Dunne); Tallaght Hospital (M Donnelly); University Hospital Galway (T Konrad)
Italy: Anesthesiology and Intensive Care (E Bonora); AO Ospedale Niguarda Ca' Granda (C Achilli); Azienda Ospedaliera Di Padova (S Rossi); Azienda Ospedaliero Universitaria Policlinico Vittorio Emanuele (G Castiglione); Careggi Teaching Hospital (A Peris); Clinicized Hospital Ss Annunziata - Chieti (D Albanese); Fondazione Irccs Ca' Granda Ospedale Maggiore Policlinico, Milano; University of Milan (N Stocchetti); H San Gerardo - Monza (G Citerio); Icu "Ceccarini" Hospital Riccione (L Mozzoni); Irccs Centro Cardiologico Monzino (E Sisillo); Irccs Centro Di Riferimento Oncologico Della Basilicata (P De Negri); Irccs Fondazione Ca' Granda - Ospedale Maggiore Policlinico (M Savioli); Ospedale Belcolle Viterbo (P Vecchiarelli); Ospedale Civile Maggiore - A.O.U.I Verona (F Puflea); Ospedale Civile Maggiore - A.O.U.I Verona (V Stankovic); Ospedale Di Circolo E Fondazione Macchi - Varese (G Minoja); Ospedale Di Trento - Azienda Provinciale Per I Servizi Sanitari Della Provincia Autonoma Di Trento (S Montibeller); Ospedale Orlandi (P Calligaro); Ospedale Regionale U.Parini-Aosta (R Sorrentino); Ospedale San Donato Arezzo (M Feri); Ospedale San Raffaele (M Zambon); Policlinico G.B. Rossi - A.O.U.I Verona (E Colombaroli); Policlinico University of Palermo (A Giarratano); Santa Maria Degli Angeli Hospital (T Pellis); Saronno Hospital (C Capra); Università Cattolica Del Sacro Cuore (M Antonelli); University Catania, Italy (A Gullo); University of Florence, Florence (C Chelazzi); University of Foggia (A De Capraris); University of Milano-Bicocca, San Gerardo Hospital (N Patroniti); University of Modena (M Girardis); University of Siena (F Franchi); University of Trieste (G Berlot)
Malta: Mater Dei Hospital (M Buttigieg)
Netherlands: Albert Schweitzer Hospital (H Ponssen); Antoni Van Leeuwenhoek Ziekenhuis (J Ten Cate); Atrium Medisch Centrum Parkstad (L Bormans); Bovenij Hospital (S Husada); Catharina Hospital Eindhoven (M Buise); Erasmus University Medical Centre (B Van Der Hoven); Martiniziekenhuis Groningen (A Reidinga); Medical Centre Leeuwarden (M Kuiper); Radboud University Nijmegen Medical Centre (P Pickkers); Slotervaart Ziekenhuis Amsterdam (G Kluge); Spaarne Ziekenhuis (S Den Boer); University Medical Centre Utrecht (J Kesecioglu); Ziekenhuis Rijnstate (H Van Leeuwen)
Norway: Haukeland University Hospital (H Flaatten); St Olavs Hospital, Trondheim University Hospital (S Mo)
Portugal: Centro Hospitalar Cova Da Beira (V Branco); Centro Hospitalar Do Porto (F Rua); Centro Hospitalar Do Tâmega E Sousa (E Lafuente); Centro Hospitalar Gaia/Espinho, Epe (M Sousa); Centro Hospitalar Médio Tejo (N Catorze); Centro Hospitalar Tondela-Viseu (M Barros); Faro Hospital (L Pereira); Hospital Curry Cabral (A Vintém De Oliveira); Hospital Da Luz (J Gomes); Hospital De Egas Moniz - Chlo (I Gaspar); Hospital De Santo António, Centro Hospitalar Do Porto (M Pereira); Hospital Divino Espírito Santo, Epe (M Cymbron); Hospital Espirito Santo - Évora Epe (A Dias); Hospital Garcia Orta (E Almeida); Hospital

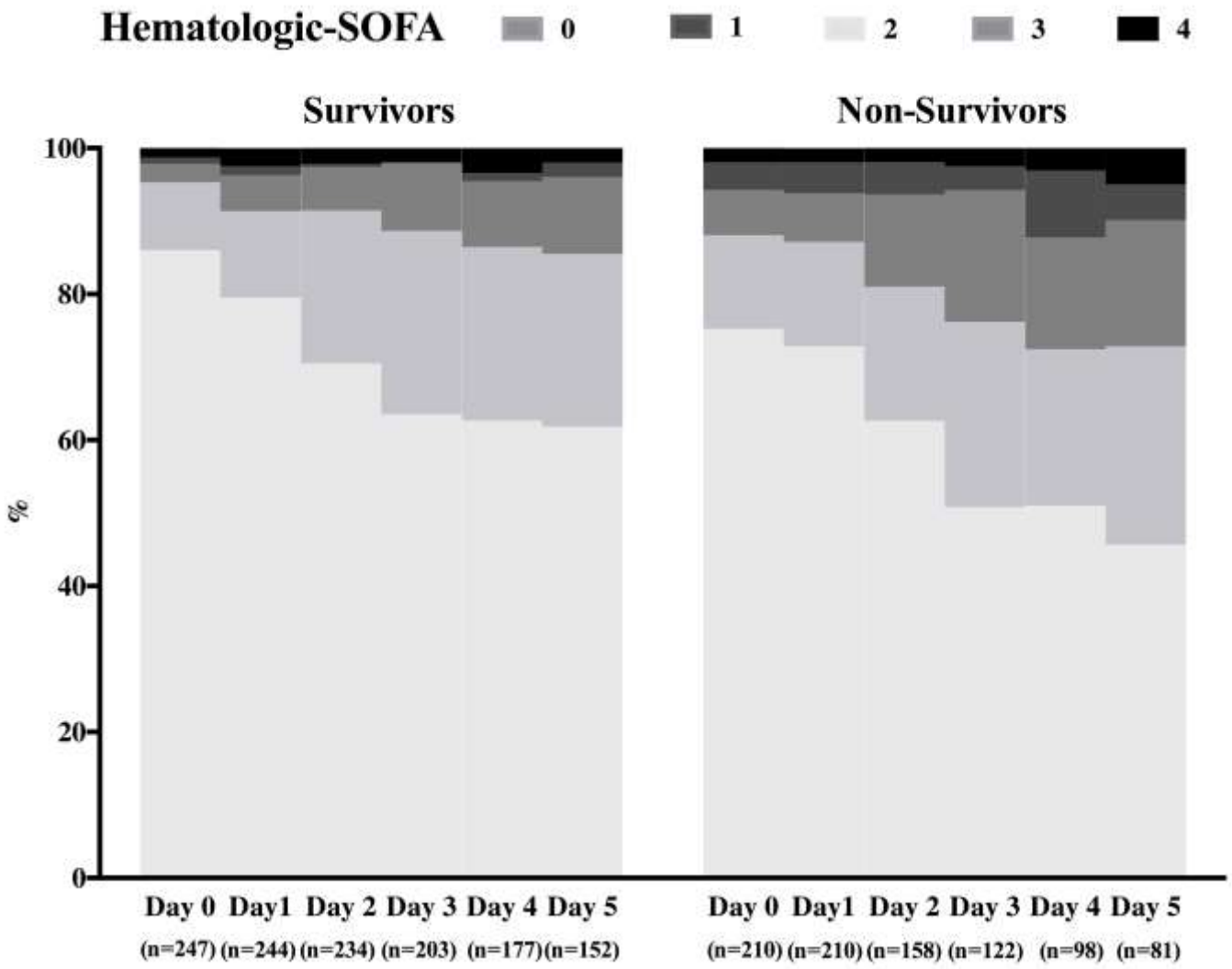
Geral Centro Hospitalar E Universitario Coimbra (S Beirao); Hospital Prof. Doutor Fernando Fonseca Epe (I Serra); Hospital São Bernardo (R Ribeiro); Hospital Sao Francisco Xavier, Chlo (P Povoa); Instituto Portugues De Oncologia Francisco Gentil, Porto (F Faria); Santa Maria Hospital (Z Costa-E-Silva); Serviço De Saúde Da Região Autonóma Da Madeira (J Nóbrega); UCIP (F Fernandes); ULS - Castelo Branco (J Gabriel)
Slovenia: General Hospital Celje (G Voga); General Hospital Izola (E Rupnik); General Hospital Novo Mesto (L Kosec); Oncological Institute (M Kerin Povšic); Ukc Maribor (I Osojnik); University Clinic of Respiratory and Allergic Diseases (V Tomic); University Clinical Centre Maribor (A Sinkovic)
Spain: CH Salamanca (J González); Clinic Hospital (E Zavala); Complejo Hospitalario De Jaén (J Pérez Valenzuela); Complejo Hospitalario De Toledo (L Marina); Complexo Hospitalario Universitario De Ourense (P Vidal-Cortés); Complexo Hospitalario Universitario De Vigo (P Posada); Corporación Sanitaria Parc Tauli (A Ignacio Martin-Loeches); Cruz Roja Hospital (N Muñoz Guillén); H Vall Hebron (M Palomar); HGGC Dr Negrín (J Sole-Violan); Hospital Clinic (A Torres); Hospital Clinico San Carlos (M Gonzalez Gallego); Hospital Clínico Universitario De Valencia (G Aguilar); Hospital Clínico Universitario Lozano Blesa (R Montoiro Allué); Hospital Clinico Valencia (M Argüeso); Hospital De La Ribera (M Parejo); Hospital De Sagunto (M Palomo Navarro); Hospital De San Juan De Alicante (A Jose); Hospital De Torrejon De Ardoz (N Nin); Hospital Del Mar (F Alvarez Lerma); Hospital Del Tajo (O Martinez); Hospital General Universitario De Elche (E Tenza Lozano); Hospital General Universitario Gregorio Marañon (S Arenal López); Hospital General Universitario Gregorio Marañon (M Perez Granda); Hospital General Universitario Santa Lucía (S Moreno); Hospital Germans Trias I Pujol (C Llubia); Hospital Infanta Margarita (C De La Fuente Martos); Hospital Infanta Sofia (P Gonzalez-Arenas); Hospital J.M. Morales Meseguer (N Llamas Fernández); Hospital J.M. Morales Meseguer (B Gil Rueda); Hospital Marina Salu. Denia. Alicante. (I Estruch Pons); Hospital Nuestra Señora Del Prado, Talavera De La Reina, Toledo. España (N Cruza); Hospital San Juan De Dios Aljarafe (F Maroto); Hospital Sas of Jerez (A Estella); Hospital Son Llatzer (A Ferrer); Hospital Universitario Central De Asturias (L Iglesias Fraile); Hospital Universitario Central De Asturias (Q Brigida); Hospital Universitario De Alava, Santiago (A Quintano); Hospital Universitario De Basurto, Bilbao (M Tebar); Hospital Universitario de Getafe (F Frutos-Vivar); Hospital Universitario De La Princesa (A Reyes); Hospital Universitario de Tarragona Joan Xxiii (A Rodríguez); Hospital Universitario Del Henares (A Abella); Hospital Universitario Fundación Alcorcón (S García Del Valle); Hospital Universitario La Paz (S Yus); Hospital Universitario La Paz (E Maseda); Hospital Universitario Rio Hortega (J Berezo); Hospital Universitario San Cecilio (Granada) (A Tejero Pedregosa); Hospital Virgen Del Camino (C Laplaza); Mutua Terrassa University Hospital (R Ferrer); Rão Hortega University Hospital (J Rico-Feijoo); Servicio Andaluz De Salud. Spain. (M Rodríguez); University Opf Navarra (P Monedero)
Sweden: Karolinska University Hospital And Karolinska Institute (K Eriksson); Sunderby Hospital, Luleå (D Lind)
Switzerland: Hôpital Intercantonal De La Broye (D Chabanel); Hôpital Neuchâtelois - La Chaux-De-Fonds (H Zender); Lindenhofspital (K Heer); Regionalspital Surselva Ilanz (Gr) Schweiz (B Frankenberger); University Hospital Bern (S Jakob); Zentrum Für Intensivmedizin (A Haller)
United Kingdom: Alexandra Hospital Redditch (S Mathew); Blackpool Teaching Hospitals (R Downes); Brighton And Sussex University Hospitals (C Barrera Groba); Cambridge

University Hospitals NHS Foundation Trust (A Johnston); Charing Cross Hospital (R Meacher); Chelsea & Westminster Hospital (R Keays); Christie Foundation Trust (P Haji-Michael); County Hospital, Lincoln (C Tyler); Craigavon Area Hospital (A Ferguson); Cumberland Infirmary (S Jones); Darent Valley Hospital (D Tyl); Dorset County Hospital (A Ball); Ealing Hospital NHS Trust (J Vogel); Glasgow Royal Infirmary (M Booth); Gloucester Royal Hospital (P Downie); The Great Western Hospital, Swindon (M Watters); Imperial College Healthcare NHS Trust (S Brett); Ipswich Hospital Nhs Trust (M Garfield); James Paget University Hospital NHS Foundation Trust (L Everett); King's College Hospital (S Heenen); King's Mill Hospital (S Dhir); Leeds Teaching Hospitals NHS Trust (Z Beardow); Lewisham Healthcare NHS Trust (M Mostert); Luton and Dunstable Hospital NHS Trust (S Brosnan); Medway Maritime Hospital (N Pinto); Musgrove Park Hospital (S Harris); Nevill Hall Hospital (A Summors); Pilgrim Hospital (N Andrew); Pinderfields Hospital, Mid Yorkshire NHS Trust (A Rose); Plymouth Hospitals Nhs Trust (R Appelboam); Princess Royal Hospital Telford (O Davies); Royal Bournemouth Hospital (E Vickers); Royal Free Hampstead NHS Foundation Trust (B Agarwal); Royal Glamorgan Hospital (T Szakmany); Royal Hampshire County Hospital (S Wimbush); Royal Liverpool University Hospital (K Williams); Royal London Hospital, Barts Health NHS Trust (R Pearse); Royal Shrewsbury Hospital (R Hollands); Royal Surrey County Hospital (J Kirk-Bayley); St Georges Healthcare (N Fletcher); Surrey & Sussex Healthcare Trust (B Bray); University College Hospital (D Brealey)

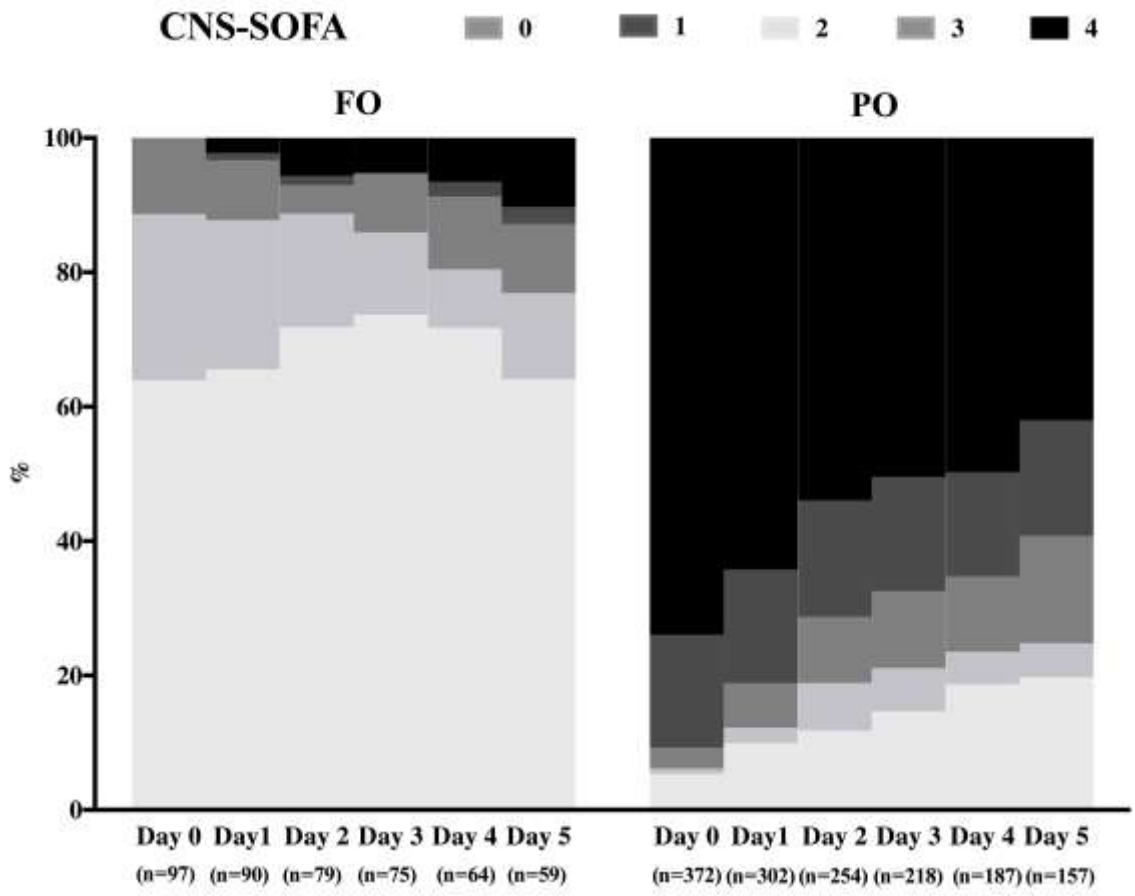
Supplemental Figure 1. Time-course of respiratory SOFA in survivors and non-survivors.



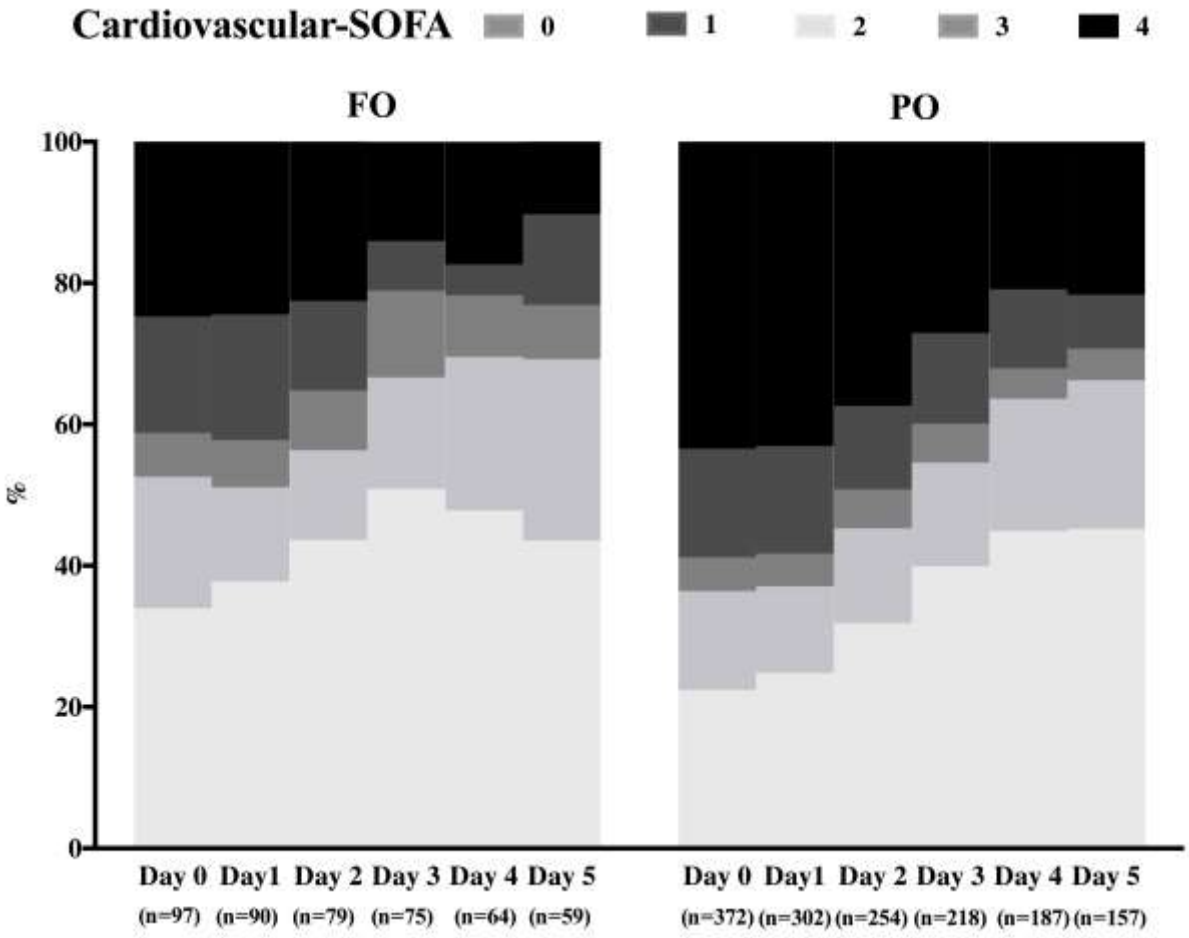
Supplemental Figure 2. Time-course of hematologic SOFA in survivors and non-survivors.



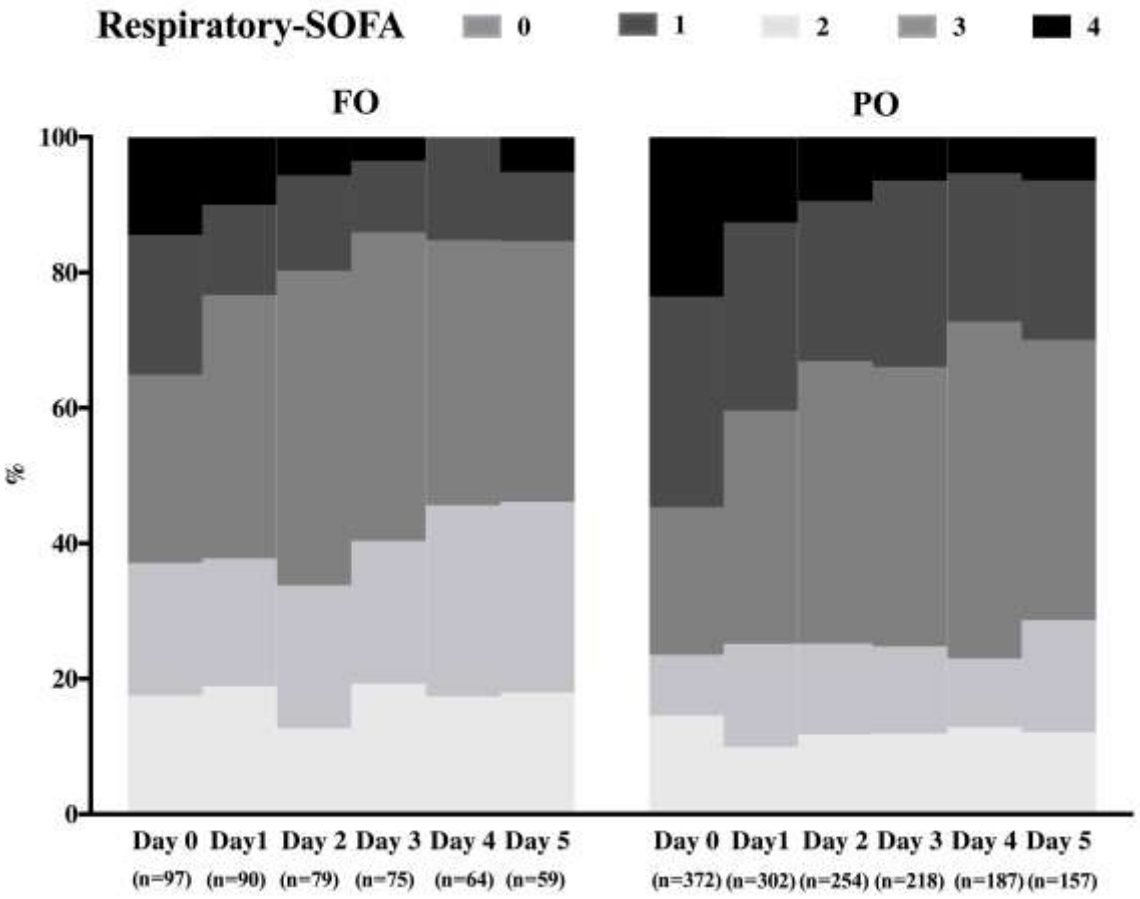
Supplemental Figure 3. Time-course of central nervous system (CNS) SOFA in patients with favorable (FO) and unfavorable (UO) neurological outcome.



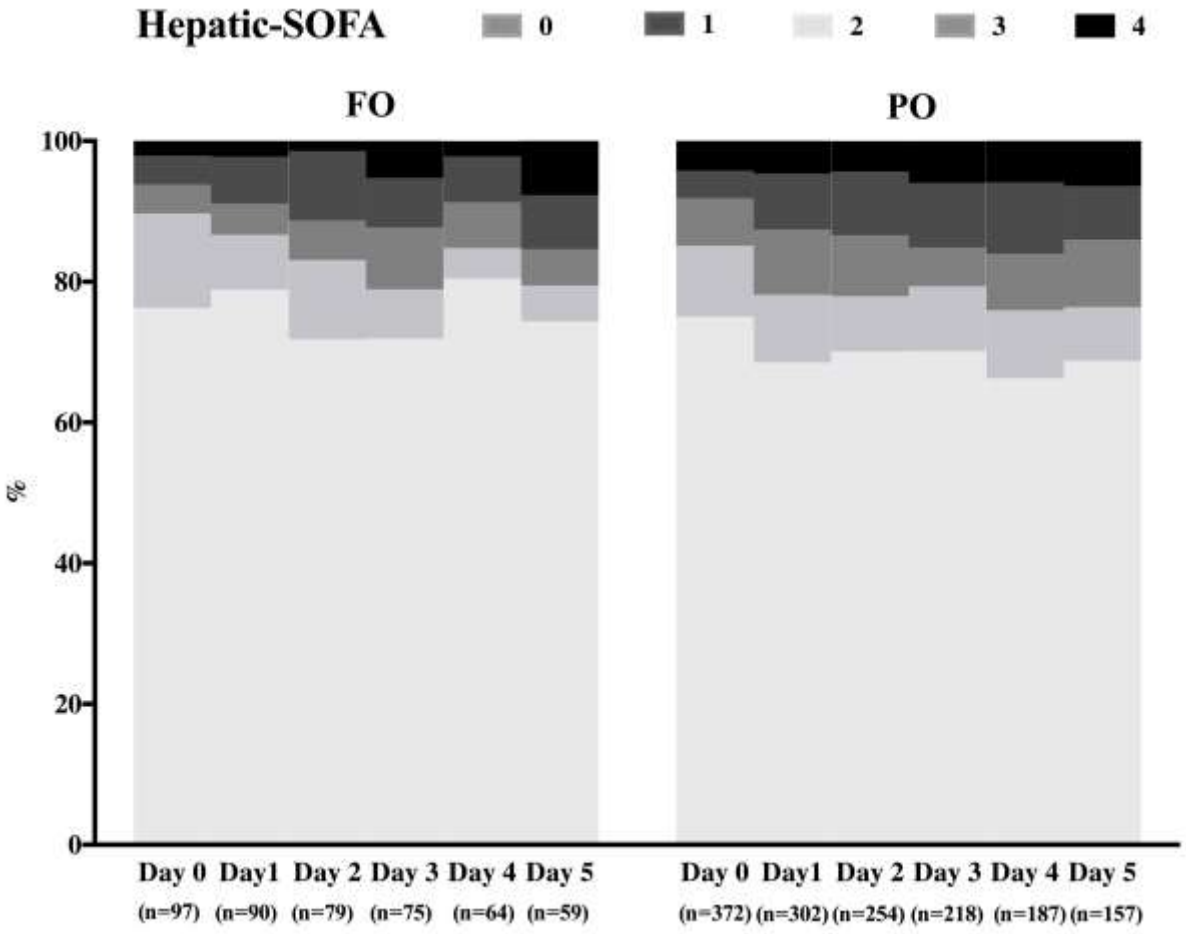
Supplemental Figure 4. Time-course of cardiovascular SOFA in patients with favorable (FO) and unfavorable (UO) neurological outcome.



Supplemental Figure 5. Time-course of respiratory SOFA in patients with favorable (FO) and unfavorable (UO) neurological outcome.



Supplemental Figure 6. Time-course of hepatic SOFA in patients with favorable (FO) and unfavorable (UO) neurological outcome.



Supplemental Figure 7. Time-course of hematologic SOFA in patients with favorable (FO) and unfavorable (UO) neurological outcome.