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ORIGINAL

Comparison of European ICU patients in 2012 (ICON) versus 2002 (SOAP)

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Abstract

Purpose: To evaluate differences in the characteristics and outcomes of intensive care unit (ICU) patients over time.

Methods: We reviewed all epidemiological data, including comorbidities, types and severity of organ failure, interventions, lengths of stay and outcome, for patients from the Sepsis Occurrence in Acutely ill Patients (SOAP) study, an observational study conducted in European intensive care units in 2002, and the Intensive Care Over Nations (ICON) audit, a survey of intensive care unit patients conducted in 2012.

Results: We compared the 3147 patients from the SOAP study with the 4852 patients from the ICON audit admitted to intensive care units in the same countries as those in the SOAP study. The ICON patients were older (62.5 ± 17.0 vs. 60.6 ± 17.4 years) and had higher severity scores than the SOAP patients. The proportion of patients with sepsis at any time during the intensive care unit stay was slightly higher in the ICON study (31.9 vs. 29.6%, $p = 0.03$). In multilevel analysis, the adjusted odds of ICU mortality were significantly lower for ICON patients than for SOAP patients, particularly in patients with sepsis [OR 0.45 (0.35–0.59), $p < 0.001$].

Conclusions: Over the 10-year period between 2002 and 2012, the proportion of patients with sepsis admitted to European ICUs remained relatively stable, but the severity of disease increased. In multilevel analysis, the odds of ICU mortality were lower in our 2012 cohort compared to our 2002 cohort, particularly in patients with sepsis.

Keywords: Epidemiology, Severity of disease, Sepsis

Introduction

Intensive care medicine is a relatively new specialty, but one that has evolved considerably over its short existence. Over the last 15 years or so, improved understanding of underlying disease pathogenesis and the role of "iatrogenic" complications has led to key changes in management and process of care in intensive care unit (ICU) patients, including use of lower tidal volume ventilation, more restrictive blood transfusion practice, and less sedation, which may have helped reduce mortality rates. Conversely, the aging world population with increased comorbidity, increased use of chemotherapy and immunosuppression, and medical advances that enable an increasing number of chronically ill patients to survive into old age, may favor admission of a sicker cohort of patients to the ICU and thus result in increased mortality rates.

Sepsis remains a leading cause of death worldwide among critically ill patients [1]. Although several recent studies have reported a substantial increase in the number of cases of sepsis per year, with a decrease in mortality of these patients [1, 2], this may largely be a reporting phenomenon associated with more complete capture of less ill patients [3, 4].

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To assess the changing epidemiology of ICU patients, and of sepsis in particular, we compared two large multinational observational studies conducted on ICU patients exactly 10 years apart, the Sepsis Occurrence in Acutely ill Patients (SOAP) study conducted in 2002 [5] and the larger worldwide Intensive Care Over Nations (ICON) audit conducted in 2012 [6]. The data collected for the two studies were almost identical and analysis was conducted in the same center, facilitating comparisons and reducing the risk of bias. We hypothesized that patients in the current ICON era would be sicker but have lower mortality rates than patients in the SOAP study.

Take-home message

This comparison of two databases created 10 years apart shows that ICU populations in Europe have changed over time. ICU patient are now slightly older and more severely ill. The number of patients with shock has increased as has the use of renal replacement therapies, whereas the proportion of patients receiving mechanical ventilation has decreased. ICU length of stay has remained unchanged and ICU mortality rates may have decreased.

Methods

The SOAP study was conducted in 24 European countries and included 3147 patients [5]. The ICON audit included 10,069 patients from 82 countries worldwide [6]. For the purposes of this comparison, we considered only the patients from ICON who were admitted to the same 24 European countries as in the SOAP study (e-Table 1, e-Appendix). For both studies, recruitment for participation was by open invitation, through national scientific societies, national and international meetings, and individual contacts. Participation was entirely voluntary, with no financial incentive. Institutional review board approval for both studies was obtained by the participating institutions according to local ethical regulations.

Participating ICUs (see e-Appendix) were asked to prospectively collect data on all adult patients admitted between May 1 and 15, 2002 for the SOAP study and between May 8 and 18, 2012 for the ICON audit. In both studies, patients who stayed in the ICU for < 24 h for routine postoperative surveillance were not considered. Re-admissions of previously included patients were also not included. Data were collected daily during the ICU stay for a maximum of 28 days. Patients were followed up for outcome data until death, hospital discharge or for 60 days.

Data were collected by the investigators using preprinted (for SOAP) and electronic (for ICON) case report forms. Data collection on admission included demographic data and comorbid diseases as well as source and reason for admission. Clinical and laboratory data for SAPS II [7] scores were reported as the worst values within 24 h after admission. The presence of microbiologically confirmed and clinically suspected infections was reported daily as were the antibiotics administered. A daily evaluation of organ function was performed using the sequential organ failure assessment (SOFA) score [8].

Definitions

Sepsis was defined as the presence of infection with the concomitant occurrence of at least one organ failure (defined as a SOFA score > 2 for the organ in question) in ICON, equivalent to the definition of "severe sepsis" used in SOAP. For the purposes of this comparison, we used this ICON definition of sepsis, recently supported by international consensus [9].

Data management and quality control

Detailed instructions explaining the aim of the study, instructions for data collection, and definitions were available through a secured website for all participants before starting data collection and throughout the study period. Additional queries were answered on a per case basis by the coordinating center during data collection. Data were further reviewed by the coordinating center for plausibility and availability of the outcome parameter, and any doubts were clarified with the center in question. There was no on-site monitoring. Missing data represented < 6% of the data collected for SOAP and 6.1% of the ICON data.

Statistical analysis

All data were processed and analyzed in the Department of Intensive Care of Erasme Hospital, University of Brussels, in collaboration with Jena University Hospital, Jena, Germany. Data were analyzed using IBM® SPSS® Statistics software, v.24 for Windows (IBM, Somers, NY, USA).

Data are summarized using means with standard deviation, medians and interquartile ranges, or numbers and percentages. Difference testing between groups was performed using Student's *t* test, Mann–Whitney test, Chi square test or Fisher's exact test, as appropriate. The Kolmogorov–Smirnov test was used, and histograms and quantile–quantile plots were examined to verify whether there were significant deviations from the normality assumption of continuous variables.

To identify the effect of being in the SOAP or ICON study on ICU mortality, and because of the hierarchical structure of the data, we performed a multivariable analysis using a multilevel binary logistic model with three levels: patient (level 1), admitted to a hospital (level 2), within a country (level 3). The dependent variable was ICU mortality. The explanatory variables considered in

the model were age, sex, SAPS II score without age component, type of admission, source of admission, treatment with mechanical ventilation or renal replacement therapy (RRT), presence of sepsis, comorbidities and the study to which the patient belonged, i.e., SOAP or ICON.

For parameter testing, the likelihood-ratio test was used. Colinearity between variables was checked by inspection of the correlation between them, looking at the correlation matrix of the estimated parameters. The interaction between explanatory variables was also tested. Three models were constructed: the first model, an unconditional model with no exposure factors, was used to discern the amount of variance that existed between hospital and country levels; the second model (the unadjusted model) contained the study to which the patient belonged, presence of sepsis and their interaction; and the third model (the adjusted model) was extended to include the other patient characteristics. The results of the fixed effects (measures of association) are given as odds ratios (ORs) with their 95% CIs. A second order penalized quasi-likelihood (PQL) estimation method was used, because this method approximates well compared to other methods [10]. The statistical significance of covariates was calculated using the Wald test. No statistical adjustments were used for multiple testing. All reported p values are two-sided and a p value of less than 0.05 was considered to indicate statistical significance.

Results

We compared the 3147 patients from the SOAP study with the 4852 patients from the ICON audit who were admitted to ICUs in the same countries as the patients in the SOAP study. The number of centers and number of patients in each country is shown in e-Table 1, the main differences being that a smaller proportion of patients were included from Belgium and France in ICON than in SOAP and a larger proportion from the UK and Spain.

The characteristics of the two patient populations are shown in Tables 1 and 2. ICON patients were older (62.5 ± 17.0 vs. 60.6 ± 17.4 years, $p < 0.001$) than SOAP patients and more likely to have co-morbid chronic obstructive pulmonary disease (COPD) and insulin-dependent diabetes mellitus. They were more likely to be receiving chemotherapy on admission and less likely to be receiving corticosteroids. ICON patients were more likely to have circulatory shock, respiratory failure and/or liver failure on admission than SOAP patients. They had higher SAPS II scores (41.9 ± 18.2 vs. 36.5 + 17.1) on admission, higher SOFA scores on admission (6.3 ± 4.3 vs. 5.1 ± 3.8) and higher max SOFA scores during the ICU stay (7.8 ± 4.8 vs. 6.6 ± 4.4) than the SOAP patients (all $p < 0.001$).

ICON patients were less likely to receive invasive mechanical ventilation during their ICU stay (59.3 vs. 64.3%, $p < 0.001$) but more likely to be treated with renal replacement therapy (RRT; 12.7 vs. 9.7%, $p < 0.001$). There was a small increase in the proportion of patients with sepsis at any time during the ICU stay between the two studies (29.6% in SOAP vs. 31.9% in ICON, $p = 0.03$). Gram-negative pathogens were more frequently isolated (66.3 vs. 60.2%, $p = 0.01$) and fungi less frequently isolated (14.8 vs. 20.7%, $p < 0.001$) in infected ICON patients than in infected SOAP patients (e-Table 2).

The ICU lengths of stay were not significantly different in the two studies, but the overall ICU mortality rate was slightly lower in ICON than in SOAP (16.8 vs. 18.5%, $p = 0.05$). Hospital (24.1% in SOAP vs. 23.9 in ICON, $p = 0.83$) and 60-day (23.4% in SOAP vs. 23.7 in ICON, $p = 0.75$) mortality rates were not different between the studies. The improvement in ICU survival was particularly notable in patients with sepsis, shock or liver failure on admission or during the ICU stay, and those with renal failure during the ICU admission (Table 2). ICU mortality rates were significantly lower in ICON for all degrees of organ failure on admission (Fig. 1) and for all numbers of failing organs during the ICU admission (Table 2). Similar patterns in ICU mortality rates were identified in patients with and without sepsis (e-Tables 3 and 4, e-Figure 1).

In multilevel analysis, the adjusted odds of ICU mortality were significantly lower for ICON patients than for SOAP patients, both with and without sepsis (Table 3). Interestingly, the reduced odds were greater for patients with sepsis than for those without in both non-adjusted ($p = 0.016$) and adjusted ($p = 0.006$) analyses. The unconditional model indicated significant between-country (var 0.21, $p = 0.015$) and between-hospital (var 0.23, $p < 0.001$) variations in the individual risk of in-ICU death (Table 3). After controlling for patient factors, the differences across hospitals remained statistically significant (var 0.29, $p < 0.0001$); in contrast, the differences across countries disappeared after adjustment (var 0.06, $p = 0.23$).

Discussion

This comparison of two databases created 10 years apart shows some important epidemiological differences in ICU populations in Europe over time. The number of patients with shock has increased as has the use of renal replacement therapies, whereas the proportion of patients receiving mechanical ventilation has decreased. Although ICU patient populations are slightly older and more severely ill, ICU survival rates have improved even after adjustment for multiple potential confounders.

The proportion of patients receiving invasive mechanical ventilation decreased over the 10-year period. Indeed, although the proportion of patients with respiratory failure at ICU admission was greater in ICON than in SOAP,

Table 1 Characteristics of the two cohorts of patients

	SOAP (2002), *n* = 3147	ICON (2012), *n* = 4852	*p* value
Age, years, mean ± SD	60.6 ± 17.4	62.5 ± 17.0	< 0.001
Male, *n* (%)	1920 (61.7)	2924 (61.0)	0.53
Severity scores, mean ± SD			
SAPS II score	36.5 ± 17.1	41.9 ± 18.2	< 0.001
SAPS II score without age	26.0 ± 16.1	30.8 ± 17.0	< 0.001
SOFA score at admission	5.1 ± 3.8	6.3 ± 4.3	< 0.001
Max SOFA score	6.6 ± 4.4	7.8 ± 4.8	< 0.001
Type of admission, *n* (%)			< 0.001
Surgical	1388 (44.1)	2075 (45.4)	
Elective	778 (24.7)	776 (17.0)	
Emergency	610 (19.4)	1076 (23.6)	
Medical	1759 (55.9)	2459 (53.9)	
Other	0 (0.0)	30 (0.7)	
Source of admission, *n* (%)			
Other hospital	345 (11.0)	446 (9.2)	< 0.001
ER/ambulance	913 (29.0)	1758 (36.2)	
OR/recovery room	784 (24.9)	910 (18.8)	
Hospital floor	793 (25.2)	1378 (28.4)	
Other	312 (9.9)	360 (7.4)	
Comorbidities, *n* (%)			
COPD	340 (10.8)	743 (15.3)	< 0.001
Cancer	415 (13.2)	568 (11.7)	0.05
Metastatic cancer	105 (3.3)	160 (3.3)	1.00
Hematologic cancer	69 (2.2)	122 (2.5)	0.37
Insulin-dependent diabetes	226 (7.2)	451 (9.3)	0.001
Heart failure, NYHA III/IV	307 (9.8)	493 (10.2)	0.57
HIV/AIDS	26 (0.9)	24 (0.5)	0.08
Cirrhosis	121 (3.8)	205 (4.2)	0.42
Steroid therapy	165 (5.2)	201 (4.1)	0.03
Chemotherapy	25 (0.8)	121 (2.5)	< 0.001
Procedures/events on admission, *n* (%)			
Mechanical ventilation	1850 (58.8)	2572 (53.0)	< 0.001
RRT	115 (3.7)	242 (5.0)	< 0.01
Sepsis	552 (17.5)	894 (18.4)	0.31
Procedures/events during the ICU stay, *n* (%)			
Central venous catheter	2272 (72.2)	3143 (64.8)	< 0.001
Pulmonary artery catheter	481 (15.3)	729 (15.0)	0.751
Mechanical ventilation	2025 (64.3)	2875 (59.3)	< 0.001
RRT	306 (9.7)	615 (12.7)	< 0.001
Sepsis	930 (29.6)	1546 (31.9)	0.03
Outcomes			
ICU stay, median (IQR)	3.0 (1.7–6.9)	3.0 (2.0–7.0)	0.31
Survivors	3.0 (1.8–6.6)	3.0 (2.0–6.0)	0.57
Non-survivors	3.3 (1.2–9.8)	3.0 (1.0–9.0)	0.20
ICU mortality, *n* (%)	583 (18.5)	796 (16.8)	0.05

Percentages were calculated after exclusion of missing values

RRT renal replacement therapy, *ICU* intensive care unit, *SAPS* simplified acute physiology score, *SOFA* sequential organ failure assessment, *ER* emergency room, *OR* operating room, *COPD* chronic obstructive pulmonary disease, *HIV* human immunodeficiency virus, *AIDS* acquired immunodeficiency syndrome

Table 2 Incidence and ICU mortality in the two cohorts according to the numbers and types of organ failures

	Incidence, *n* (%)			ICU mortality, *n* (%)		
	SOAP (2002)	ICON (2012)	*p* value (if < 0.05)	SOAP (2002)	ICON (2012)	*p* value (if < 0.05)
Sepsis on admission	552 (17.5)	894 (18.4)		185 (33.5)	227 (25.6)	0.001
Type of organ failure[a] on admission, *n* (%) (alone or in combination)						
Cardiovascular	776 (24.7)	1557 (32.1)	< 0.001	278 (35.8)	428 (27.9)	< 0.001
Respiratory	696 (22.1)	1194 (24.6)	0.010	207 (29.7)	360 (30.5)	
CNS	683 (21.7)	1094 (22.5)		255 (37.3)	395 (37.1)	
Renal	575 (18.3)	898 (18.5)		173 (30.1)	300 (33.8)	
Coagulation	149 (4.7)	196 (4.0)		60 (40.3)	69 (36.1)	
Hepatic	85 (2.7)	440 (9.1)	< 0.001	29 (34.1)	79 (18.4)	0.001
No of organ failures[a] on admission, *n* (%)						
None	1338 (42.5)	1834 (37.8)	< 0.001	84 (6.3)	78 (6.0)	
1 organ	979 (31.1)	1476 (30.4)	< 0.001	180 (18.4)	122 (11.3)	< 0.001
2 organs	564 (17.9)	915 (18.9)	< 0.001	175 (31.0)	199 (25.8)	0.036
3 organs	215 (6.8)	458 (9.4)	< 0.001	111 (51.6)	166 (42.6)	0.033
4 + organs	51 (1.6)	169 (3.5)	< 0.001	33 (64.7)	87 (62.4)	
Sepsis during the ICU stay	930 (29.6)	1546 (31.9)	0.029	299 (32.2)	386 (25.1)	< 0.001
Type of organ failure[a] during the ICU stay, *n* (%) (alone or in combination)						
Cardiovascular	1052 (33.4)	1978 (40.8)	< 0.001	403 (38.3)	571 (29.3)	< 0.001
Respiratory	1301 (41.3)	1778 (36.6)	< 0.001	393 (30.2)	548 (31.3)	
CNS	839 (26.7)	1374 (28.3)		347 (41.4)	529 (39.4)	
Renal	1120 (35.6)	2280 (47.0)	< 0.001	338 (30.2)	559 (24.8)	< 0.001
Coagulation	309 (9.8)	451 (9.3)		141 (45.6)	178 (40.0)	
Hepatic	168 (5.3)	944 (19.5)	< 0.001	65 (38.9)	185 (19.9)	< 0.001
No of organ failures[a] during the ICU stay, *n* (%)						
None	903 (28.7)	1120 (23.1)	< 0.001	17 (1.9)	35 (3.8)	0.017
1 organ	994 (31.6)	1257 (25.9)	< 0.001	71 (7.1)	32 (4.0)	0.004
2 organs	717 (22.8)	955 (19.7)	< 0.001	195 (27.2)	90 (13.0)	< 0.001
3 organs	368 (11.7)	744 (15.3)	< 0.001	178 (48.5)	191 (30.4)	< 0.001
4 + organs	165 (5.2)	776 (16.0)	< 0.001	122 (73.9)	304 (47.2)	< 0.001

Percentages were calculated after exclusion of missing values

[a] As defined by a SOFA score > 2 for the organ in question

the proportion during the ICU stay was lower. Moreover, we can speculate that more patients with respiratory failure are now managed using non-invasive mechanical ventilation [11] and/or high-flow nasal cannula oxygen [12]. We chose not to record data on non-invasive ventilation as it is difficult to evaluate over 24-h periods. It is also possible that mechanical ventilation was more frequently withheld in the ICON cohort; however, the decreased mortality rate in a sicker cohort of patients argues against this possibility. In contrast to the reduced use of mechanical ventilation, there was an increased use of RRT in the ICON population, as expected with the larger proportion of patients with renal failure during the ICU stay. Sakhuja et al. also recently reported an increased incidence of acute kidney injury requiring dialysis in patients with sepsis between 2000 and 2009 [13].

A number of studies have reported that the incidence of sepsis has increased dramatically over time. However, as suggested by Rhee et al. [14], this may be largely a reporting phenomenon associated with financial reimbursement or increasing awareness of and familiarity with sepsis-related definitions and coding among medical staff [15–17]. Using clinical data alone, these same authors recently reported no increase in sepsis incidence between 2009 and 2014 in almost 8,000,000 admissions to US hospitals, although again incidence increased when sepsis was defined using ICD codes [18]. Our study also suggests that the rate of sepsis (as defined using the criteria of infection associated with organ dysfunction as in the most recent guidelines [9]) has remained relatively stable over the 10-year period. Martin et al. reported an increase in the severity of illness of patients with sepsis across US hospitals over a 22-year

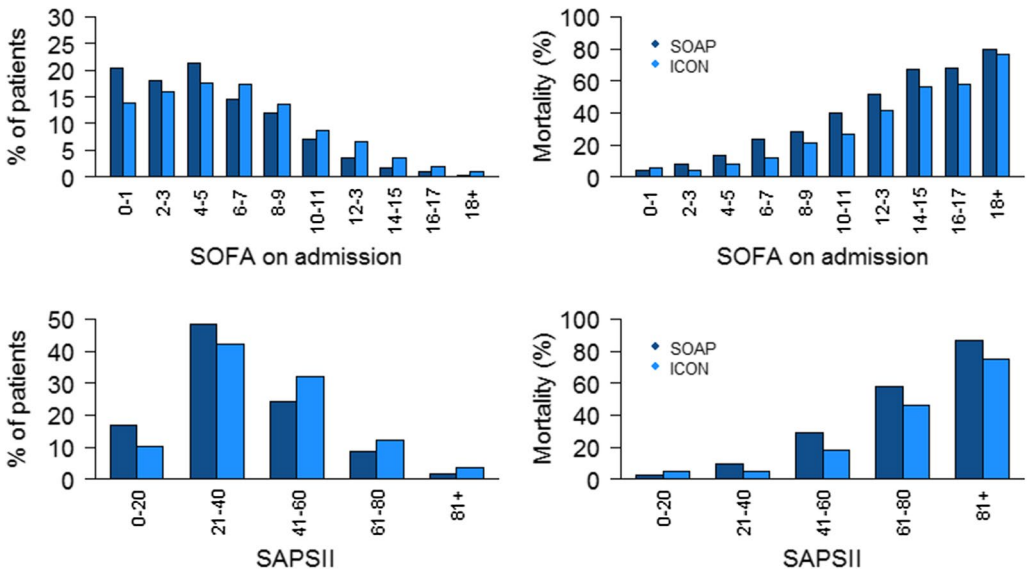

Fig. 1 Percentage of patients (left panel) and ICU mortality rates (right panel) in ICON (2012) and SOAP (2002) studies according to sequential organ failure assessment (SOFA) scores on admission (upper panel) and Simplified Acute Physiology Score (SAPS) II (lower panel)

period, but a decrease in hospital mortality from 27.8% in 1979–1984 to 17.9% in 1995–2000 [19]. Also in the US, Kumar et al. reported increasing severity of illness, as assessed by the mean number of organ system failures during the ICU stay, during the period 2000–2007, but decreasing mortality rates from 39 to 27% [20]. And Stoller et al. made similar findings during the period 2008–2012 [21]. In Spain, Bouza et al. reported a decrease in case fatality rates from 45 to 40% between 2006 and 2011, despite increasing disease severity [22], and Kaukonen et al. [2] reported a decrease in mortality from 2000 to 2012 for patients with severe sepsis that persisted when adjusted for severity of illness. The decrease in mortality over time, particularly among patients with sepsis, parallel to the increase in disease severity, is an interesting phenomenon that has been reported previously [19–22], and suggests that progress has been made in the field of intensive care medicine. Indeed, multiple aspects of ICU patient management have changed over the last decade or so, including, among others, more widespread use of lower tidal volume ventilation [23], more restrictive blood transfusion practice [24], reduced sedative use [25] and earlier mobilization, and more rapid appropriate intervention in patients with sepsis [26], some of which have been associated with improved outcomes. Of note, in-hospital and 60-day mortality rates were not significantly different in our two cohorts. Our data do not enable us to determine the reasons for this observation, although it is interesting to speculate that ICU management may have improved more than post-ICU care.

The strengths of our study are the comparison of two large multicenter registries conducted 10 years apart in the same month of the year, and which prospectively included almost identical variables, analyzed in the same center. But our study also has important limitations. First, although data collection was prospective, our study was observational in nature and the analysis retrospective; we therefore cannot discount that unmeasured factors may have confounded our results. Moreover, because of multiple comparisons, an inflated type 1 error may be possible. In addition, although we clearly demonstrate improved survival of critically ill patients over time, notwithstanding the increased severity of illness, we can only speculate on the mechanism of these improved outcomes. Indeed, the observed increased severity of illness may in part be related to changes in ICU admitting practices or in improved capabilities to care for patients in non-ICU settings. These are important areas of future research. Second, we do not have any information about end-of-life decisions or on outcomes after 60 days. We are also unable to comment on differences in the quality of life of the survivors. Return to reasonable physical, mental and cognitive functionality is an important aspect of patient-centered outcomes. Third, although we included centers from the same countries, we were unable to perform a center-by-center comparison. Over time, hospital names and networks have changed, making a direct comparison impractical. Moreover, we had no data to assess how representative the participating hospitals were of their country. Finally, the SOAP study included patients over a longer period of time (15 days) than the ICON study (11 days). However, this is unlikely to have influenced the results.

Despite these limitations, the present observations show that ICU patients were sicker in our 2012 cohort than in our 2002 cohort. Multilevel analysis showed that survival was improved in the later cohort, especially for

Table 3 Summary of multilevel analysis with ICU mortality as the dependent variable

Variables	Model 1 OR (95% CI)	Model 2 OR (95% CI)	*p* value	Model 3 OR (95% CI)	*p* value
Fixed-effects, varying within clusters					
Age	–	–		1.02 (1.02–1.03)	< 0.001
Sex, male	–	–		0.92 (0.85–1.00)	0.037
SAPSII[a]	–	–		1.06 (1.06–1.07)	< 0.001
Type of admission (%)					
Surgical	–	–			
Medical	–	–		1.49 (1.22–1.82)	< 0.001
Other	–	–		1.81 (1.09–2.98)	0.021
Source of admission					
OR/recovery	–	–			
Other hospital	–	–		1.17 (0.88–1.57)	0.282
ER/ambulance	–	–		1.31 (1.13–1.53)	0.001
Hospital floor	–	–		1.47 (1.18–1.84)	0.001
Other	–	–		1.42 (0.98–2.06)	0.062
Comorbidities					
COPD	–	–		1.07 (0.90–1.28)	0.423
Cancer	–	–		1.25 (1.00–1.55)	0.050
Insulin-dependent diabetes	–	–		0.72 (0.57–0.92)	0.008
Heart failure, NYHA III/IV	–	–		1.22 (1.00–1.49)	0.053
HIV infection				1.38 (0.78–2.44)	0.271
Cirrhosis				2.15 (1.70–2.71)	<0.001
Procedures					
Mechanical ventilation	–	–		3.57 (2.57–4.95)	< 0.001
Renal replacement therapy	–	–		1.86 (1.51–2.30)	< 0.001
Study (ICON vs. SOAP)					
Non-sepsis		0.95 (0.77–1.17)	0.611	0.64 (0.53–0.77)	< 0.001
Sepsis		0.70 (0.54–0.91)	0.009	0.45 (0.35–0.59)	< 0.001
Random-effects					
Country					
Variance (SE)	0.21 (0.09)	0.14 (0.07)		0.06 (0.05)	
p value	0.015	0.033		0.229	
Centers					
Variance	0.23 (0.05)	0.23 (0.05)		0.29 (0.07)	
p value	< 0.001	< 0.001		< 0.001	

The interaction between sepsis/non-sepsis and SOAP/ICON is significant

[a] Without age component

patients with sepsis. These results are encouraging and suggest that progress has been made in the field of intensive care medicine over just a 10-year period.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-017-5043-2) contains supplementary material, which is available to authorized users.

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Author contributions
JLV designed the study, analyzed the data and drafted the article; YS participated in the original ICON and SOAP studies, helped analyze the data and draft the article; JYL, KK, RN, IML, XW, SGS, and PP participated in the original ICON study and revised the article for critical content; RM participated in the original SOAP study and revised the article for critical content. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflicts of interest
The authors have no conflicts of interest to declare.

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e-Appendix

Alphabetical list of SOAP participating centers by country

Austria: University Hospital of Vienna (G. Delle Karth); LKH Steyr (V. Draxler); LKH-Deutschlandsberg (G. Filzwieser); Otto Wagner Spital of Vienna (W. Heindl); Krems of Donau (G. Kellner, T. Bauer); Barmherzige Bruede of Linz (K. Lenz); KH Floridsdorf of Vienna (E. Rossmann); University Hospital of Innsbruck (C. Wiedermann)
Belgium: CHU of Charleroi (P. Biston); Hôpitaux Iris Sud of Brussels (D. Chochrad); Clinique Europe Site St Michel of Brussels (V. Collin); C.H.U. of Liège (P. Damas); University Hospital Ghent (J. Decruyenaere, E. Hoste); CHU Brugmann of Brussels (J. Devriendt); Centre Hospitalier Jolimont-Lobbes of Haine St Paul (B. Espeel); CHR Citadelle of Liege (V. Fraipont); UCL Mont-Godinne of Yvoir (E. Installe); ACZA Campus Stuivenberg (M. Malbrain); OLV Ziekenhuis Aalst (G. Nollet); RHMS Ath-Baudour-Tournai (J.C. Preiser); AZ St Augustinus of Wilrijk (J. Raemaekers); CHU Saint-Pierre of Brussels (A. Roman); Cliniques du Sud-Luxembourg of Arlon (M. Simon); Academic Hospital Vrije Universiteit Brussels (H. Spapen); AZ Sint-Blasius of Dendermonde (W. Swinnen); Clinique Notre-Dame of Tournai (F. Vallot); Erasme University Hospital of Brussels (J.L. Vincent)
Czech Republic: University Hospital of Plzen (I. Chytra); U SV.Anny of Brno (L. Dadak); Klaudians of Mlada Boleslav (I. Herold); General Faculty Hospital of Prague (F. Polak); City Hospital of Ostrava (M. Sterba); *Denmark :* Gentofte Hospital, University of Copenhagen (M. Bestle); Rigshospitalet of Copenhagen (K. Espersen); Amager Hospital of Copenhagen (H. Guldager); Rigshospitalet, University of Copenhagen (K-L. Welling)
Finland: Aland Central Hospital of Mariehamn (D. Nyman); Kuopio University Hospital (E. Ruokonen); Seinajoki Central Hospital (K. Saarinen)
France: Raymond Poincare of Garches (D. Annane); Institut Gustave Roussy of Villejuif (P. Catogni); Jacques Monod of Le Havre (G. Colas); CH Victor Jousselin of Dreux (F. Coulomb); Hôpital St Joseph & St Luc of Lyon (R. Dorne); Saint Joseph of Paris (M. Garrouste); Hôpital Pasteur of Nice (C. Isetta); CHU Brabois of Vandoeuvre Les Nancy (J. Larché); Saint Louis of Paris (J-R. LeGall); CHU de Grenoble (H. Lessire); CHU Pontchaillou of Rennes (Y. Malledant); Hôpital des Hauts Clos of Troyes (P. Mateu); CHU of Amiens (M. Ossart); Hôpital Lariboisière of Paris (D. Payen); CHD Félix Gyuon of Saint Denis La Reunion (P. Schlossmacher); Hôpital Bichat of Paris (J-F. Timsit); Hôpital Saint Andre of Bordeaux (S. Winnock); Hôpital Victor Dupouy of Argentueil (J-P. Sollet); CH Auch (L. Mallet); CHU Nancy-Brabois of Vandoeuvre (P. Maurer); CH William Morey of Chalon (JM. Sab); Victor Dupouy of Argenteuil (JP. Sollet)
Germany: University Hospital Heidelberg (G. Aykut); Friedrich Schiller University Jena (F. Brunkhorst); University Clinic Hamburg-Eppendorf (A. Nierhaus); University Hospital Mainz (M. Lauterbach); University Hospital Carl Gustav Carus of Dresden (M. Ragaller); Hans Sushemihl Krankenhaus of Emden (R. Gatz); Vivantes-Klinikum Neukoelln of Berlin (H. Gerlach); University Hospital RWTH Aachen (D. Henzler); Kreisklinik Langen-Seligenstadt (H-B Hopf**);** GKH Bonn (H. Hueneburg); Zentralklinik Bad Berka (W. Karzai); Neuwerk of Moenchengladbach (A. Keller); Philipps University of Marburg (U. Kuhlmann); University Hospital Regensburg (J. Langgartner); ZKH Links der Weser of Bremen (C. Manhold); University Hospital of Dresden (M. Ragaller); Universtiy of Wuerzburg (B. Reith); Hannover Medical School (T. Schuerholz); Universitätsklinikum Charité Campus Mitte of Berlin (C. Spies); Bethanien Hospital of Moers (R. Stögbauer); KhgmbH Schongau (J. Unterburger)
Greece: Thriassio Hospital of Athens (P-M. Clouva-Molyvdas); Sismanoglion General Hospital of Athens (G. Giokas); KAT General Hospital of Athens (E. Ioannidou); G. Papanikolaou General Hospital of Thessaloniki (A. Lahana); Agios Demetrios of Thessaloniki (A. Liolios); Onassis Cardiac Surgery Center of Athens (K. Marathias); University Hospital of Ioannina (G. Nakos); Tzanio Hospital of Athens (A. Tasiou); Athens General Hospital Gennimatas (H. Tsangaris)
Hungary: Peterfy Hospital of Budapest (P. Tamasi)
Ireland: Mater Hospital of Dublin (B. Marsh); Beaumont Hospital of Dublin (M. Power)
Israel: Hadassah Hebrew University Medical Center (C. Sprung)
Italy: Azienda Ospedaliera Senese o Siena (B. Biagioli); S. Martino of Genova (F. Bobbio Pallavicini); Azienda Ospedaliera S. Gerardo dei Tintori of Monza (A. Pesenti); Osp Regionale of Saronno (C. Capra); Ospedale Maggiore - University A. Avogadro of Novara (F. Della Corte); Osp. Molinette of Torino (P. P. Donadio); A.O. Umberto I Ancona, Rianimazione Clinica (A. Donati); Azienda Ospedaliera Universitaria Policlinico of Palermo (A. Giarratano); San Giovanni Di Dio of Florence (T. Giorgio); H San Raffaele IRCCS of Milano (D. Giudici); Ospedale Di Busto Arsizio (S. Greco); Civile Di Massa (A. Guadagnucci); San Paolo of Milano (G. Lapichino); S.Giovanni Bosco Torino (S. Livigni); Osp. San Giovanni of Sesto (G. Moise); S Camillo of Roma (G. Nardi); Vittorio Emanuele of Catania (E. Panascia); Hospital of Piacenza (M. Pizzamiglio); Universita di Torino-Ospedale S. Giovanni Battista (V. M. Ranieri); Policlinico Le Scotte of Siena (R. Rosi); Ospedale Maggiore Policlinico IRCCS

of Milano (A. Sicignano); A. Uboldo of Cernusco Sul Naviglio (M. Solca); P.O. Civile Carrara of Massa (G. Vignali); San Giovanni of Roma (I. Volpe Rinonapoli)
Netherlands: Boven IJ Ziekenhuis of Amsterdam (M. Barnas); UMC St Radboud of Nijmegen (E.E. De Bel); Academic Medical Center of Amsterdam (A-C. De Pont); VUMC of Amsterdam (J. Groeneveld); Groningen University Hospital (M Nijsten); Waterlandziekenhuis of Purmerend (L Sie); OLVG of Amsterdam (D. F. Zandstra)
Norway: Sentralsjukehuset i Rogaland of Stavanger (S. Harboe); Sykehuset Østfold of Fredrikstad (S. Lindén); Aker University Hospital of Oslo (R. Z. Lovstad); Ulleval University Hospitalof Oslo (H. Moen); Akershus University Hospital of Nordbyhagen (N. Smith-Erichsen)
Poland: Paediatric University Hospital of Lodz (A. Piotrowski); Central Clinic Hospital SLAM of Katowice (E. Karpel)
Portugal : Garcia de Orta of Almada (E. Almeida); Hospital de St. António dos Capuchos of Lisboa (R. Moreno); Hospital de Santa Maria of Lisboa (A. Pais-De-Lacerda); Hospital S.Joao of Porto (J. A. Paiva); Fernado Fonseca of Masama (I. Serra); São Teotonio Viseu (A. Pimentel)
Romania: Inst of Cardiovascular Diseases of Bucharest (D. Filipescu)
Serbia: Military Medical Academy of Belgrade (K. Jovanovic)
Slovakia: SUSCH of Bratislava (P. Malik)
Slovenia: General Hospital of Novo Mesto (K. Lucka); General Hospital of Celje (G. Voga)
Spain: Hospital Universitario Rio Hortega of Valladolid (C. Aldecoa Alvarez-Santullano); Sabadell Hospital (A. Artigas); Hospital Clinic of Barcelona (E. Zavala, A. Escorsell, J. Nicolas); Virgen del Camino of Pamplona (J. J. Izura Cea); Virgen de la Salud of Toledo (L. Marina); 12 de Octubre of Madrid (J. Montejo); Gregorio Maranon of Madrid (E. Palencia); General Universitario de Elche (F. Santos); Puerta del Mar of Cadiz (R. Sierra-Camerino); Fundación Jiménez Díaz of Madrid (F. Sipmann); Hospital Clinic of Barcelona (E. Zavala)
Sweden: Central Hospital of Kristianstad (K. Brodersen); Stockholm Soder Hospital (J. Haggqvist); Sunderby Hospital of Luleå (D. Hermansson); Huddinge University Hospital of Stockholm (H. Hjelmqvist)
Switzerland: Kantonsspital Luzern (K. Heer); Hirslanden Klinik Beau-Site of Bern (G. Loderer); University Hospital of Zurich (M. Maggiorini); Hôpital de la ville of La Chaux-de-Fonds (H. Zender)
United Kingdom: Edinburgh Western General Hospital (P. Andrews); Peterborough Hospitals NHS Trust of Peterborough (B. Appadu); University Hospital Lewisham, London (C. Barrera Groba); Bristol Royal Infirmary (J. Bewley); Queen Elizabeth Hospital Kings Lynn (K. Burchett); Milton Keynes General (P. Chambers); Homerton University Hospital of London (J. Coakley); Charing Cross Hospital of London (D. Doberenz); North Staffordshire Hospital of Stoke On Trent (N. Eastwood); Antrim Area Hospital (A. Ferguson); Royal Berkshire Hospital of Reading (J. Fielden); The James Cook University Hospital of Middlesbrough (J. Gedney); Addenbrookes of Cambridge (K. Gunning); Rotherham DGH (D. Harling); St.Helier of Carshalton (S. Jankowski); Southport & Formby (D. Jayson); Freeman of Newcastle Upon Tyne (A. Kilner); University Hospital of North Tees at Stockton on Tees (V. Krishna-Kumar); St. Thomas Hospital of London (K. Lei); Royal Infirmary of Edinburgh (S. Mackenzie); Derriford of Plymouth (P. Macnaughton); Royal Liverpool University Hospital (G. Marx); Stirling Royal Infirmary (C. McCulloch); University Hospital of Wales, Cardiff (P. Morgan); St George's Hospital of London (A. Rhodes); Gloucestershire Royal Hospital (C. Roberts); St Peters of Chertsey (M. Russell); James Paget Hospital of Great Yarmouth (D. Tupper-Carey, M. Wright); Kettering General Hospital (L. Twohey); Burnley DGH (J. Watts); Northampton General Hospital (R. Webster); Dumfries Royal Infirmary (D. Williams)

Alphabetical list of ICON participating centers by region and country (for the same countries as were included in SOAP)

East Europe

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)
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)
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); "Luliu Hatieganu" University of Medicine and Pharmacy, Teaching Hospital of Infectious Diseases, Cluj-Napoca (A Slavcovici)
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)

Middle East
Israel: Rabin Medical Centre (J Cohen); Sourasky Tel Aviv Medical Centre (O Sold)

West Europe
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 (JY 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)
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)
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 (B Quindos); Hospital Universitario De Alava, Santiago (A Quintano); Hospital Universitario De Basurto, Bilbao (M Tebar); Hospital Universitario de Getafe (P Cardinal); 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 (I Welters); 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)

e-Table 1. Numbers of patients in participating countries in SOAP and ICON

Country	SOAP			ICON			Total	
	N. patients	**N. centers**	**ICU mortality (%)**	**N. patients**	**N. centers**	**ICU mortality (%)**	**N. patients**	**N. centers**
Belgium	703	19	12.2	487	27	14.2	1190	46
UK	424	32	26.2	758	47	17.3	1182	79
France	332	21	19.0	355	27	22.3	687	48
Germany	329	21	11.9	757	39	12.4	1086	60
Italy	237	24	25.7	301	33	21.0	538	57
Spain	202	13	21.9	646	53	11.3	848	66
Netherlands	144	7	22.9	222	13	14.5	366	20
Switzerland	114	4	7.9	151	6	6.0	265	10
Greece	109	10	16.5	45	12	36.4	154	22
Portugal	69	6	34.8	193	23	24.1	262	29
Austria	68	8	20.6	62	10	10.0	130	18
Sweden	68	4	10.3	37	2	8.1	105	6
Norway	61	5	21.3	29	2	24.1	90	7
Finland	51	3	11.8	33	2	6.1	84	5
Slovenia	46	2	17.4	79	7	14.1	125	9
Czech Republic	45	5	20.0	108	12	18.9	153	17
Romania	44	2	25.0	189	10	39.2	233	12
Ireland	33	2	33.3	75	7	17.6	108	9
Denmark	29	4	10.3	49	3	10.2	78	7
Poland	13	2	61.5	55	10	35.8	68	12
Israel	13	1	15.4	23	2	30.4	36	3
Hungary	8	1	25.0	55	5	32.1	63	6
Slovakia	3	1	33.3	17	4	17.6	20	5
Serbia	2	1	0.0	126	9	11.9	128	10
Total	**3147**	**198**	**18.5**	**4852**	**365**	**16.8**	**7999**	**563**

e-Table 2. Types of microorganisms (%) in patients with positive microbiological cultures

	SOAP n=581	ICON n=1097	p value
Gram-positive	343 (59.0)	610 (55.6)	0.18
Gram-negative	350 (60.2)	727 (66.3)	0.01
Anaerobes	28 (4.8)	55 (5.0)	0.86
Other bacteria	5 (0.9)	6 (0.5)	0.34
Fungi	157 (27.0)	162 (14.8)	<0.001
Viruses and parasites	11 (1.9)	45 (4.1)	0.02

e-Table 3. Incidence and ICU mortality in the sepsis patients from the two cohorts according to the numbers and types of organ failures

Sepsis	Incidence, n (%)		ICU mortality, n (%)	
	SOAP (n= 930)	ICON (n=1546)	SOAP	ICON
Type of organ failure on admission, n (%) (alone or in combination)				
Cardiovascular	420 (45.2)	834 (53.9)‡	169 (40.2)	235 (28.4)‡
Respiratory	330 (35.5)	638 (41.3)†	122 (37.0)	200 (31.5)
CNS	287 (30.9)	517 (33.4)	103 (35.9)	165 (32.2)
Renal	260 (28.0)	389 (25.2)	94 (36.2)	140 (36.1)
Coagulation	86 (9.2)	106 (6.9)*	43 (50.0)	41 (39.4)
Hepatic	52 (5.6)	215 (13.9)‡	22 (42.3)	46 (21.4)†
No. of organ failures on admission, n (%)				
None	137 (14.7)	156 (10.1)‡	37 (27.2)	35 (22.6)
1 organ	348 (37.4)	562 (36.4)	84 (24.1)	88 (15.7)†
2 organs	291 (31.3)	456 (29.5)	94 (32.3)	111 (24.5)*
3 organs	117 (12.6)	278 (18.0)‡	60 (51.3)	100 (36.2)†
4+ organs	37 (4.0)	94 (6.1)*	24 (64.9)	52 (55.9)
Type of organ failure during the ICU stay, n (%) (alone or in combination)				
Cardiovascular	582 (62.6)	1105 (71.5)‡	246 (42.3)	336 (30.7)‡
Respiratory	708 (76.1)	1015 (65.7)‡	244 (34.5)	325 (32.3)
CNS	385 (41.4)	705 (45.6)*	169 (44.0)	257 (36.8)*
Renal	476 (51.2)	938 (60.7)‡	196 (41.2)	300 (32.1)‡
Coagulation	187 (20.1)	284 (18.4)	99 (52.9)	124 (44.1)
Hepatic	113 (12.2)	499 (32.3)‡	51 (45.5)	127 (25.5)‡
No. of organ failures during the ICU stay, n(%)				
1 organ	235 (25.3)	238 (15.4)‡	17 (7.2)	8 (3.4)
2 organs	356 (38.3)	384 (24.8)‡	95 (26.7)	37 (9.7)‡
3 organs	219 (23.5)	403 (26.1)	100 (45.9)	109 (27.0)‡
4+ organs	120 (12.9)	521 (33.7)‡	87 (72.5)	232 (45.0)‡

Statistically significant vs SOAP: ‡ <0.001; † <0.01 and * <0.05.

e-Table 4. Incidence and ICU mortality in the non-sepsis patients from the two cohorts according to the numbers and types of organ failures

Non sepsis	Incidence, n (%)		ICU mortality, n (%)	
	SOAP (n=2217)	ICON (n=3306)	SOAP	ICON
Type of organ failure on admission, n(%) (alone or in combination)				
Cardiovascular	356 (16.1)	723 (21.9)‡	109 (30.6)	193 (27.3)
Respiratory	366 (16.5)	556 (16.8)	85 (23.2)	160 (29.4)*
CNS	396 (17.9)	577 (17.5)	152 (38.4)	230 (41.5)
Renal	315 (14.2)	509 (15.4)	79 (25.1)	160 (32.1)*
Coagulation	63 (2.8)	90 (2.7)	17 (27.0)	28 (32.2)
Hepatic	33 (1.5)	225 (6.8)‡	7 (21.2)	33 (15.4)
No. of organ failures on admission, n(%)				
None	1201 (54.2)	1678 (50.8)*	47 (3.9)	70 (4.4)
1 organ	631 (28.5)	914 (27.6)	96 (15.2)	76 (8.5)‡
2 organs	273 (12.3)	459 (13.9)	81 (29.7)	121 (27.1)
3 organs	98 (4.4)	180 (5.4)	51 (52.0)	92 (52.6)
4+ organs	14 (0.6)	75 (2.3)‡	9 (64.3)	51 (70.8)
Type of organ failure during the ICU stay, n (%) (alone or in combination)				
Cardiovascular	470 (21.2)	873 (26.4)‡	157 (33.4)	235 (27.6)*
Respiratory	593 (26.7)	763 (23.1)†	149 (25.1)	223 (29.9)
CNS	454 (20.5)	669 (20.2)	178 (39.2)	272 (42.2)
Renal	644 (29.0)	1342 (40.6)‡	142 (22.0)	259 (19.6)
Coagulation	122 (5.5)	167 (5.1)	42 (34.4)	54 (32.9)
Hepatic	55 (2.5)	445 (13.5)‡	14 (25.5)	58 (13.5)*
No of organ failures during the ICU stay, n (%)				
None	903 (40.7)	1120 (33.9)‡	17 (1.9)	40 (3.8)*
1 organ	759 (34.2)	1019 (30.8)†	54 (7.1)	42 (4.2)†
2 organs	361 (16.3)	571 (17.3)	100 (27.7)	85 (15.3)‡
3 organs	149 (6.7)	341 (10.3)‡	78 (52.3)	115 (34.5)‡
4+ organs	45 (2.0)	255 (7.7)‡	35 (77.8)	128 (52.0)†

Statistically significant vs SOAP: ‡ <0.001; † <0.01 and * <0.05.

e-Figure 1. ICU mortality rates in ICON and SOAP studies according to number of failing organs in patients with sepsis (top panel) and without sepsis (bottom panel)