Sepsis in the ICU: worldwide data

Abstract

Background: There is a need to better define the epidemiology of sepsis in ICUs around the globe.

Methods: The ICON audit prospectively collected data on all adult (> 16 years) patients admitted to the ICU between May 8 and May 18, 2012, except those admitted for less than 24 hours for routine postoperative surveillance. Data were collected daily for a maximum of 28 days in the ICU and patients were followed up for outcome data until death, hospital discharge, or for 60 days. Participation was entirely voluntary.

Findings: The audit included 10,069 patients from Europe (54.1%), Asia (19.2%), America (17.1%) and other continents (9.6%). Sepsis, defined as infection with associated organ failure, was identified during the ICU stay in 2,973 (29.5%) patients, including in 1,808 (18.0%) already at ICU admission. Occurrence rates of sepsis varied from 13.6% to 39.3% in the different regions. Overall ICU and hospital mortality rates were 25.8% and 35.3%, respectively, in patients with sepsis, but varied from 11.9% and 19.3% (Oceania) to 39.5% and 47.2% (Africa), respectively. After adjustment for possible confounders in a multilevel analysis, independent risk factors for in-hospital death included older age, higher SAPS II score, comorbid cancer, chronic heart failure (NYHA III/IV), cirrhosis, use of mechanical ventilation or renal replacement therapy and infection with *Acinetobacter*.

Interpretation: Sepsis remains a major health problem in ICU patients worldwide, associated with high mortality rates. However, there is a wide variability in the sepsis rate in ICU patients around the globe.

Funding: None

Introduction

Sepsis is a major cause of morbidity and mortality in modern intensive care units (ICUs). Although a number of studies have provided epidemiological data on sepsis in ICU patients in the developed world,[1-6] there is limited information on the global burden of sepsis worldwide.[7, 8] Yet, such data are crucially important to increase awareness of the global impact of sepsis, to highlight the need for continued research into potential preventive and therapeutic interventions, and to help guide resource allocation.[9] Information on patterns of sepsis around the globe are also of interest, including causative microorganisms, primary source of infection, and associated outcomes.

In 2012, the World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM) conducted a worldwide audit of data from ICUs around the world, providing a large database from which to extract information. We used these data to explore the characteristics of patients with sepsis, defined according to recent consensus as infection plus organ dysfunction,[10] around the world, including international differences in occurrence rates, causative microorganisms and outcomes. We also evaluated the factors associated with in-hospital mortality in these patients.

METHODS

The worldwide ICON audit recruited ICUs by open invitation, through national scientific societies, national and international meetings, email lists and individual contacts. Participation was entirely voluntary, with no financial incentive. Ethics committee approval was obtained by the participating institutions according to local ethical regulations. Informed consent was not required for this observational and anonymous audit. Of the 730 ICUs contributing to the study from 84 countries, 419 (57.4%) were located in university/academic hospitals. The organizational characteristics of these centres have been described previously.[11]

Each ICU was asked to prospectively collect data on all adult (>16 years) patients admitted to their ICU (see the participants list in Appendix 1) between May 8 and May 18, 2012, except those who stayed in the ICU for <24 hours for routine postoperative surveillance. Re-admissions of previously included patients were not included. Data were collected daily for a maximum of 28 days in the ICU. Outcome data were collected at the time of ICU and hospital discharge, or at 60 days. Data were entered anonymously using electronic case report forms (CRFs) via a secured internet-based website. Data collection on admission included demographic data and comorbid diseases. Clinical and laboratory data for SAPS II[12]

and APACHE II[13] scores were reported as the worst values within the first 24 hours after admission. A daily evaluation of organ function was performed according to the sequential organ failure assessment (SOFA) score[14]; organ failure was defined as a SOFA subscore >2 for the organ in question. Clinical and microbiologic infections were reported daily as well as antibiotic therapy.

Infection was defined according to the criteria of the International Sepsis Forum.[15] Only clinically relevant infections requiring administration of antimicrobial agents were considered. Sepsis was defined as the presence of infection with associated organ failure.[10, 16] Septic shock was defined as sepsis associated with cardiovascular failure requiring vasopressor support (SOFA cardiovascular of 3 or 4). ICU-acquired infection was defined as infection identified at least 48 hours after ICU admission. Non-ICU acquired infection was defined as infection present on admission or within the first 48 hours after ICU admission.

Surgical admissions referred to patients who had had surgery in the 4 weeks preceding admission. We also noted the presence of comorbid conditions, including chronic obstructive pulmonary disease (COPD), cancer, cirrhosis, severe heart failure (NYHA III-IV), severe malnutrition, chronic renal failure (need for chronic renal support or history of previous serum creatinine over 3.6 mg/dL [300 µmol/L]), insulin-dependent diabetes mellitus (the need, prior to ICU admission, for insulin injections to control blood sugar levels), human immunodeficiency virus (HIV) infection, other forms of immune deficiency or immunosuppressive therapy (administration of immunosuppressive agents within the previous 6 months or steroid treatment with at least 0.3 mg/kg/day prednisolone for at least one month).

Detailed instructions were available through a secured website for all participants before starting data collection and throughout the study period. Any additional queries were answered on a per case basis. Validity checks were made at the time of electronic data entry, including plausibility checks within each variable and between variables. Data were further reviewed by the coordinating centre for completeness and plausibility, and any doubts were clarified with the participating centre. There was no on site monitoring. We did not attempt to verify the pathogenicity of the microorganisms, including the relevance of *Staphylococcus epidermidis* or the distinction between colonization and infection.

For the purposes of this audit, we divided the world into 8 geographic regions: North America, South America, Western Europe, Eastern Europe, South Asia, East and South-East Asia, Oceania and Africa. Individual countries were also classified into three income groups according to the 2011 gross national income (GNI) per capita, calculated using the World

Bank Atlas method:[17] GNI < $4,035 = low and lower middle income; GNI $4,036–12,475 = upper middle income; and GNI >$12,476 = high income.

Statistical analysis

Data are shown as means with standard deviation (SD), mean and 95% confidence intervals (CI), medians and interquartile ranges (IQ), numbers and percentages or the percentage and 95% CI. Differences between groups in distribution of variables were assessed using analysis of variance (ANOVA), Kruskal Wallis test, Student's t-test, Mann-Whitney test, chi-square test or Fisher's exact test as appropriate.

To identify the risk factors associated with in-hospital mortality in septic patients we used a three-level multilevel technique with the structure of a patient (level 1) admitted to a hospital (level 2) within a country (level 3). The explanatory variables considered in the model were:

- Individual-level factors: age, sex, SAPS II score, type of admission, source of admission, mechanical ventilation, renal replacement therapy, comorbidities, onset of infection, site of infection and the most common microorganisms.
- Hospital-level factors: type of hospital; ICU specialty; total number of ICU patients in 2011; number of staffed ICU beds.
- Country-level factors: GNI.

Individual-level variables to be included in the final model were selected in two steps. In the first step, and on the basis of a multilevel models including country-level and hospital-level factors and each of the individual-level factors, variables with a p-value less than 0.2 was considered in the last step. The collinearity between variables was checked by inspection of the correlation between them, by looking at the correlation matrix of the estimated parameters, and by looking at the change of parameter estimates and at their estimated standard errors. Q-Q plots were drawn to check for normality in the residuals. The results of fixed effects (measures of association) are given as odds ratios (OR) with their 95% confidence intervals and the 80% interval OR (IOR-80). Random effects (measures of variation) measures included the variance (var) and its standard error (se) and the median odds ratio (MOR). The statistical significance of covariates was calculated using the Wald test.

Data were analyzed using IBM® SPSS® Statistics software, version 22 for Windows and R software, version 2.0.1 (CRAN project). All reported p-values are two-sided and a p-value of less than 0.05 was considered to indicate statistical significance. The results of fixed effects are given as odds ratios (OR) with their 95% confidence intervals.

Results

Characteristics of the study group

A total of 10,069 patients were included in the audit. Overall 2,973 patients (29.5%) had sepsis, including 1,808 (18.0%) already at ICU admission (Figure 1). In the whole cohort, antibiotics were given to 5,975 (59.3%) patients during their ICU stay. Patients with sepsis were older, had higher severity scores on admission to the ICU, had more comorbid conditions and were more commonly receiving mechanical ventilation and renal replacement therapy on admission to the ICU than patients without sepsis (Table 1). Patients with sepsis also had more organ failures than the other patients (3 [1-4] vs. 1 [0-2] organs, p<0.001).

Patterns of infections

The most common source of sepsis was the respiratory tract (67.4%) followed by the abdomen (21.8%) and the blood stream (21.0%) (Table E1). Positive isolates were retrieved in 69.6% (n=2,069) of patients with sepsis; two thirds of the positive isolates were Gram-negative microorganisms and one half were Gram-positive (Table 2). The most commonly isolated microorganisms were *Escherichia coli* (22.7%), *Staphylococcus aureus* (19.7%), *Klebsiella* (17.2%), *Pseudomonas* (16.3%), and *Acinetobacter* (11.7%). Microbiological patterns varied around the globe (Table 2), with Gram-positive isolates being much less frequent (21.4%) in South Asia than in other regions. Methicillin-resistant *Staphylococcus aureus* (MRSA) was more common in the Middle East (14.4%) and North America (12.8%) than in Western Europe (6.1%). *Klebsiella* isolates were most commonly reported in Africa (31.3%), Eastern Europe (28.5%), and South America (24.7%), and *Pseudomonas* was most frequent in Eastern Europe (21.1%) and South America (20.4%). Fungal organisms contributed to 14.5% and 14.8% of isolates in Western and Eastern Europe, respectively, but to only 5.1% of isolates in North America. Patients with urinary tract (82.6% vs 43.9%), abdominal (77.1% vs 50.8%) and respiratory tract (70.0% vs 51.4%) infections were more

likely to have Gram-negative than Gram-positive isolates (Table E1). The most commonly isolated microorganisms for patients with respiratory tract infections were coagulase-negative staphylococci (23.9%), *Pseudomonas* species (19.6%), *E. coli* (19.1%) and *Klebsiella* (18.6%). *E. coli* was the most commonly isolated microorganism in patients with urinary tract infections (40.2%).

Patients with ICU-acquired sepsis (n=764) were younger, more likely to be surgical admissions, and had lower SAPS II and SOFA scores on admission to the ICU, compared to those who had infections within the first 48 hours of in the ICU (Table 3 and Table E2). Respiratory and catheter-associated infections were more frequent and abdominal infections less frequent in patients with ICU-acquired than in those with non-ICU-acquired infections (Table E2). Patients with ICU-acquired infections were more likely to have positive isolates than patients with non-ICU-acquired infections (79.5% vs 66.2%, p<0.001) (Table E3)

Outcome and risk factors

ICU mortality rates were 25.8 % in patients with sepsis and 12.1% in those without (p<0.001); hospital mortality rates were 35.3 vs. 16.7%, p<0.001). ICU and hospital mortality rates varied from 11.9 and 19.3% (Oceania) to 39.5 and 47.2% (Africa), respectively (Table 2). ICU length of stay was longer (6 [3-13] vs. 2 [1-4] days, p<0.001) in patients with than in those without sepsis. As expected, there was a stepwise increase in ICU and hospital mortality rates according to the severity of sepsis (Table 3). Although patients with ICU-acquired sepsis had longer ICU lengths of stay than those who had sepsis within 48 hours of admission to the ICU, they did not have higher mortality rates (Table 3).

The crude risk of in-hospital death was higher in patients with *Pseudomonas*, fungal and *Acinetobacter* infections (Table 4). In multilevel analysis, independent risk factors for in-hospital death in patients with sepsis included older age, higher SAPS II score, cirrhosis, metastatic cancer, chronic heart failure (NYHA III/IV), the use of mechanical ventilation or renal replacement therapy at any time during the ICU stay, and infection with *Acinetobacter* (Table E4). The use of mechanical ventilation and presence of comorbid cirrhosis more than doubled the risk of death. The model suggested significant between-hospital variation (var=0·28, p=0·001) in the individual risk of in-hospital death but the between-country variation was not significant.

Discussion

The present audit highlights the considerable burden that sepsis presents in modern ICUs. This large study, including more than 10,000 patients from 730 ICUs, indicates that about 30% of all ICU patients have sepsis, as defined by recent definitions.[16] This percentage is identical to that (29.5%) reported in the earlier SOAP study, a large European study that used the same methodology,[1] but somewhat higher than in some other large studies.[5, 18, 19] Two major elements can account for these differences. Firstly, we did not include all patients admitted to the ICU, but only critically ill patients, excluding patients admitted to the ICU for postoperative surveillance without complications. Secondly, other studies often focused on admission data. If we consider only the patients who had sepsis on admission in our study, the case rate decreases to 18%. Importantly, the percentage of ICU patients with sepsis varied around the globe, with particularly high rates in East and South East Asia.

A strength of the present study compared to studies assessing only sepsis on admission or prevalence studies (e.g., EPIC II[2]), is that patients were followed throughout the ICU course, enabling evaluation of sepsis on admission as well as during the ICU stay. Interestingly, patients with ICU-acquired infection were less severely ill than the other patients with sepsis, but had similar outcomes, suggesting that the attributable mortality of ICU-acquired infection is actually quite low. This observation is in agreement with the recent study by van Vught et al.[20] showing a low attributable mortality of ICU-acquired infections. Our results illustrate the importance of nosocomial respiratory infections, accounting for three quarters of ICU-acquired infections. They also stress the important problem of catheter-related infections, which accounted for 16% of ICU-acquired cases of sepsis.

Pathogenic microorganisms were identified in only 70% of cases, a similar finding to that reported in other studies.[18, 21-23] Gram-negative organisms accounted for two thirds and Gram-positive for about one half of the isolates. The most common Gram-negative microorganisms recovered were *E. coli*, *Klebsiella*, *Pseudomonas* and *Acinetobacter*, as in previous studies.[21-23] Interestingly, Gram-negative organisms were less common in North America than in other parts of the world; MRSA was also more common in North America than in other parts of the world except the Middle East. The results also stress the importance of fungal infections, which were involved in 13% of cases of sepsis overall, although the frequency was lower in the US (5%), perhaps because more stringent criteria are used to characterize fungal infections in the US.

ICU mortality rates in patients with sepsis were around 26% and were twice as high as those in non-septic patients. This percentage is lower than the 32% observed in the SOAP study[1] and in other studies.[18, 21-23] ICU mortality rates in patients with septic shock were around 35%, a percentage that is also lower than that reported in earlier studies.[1, 5] Increased awareness of sepsis diagnosis and improved early management may have contributed to improved outcomes over time.

As expected, non-survivors were older and had more comorbidities. As in previous ICU studies,[1, 2] *Pseudomonas* and fungal infections were associated with worse outcomes, although only Acinetobacter infection was an independent predictor for hospital death in the multilevel analysis. Mechanical ventilation and cirrhosis were also important prognostic factors, more than doubling the risk of death. We also identified significant between-center variation suggesting that differences in local ICU organization may impact on outcomes of patients with sepsis. In an international cohort of 13,796 ICU patients, Sakr et al. reported that a high nurse:patient ratio was independently associated with a lower risk of in-hospital death.[24] Gaieski and colleagues reported that sepsis outcomes were improved in centres with higher sepsis case volumes.[25] In a multicentre study in Canada, Yergens et al. reported that ICU occupancy > 90 % was associated with an increase in hospital mortality in patients with sepsis admitted from the emergency department.[26] We are unable to identify which particular organizational factors may have influenced outcomes from our data and this is an area that needs further study.

Our database was very large, including considerable data on demographics, organ function and outcomes. Nevertheless, to successfully collect a large amount of data in many ICUs requires some selection of the collected data, and we did not collect precise data on all subtypes of microorganisms or their resistance patterns. Moreover, data were collected by ICU doctors or research nurses who may not have specific expertise in infectious diseases. Our study has other limitations. Firstly, although the audit included a large number of ICUs, the purely voluntary nature of the participation may impact on the representativeness of the data. Secondly, data collection was not monitored so that small errors could not be corrected; only incongruous data were verified. Thirdly, in some countries, identification of microorganisms may have been incomplete because of the limited microbiological tests available. Finally, the results of the multilevel analysis may not have taken into consideration unmeasured variables, but we adjusted for a large number of variables that may influence outcome.

Conclusions

Sepsis, as defined by infection with organ dysfunction, remains a major health problem in ICU patients worldwide, associated with high mortality rates. There is wide variation in sepsis rates, causative microorganisms and associated mortality in ICU patients around the globe. A history of liver cirrhosis or metastatic cancer, use of mechanical ventilation or renal replacement therapy, and Acinetobacter infection were independently associated with an increased risk of in-hospital death. Global epidemiological data such as these help increase awareness of sepsis and provide crucial information for future healthcare planning.

Acknowledgements

We would like to thank Hassane Njimi, MSc, PhD, Department of Intensive Care, Erasme University Hospital, Brussels, Belgium, for his statistical support.

References

1 Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall JR, Payen D. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006; **34**: 344-53.

2 Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K. International study of the prevalence and outcomes of infection in intensive care units. *J A M A* 2009; **302**: 2323-9.

3 Lagu T, Rothberg MB, Shieh MS, Pekow PS, Steingrub JS, Lindenauer PK. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. *Crit Care Med* 2012; **40**: 754-61.

4 SepNet Critical Care Trials Group. Incidence of severe sepsis and septic shock in German intensive care units: the prospective, multicentre INSEP study. *Intensive Care Med* 2016; **42**: 1980-9.

5 Sakr Y, Elia C, Mascia L, Barberis B, Cardellino S, Livigni S, Fiore G, Filippini C, Ranieri VM. Epidemiology and outcome of sepsis syndromes in Italian ICUs: a muticentre, observational cohort study in the region of Piedmont. *Minerva Anestesiol* 2013; **79**: 993-1002.

6 Yebenes JC, Ruiz-Rodriguez JC, Ferrer R, Cleries M, Bosch A, Lorencio C, Rodriguez A, Nuvials X, Martin-Loeches I, Artigas A. Epidemiology of sepsis in Catalonia: analysis of incidence and outcomes in a European setting. *Ann Intensive Care* 2017; **7**: 19.

7 Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. *Lancet* 2010; **376**: 1339-46.

8 Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, Angus DC, Reinhart K. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. *Am J Respir Crit Care Med* 2016; **193**: 259-72.

9 Finfer S, Machado FR. The global epidemiology of sepsis. Does it matter that we know so little? *Am J Respir Crit Care Med* 2016; **193**: 228-30.

10 Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**: 801-10.

11 Vincent JL, Marshall JC, Namendys-Silva SA, Francois B, Martin-Loeches I, Lipman J, Reinhart K, Antonelli M, Pickkers P, Njimi H, Jimenez E, Sakr Y. Assessment of the worldwide burden of critical illness: the Intensive Care Over Nations (ICON) audit. *Lancet Respir Med* 2014; **2**: 380-6.

12 Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *J A M A* 1993; **270**: 2957-63.

13 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818-29.

14 Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related

Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; **22**: 707-10.

15 Calandra T, Cohen J. The international sepsis forum consensus conference on definitions of infection in the intensive care unit. *Crit Care Med* 2005; **33**: 1538-48.

16 Vincent JL, Opal S, Marshall JC, Tracey KJ. Sepsis definitions: Time for change. *Lancet* 2013; **381**: 774-5.

17 The World Bank. GNI per capita, Atlas method (current US$). http://data.worldbank.org/indicator/NY.GNP.PCAP.CD . 2011.

Ref Type: Internet Communication

18 Brun-Buisson C, Meshaka P, Pinton P, Vallet B. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. *Intensive Care Med* 2004; **30**: 580-8.

19 Padkin A, Goldfrad C, Brady AR, Young D, Black N, Rowan K. Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. *Crit Care Med* 2003; **31**: 2332-8.

20 van Vught LA, Klein Klouwenberg PM, Spitoni C, Scicluna BP, Wiewel MA, Horn J, Schultz MJ, Nurnberg P, Bonten MJ, Cremer OL, van der Poll T. Incidence, risk factors, and attributable mortality of secondary infections in the intensive care unit after admission for sepsis. *JAMA* 2016; **315**: 1469-79.

21 Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le G, Jr., Payen D. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006; **34**: 344-53.

22 Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009; **302**: 2323-9.

23 Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, Wolff M, Spencer RC, Hemmer M. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. *JAMA* 1995; **274**: 639-44.

24 Sakr Y, Moreira CL, Rhodes A, Ferguson ND, Kleinpell R, Pickkers P, Kuiper MA, Lipman J, Vincent JL. The impact of hospital and ICU organizational factors on outcome in critically ill patients: results from the Extended Prevalence of Infection in Intensive Care study. *Crit Care Med* 2015; **43**: 519-26.

25 Gaieski DF, Edwards JM, Kallan MJ, Mikkelsen ME, Goyal M, Carr BG. The relationship between hospital volume and mortality in severe sepsis. *Am J Respir Crit Care Med* 2014; **190**: 665-74.

26 Yergens DW, Ghali WA, Faris PD, Quan H, Jolley RJ, Doig CJ. Assessing the association between occupancy and outcome in critically Ill hospitalized patients with sepsis. *BMC Emerg Med* 2015; **15**: 31.

Table 1. Characteristics of the study cohort on admission to the ICU according to the presence of sepsis

Characteristic	All patients N=10069	No sepsis N=7096	Sepsis N=2973	*P* value
Age, years, mean ± SD	60.0±18.0	59.4 ±18.4	61.5 ±17.0	<0.001
Male, n (%)	5973 (60.1)	4177 (59.7)	1796 (61.0)	0.21
Severity scores, mean ± SD				
SAPS II score	40.2±18.2	36.4 ±17.4	49.2 ±16.6	<0.001
SOFA score	5 [3-9]	4 [2-7]	8 [6-11]	<0.001
Type of admission (%)				<0.001
Surgical	3432 (36.0)	2475 (37.0)	957 (33.7)	
Medical	5382 (56.5)	3646 (54.6)	1736 (61.1)	
Trauma	643 (6.8)	512 (7.7)	131 (4.6)	
Other	66 (0.7)	49 (.7)	17 (.6)	
Source of admission				<0.001
ER/ambulance	3814 (37.9)	2780 (39.2)	1034 (34.8)	
Hospital floor	2625 (26.1)	1664 (23.4)	961 (32.3)	
OR/recovery	1811 (18.0)	1363 (19.2)	448 (15.1)	
Other hospital	981 (9.7)	652 (9.2)	329 (11.1)	
Other	838 (8.3)	637 (9.0)	201 (6.8)	
Comorbidities, n (%)				
COPD	1240 (12.3)	788 (11.1)	452 (15.2)	<0.001
Cancer	1049 (10.4)	710 (10.0)	339 (11.4)	0.04
Diabetes mellitus, insulin-dependent	972 (9.7)	664 (9.4)	308 (10.4)	0.12
Heart failure, NYHA III/IV	921 (9.1)	588 (8.3)	333 (11.2)	<0.001
Chronic renal failure	912 (9.1)	582 (8.2)	330 (11.1)	<0.001
Cirrhosis	349 (3.5)	217 (3.1)	132 (4.4)	<0.001
Immunosuppression	346 (3.4)	177 (2.5)	169 (5.7)	<0.001
Metastatic cancer	332 (3.3)	221 (3.1)	111 (3.7)	0.11
Haematologic cancer	212 (2.1)	99 (1.4)	113 (3.8)	<0.001
HIV infection	71 (.7)	37 (.5)	34 (1.1)	<0.001
Number of comorbidities, n (%)				<0.001
None	5512 (54.7)	4145 (58.4)	1367 (46.0)	
1	2800 (27.8)	1880 (26.5)	920 (30.9)	
2	1207 (12.0)	740 (10.4)	467 (15.7)	
3	416 (4.1)	249 (3.5)	167 (5.6)	
≥4	134 (1.3)	82 (1.2)	52 (1.7)	
Procedures, n (%)				
Mechanical ventilation	4776 (47.4)	2755 (38.8)	2021 (68.0)	<0.001
Renal replacement therapy	537 (5.3)	264 (3.7)	273 (9.2)	<0.001

Valid percentages are given after exclusion of missing values (data missing from 546 patients for type of admission). COPD: chronic obstructive pulmonary disease, HIV: human immunodeficiency viral infection, ICU: intensive care unit, NYHA: New York Heart Association Classification, SAPS: simplified acute physiology, SOFA: sequential organ assessment, SD: standard deviation, ER: emergency room, OR: operating room.

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