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A worldwide perspective of sepsis epidemiology and survival according to age: Observational data from the ICON audit

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ABSTRACT

Purpose: To investigate age-related differences in outcomes of critically ill patients with sepsis around the world.
Methods: We performed a secondary analysis of data from the prospective ICON audit, in which all adult (>16 years) patients admitted to participating ICUs between May 8 and 18, 2012, were included, except admissions for routine postoperative observation. For this sub-analysis, the 10,012 patients with completed age data were included. They were divided into five age groups – ≤50, 51–60, 61–70, 71–80, >80 years. Sepsis was defined as infection plus at least one organ failure.
Results: A total of 2963 patients had sepsis, with similar proportions across the age groups (≤50 = 25.2%; 51–60 = 30.3%; 61–70 = 32.8%; 71–80 = 30.7%; >80 = 30.9%). Hospital mortality increased with age and in patients >80 years was almost twice that of patients ≤50 years (49.3% vs 25.2%, $p < .05$). The maximum rate of increase in mortality was about 0.75% per year, occurring between the ages of 71 and 77 years. In multilevel analysis, age > 70 years was independently associated with increased risk of dying.
Conclusions: The odds for death in ICU patients with sepsis increased with age with the maximal rate of increase occurring between the ages of 71 and 77 years.

1. Introduction

Sepsis-related mortality and morbidity are major healthcare problems worldwide [1-4]. The percentage of patients older than 80 years who are admitted to the intensive care unit (ICU) is increasing [5]. This trend will likely continue with estimates suggesting that by the year 2050 > 9% of European and North American populations will be octogenarians [6].

Studies have suggested that older people are more likely to develop sepsis than younger patients [7,8]. There are various reasons why this may be the case, including increased rates of comorbidities (e.g., diabetes, chronic obstructive pulmonary disease [COPD]), and associated, often immune suppressant, therapies; poorer pre-admission status, including malnutrition; immunosenescence, i.e., age-related defects in the immune system; and increased colonization with Gram-negative organisms, especially in patients from long-term care facilities [9-11]. For similar reasons, older people also have a greater risk of in-hospital death once they develop sepsis [9]. Moreover, long-term outcomes of older sepsis survivors are worse than in their younger counterparts, not only in terms of increased risk of death but also greater post-ICU cognitive and functional decline, heightened risk of hospital readmission and higher probability of discharge to long-term care facilities [12-15].

Despite the increasing numbers of older patients being admitted to the ICU [16], there are relatively few international data regarding the epidemiology and outcomes of older patients with sepsis. To quantify the association between age and outcome in septic patients and to

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[1] Appendix A.

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assess differences between geographical regions, we used the Intensive Care Over Nations (ICON) database [17] to describe differences in epidemiology and outcomes of patients with sepsis above the age of 50, divided into deciles of age (51–60, 61–70, 71–80, 81+ years), compared to outcomes in younger patients (≤50 years).

2. Methods

2.1. Study population

Data for this analysis were obtained from the prospective observational ICON audit, which included all adult patients (>16 years) admitted to participating ICUs (see Appendix) between May 8 and May 18, 2012 [17]. ICU admissions for routine postoperative surveillance for <24 h after uncomplicated surgery were not included. Data were collected anonymously and entered voluntarily by the investigators with no financial incentives. Each participating institution obtained institutional review board approval according to local ethical regulations. Due to the observational nature of this audit, informed consent was not required. Only patients with completed age data were included in the present substudy.

2.2. Data acquisition

Demographic and clinical parameters were recorded as listed previously [17], as well as microbiology and laboratory findings, interventions and outcomes including ICU and hospital lengths of stay and mortality. Investigators entered the collected data into electronic case report forms (eCRFs) using a secure internet-based website. Data were collected daily for a maximum of 28 days in the ICU. Follow-up data were collected until hospital discharge or death for a maximum of 60 days after the day of admission to the ICU.

2.3. Definitions

Full details of the study methodology and definitions have been reported in detail elsewhere [17]. Investigators were asked to indicate the presence of the following comorbid conditions for each patient: chronic obstructive pulmonary disease (COPD), cancer (solid, metastatic, hematologic), insulin-dependent diabetes mellitus, heart failure (NYHA III-IV), chronic renal failure, HIV infection, cirrhosis, immunosuppression, steroid therapy, chemotherapy. Infection was defined in accordance with the definitions of the International Sepsis Forum [18]. Sepsis was defined as the presence of infection with the concomitant occurrence of at least one organ failure (defined as a sequential organ failure assessment [SOFA] score > 2 for the organ in question). Participating centers were grouped into nine geographical regions: North America, South and Central America, western Europe, eastern Europe, Middle East, south Asia, east and southeast Asia, Oceania, and Africa. Individual countries were classified into three income groups in accordance with their 2011 gross national income (GNI) per person, using thresholds defined by the World Bank Atlas method: GNI less than US $4035 was defined as low and lower-middle income, $4036–$12,475 was defined as upper-middle income, and greater than $12,475 was defined as high income [19].

2.4. Statistical analysis

For descriptive statistics, data are reported using means with standard deviation (SD), medians and interquartile ranges (IQR), or numbers and percentages. For continuous variables, normality assumption analysis was performed. To analyze differences between groups in distribution of variables we used analysis of variance (ANOVA), Kruskal-Wallis test, Student's *t*-test, Mann-Whitney test, chi-square test or Fisher's exact test as appropriate. The least significant difference testing procedure was used for pairwise comparisons. For the binary outcome of in-hospital death we performed a multivariable analysis using a multilevel binary logistic model with three levels: patient (level 1: age categories, sex, SAPS II score [excluding age], type of admission, source of admission, treatment with mechanical ventilation or renal replacement therapy [RRT] at baseline, comorbidities), hospital (level 2: type of hospital, ICU specialty, ICU volume, number of staffed ICU beds), and country (level 3: GNI). For parameter testing, the likelihood-ratio test was used. Co-linearity between variables was checked by inspection of the correlation between them, by looking at the correlation matrix of the estimated parameters. The results of fixed effects (measures of association) are given as odds ratios (ORs) with their 95% CIs. Data were analyzed using IBM® SPSS® statistics software. All reported *p*-values are two-sided and a p-value <.05 was considered to indicate statistical significance.

3. Results

3.1. Characteristics of the study group

The ICON audit included 10,069 patients from 730 participating centers in 84 countries. Age data were missing from 57 patients; 10 of whom had sepsis. The median [IQR] age in the whole population was 63 [49–74] years and in the septic population 64 [52–74] years. The proportions of patients in the different age groups varied according to geographical region, with Africa having the smallest proportion of patients >50 years and western Europe the greatest; South and Central America had the largest percentage of patients >80 years old and south Asia the smallest (Fig. 1). A total of 2963 patients (29.6%) had sepsis at some point during the study period (2201 [74.3%] on or within 48 h of admission and 762 [25.7%] >48 h after admission), with similar proportions across the age groups (≤50 = 25.2%; 51–60 = 30.3%; 61–70 =

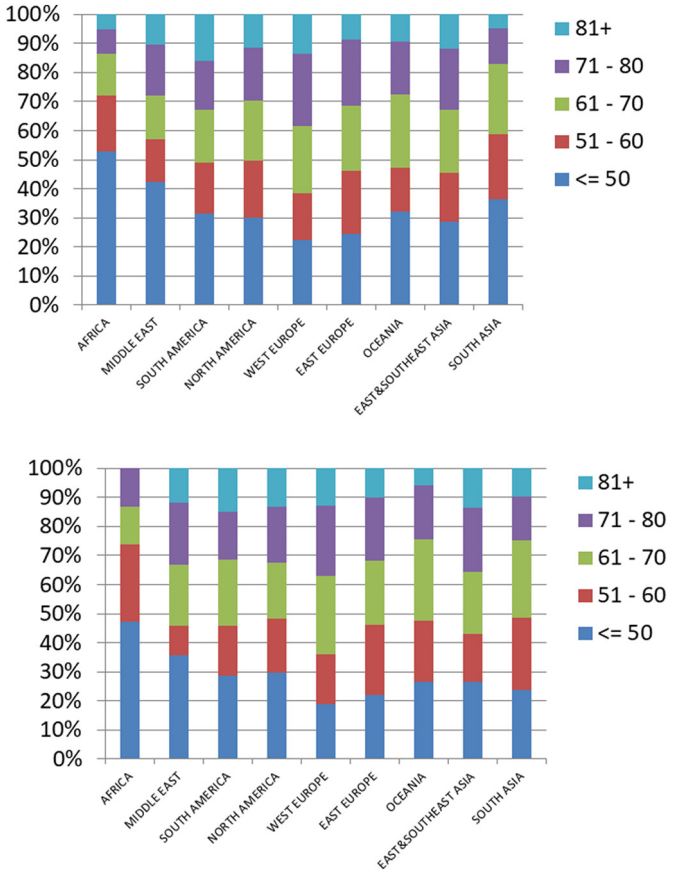

Fig. 1. Proportions of patients in the different age groups according to geographical region. Upper panel: all patients; lower panel: patients with sepsis.

32.8%; 71–80 = 30.7%; >80 = 30.9%). The geographic distribution of sepsis across age groups was similar to the general geographic distribution of critically ill patients (Fig. 1).

3.2. Characteristics of the patients with sepsis

In the patients with sepsis, there were more male than female patients in all age groups except those older than 80 years (Table 1). Medical admissions were more frequent in patients >80 years than in those ≤50 and surgical admissions most frequent in patients aged 71–80 years. Trauma admissions were more frequent in patients ≤50 years than in older patients (11.6% in patients ≤50 years vs 2.3% in patients >80 years). A greater proportion of patients >50 years of age had COPD, cancer, insulin-dependent diabetes mellitus, heart failure (NYHA III/IV) and chronic renal failure compared to those ≤50 years of age. The number of patients with HIV infection, cirrhosis or immunosuppression decreased with age. Patients >80 years were less likely to receive mechanical ventilation on admission or at any time during the ICU stay (Table 1).

3.3. Organ dysfunction and infections during the ICU stay

Patients with sepsis aged >50 years were more likely to have cardiovascular failure at some time during the ICU stay than those ≤50 (Supplemental Table S1). Patients >60 years of age were more likely to have renal failure than were patients ≤50 years of age and respiratory failure was more common in patients aged between 51 and 80 than in those ≤50 years. The numbers of failing organs during the ICU stay were generally similar across age groups (Supplemental Table S1).

Abdominal infections were more common in patients >50 years of age than in younger patients (Supplemental Table S2). There were no other significant differences in site of infection or in isolated microorganisms across the age groups (Supplemental Table S2).

Table 1
Demographic data and co-morbidities of all patients with sepsis stratified according to age.

	≤50	51–60	61–70	71–80	81+
N. of patients, n (%)	698 (23.6)	538 (18.2)	724 (24.4)	641 (21.6)	362 (12.2)
Sex, male, n (%)	415 (59.9)	341 (64.0)	448 (62.7)	413 (64.8)	177 (49.2)*
Severity scores, mean ± SD					
SAPS II score without age	38.2 ± 15.7	38.2 ± 15.9	38.3 ± 15.8	38.4 ± 14.7	39.6 ± 15.9
SOFA score at admission	8.3 ± 4.0	8.6 ± 4.0	8.9 ± 3.9*	9.0 ± 3.8*	9.0 ± 4.0*
Max SOFA score	10.7 ± 4.4	11.2 ± 4.2	11.4 ± 4.2*	11.4 ± 4.1*	11.4 ± 4.1*
Type of admission, n (%)					
Surgical (non-trauma)	199 (29.7)	177 (34.4)	237 (34.3)	233 (38.1)*	110 (31.7)
Medical	386 (57.5)	314 (61.1)	439 (63.6)*	364 (59.5)	228 (65.7)*
Trauma	78 (11.6)	20 (3.9)*	12 (1.7)*	12 (2.0)*	8 (2.3)*
Other	8 (1.2)	3 (0.6)	2 (0.3)	3 (0.5)	1 (0.3)
Source of admission, n (%)					
Other hospital	115 (16.5)	60 (11.2)*	74 (10.2)*	58 (9.0)*	21 (5.8)*
ER/ambulance	267 (38.3)	195 (36.2)	235 (32.5)*	191 (29.8)*	144 (39.8)
OR/recovery room	98 (14.0)	72 (13.4)	111 (15.3)	114 (17.8)	53 (14.6)
Hospital floor	179 (25.6)	177 (32.9)*	250 (34.5)*	240 (37.4)*	111 (30.7)
Other	39 (5.6)	34 (6.3)	54 (7.5)	38 (5.9)	33 (9.1)*
Comorbidities, n (%)					
COPD	24 (3.4)	64 (11.9)*	142 (19.6)*	148 (23.1)*	73 (20.2)*
Cancer	32 (4.6)	54 (10.0)*	107 (14.8)*	107 (16.7)*	39 (10.8)*
Metastatic cancer	13 (1.9)	27 (5.0)*	28 (3.9)*	31 (4.8)*	11 (3.0)
Hematologic cancer	28 (4.0)	27 (5.0)	32 (4.4)	17 (2.7)	8 (2.2)
Insulin-dependent diabetes mellitus	32 (4.6)	55 (10.2)*	97 (13.4)*	92 (14.4)*	31 (8.6)*
Heart failure, NYHA III/IV	27 (3.9)	38 (7.1)*	83 (11.5)*	115 (17.9)*	69 (19.1)*
Chonic renal failure	30 (4.3)	41 (7.6)*	96 (13.3)*	110 (17.2)*	51 (14.1)*
HIV infection	16 (2.3)	12 (2.2)	3 (0.4)*	2 (0.3)*	1 (0.3)*
Cirrhosis	35 (5.0)	41 (7.6)	30 (4.1)	21 (3.3)	4 (1.1)*
Immunosuppression	54 (7.7)	46 (8.6)	38 (5.2)	20 (3.1)*	10 (2.8)*
Steroid therapy	33 (4.7)	37 (6.9)	33 (4.6)	27 (4.2)	20 (5.5)*
Chemotherapy	16 (2.3)	31 (5.8)*	31 (4.3)*	19 (3.0)	4 (1.1)
No. of comorbidities, n (%)					
None	471 (67.5)	245 (45.5)*	283 (39.1)*	212 (33.1)*	152 (42.0)*
One	150 (21.5)	171 (31.8)*	245 (33.8)*	224 (34.9)*	130 (35.9)*
Two or more	77 (11.0)	122 (22.7)*	196 (27.1)*	205 (32.0)*	80 (22.1)*
Procedures, n (%)					
RRT					
On admission	61 (8.7)	40 (7.4)	80 (11.0)	64 (10)	28 (7.7)
At any time during ICU stay	145 (20.8)	121 (22.5)	203 (28.0)*	169 (26.4)*	79 (21.8)
MV					
On admission	473 (67.8)	380 (70.6)	511 (70.6)	429 (66.9)	221 (61.0)*
At any time during ICU stay	545 (78.1)	447 (83.1)*	585 (80.8)	514 (80.2)	260 (71.8)*
Life-sustaining treatment limitation decision[a]	95 (13.6)	101 (18.8)*	122 (16.9)	146 (22.8)*	99 (27.3)*

SD – standard deviation, n – number of patients, ER – emergency room, OR – operating room, COPD – chronic obstructive pulmonary disease, NYHA – New York Heart Association, RRT – renal replacement therapy, MV – mechanical ventilation, SOFA – sequential organ failure assessment, SAPS – simplified acute physiology score.
Percentages are calculated after excluding missing values (sex: 31).
[a] At any time during the ICU stay.
* p value <.05 as compared to patients age ≤ 50 years of age.

3.4. Mortality and length of stay according to age

Patients >80 years were more likely to have had a documented life-sustaining treatment limitation decision than younger patients (27.3% vs 13.6% in patients ≤50 years, $p < .05$). ICU and hospital lengths of stay in ICU survivors were similar in all age groups, except for the over 80s in whom lengths of stay were shorter (Table 2). ICU and hospital mortality increased with age, with the hospital mortality for patients >80 years almost twice that of patients ≤50 years (49.3% vs 25.2%, $p < .001$). The maximum rate of increase in hospital mortality was about 0.75% per year, achieved between the ages of 71 and 77 years (Fig. 2). The probability of death was lower in ICUs from North America, Western Europe and Oceania than from other regions for all age groups, but the increase in mortality rates with age was similar across regions (Fig. 2; Supplemental Fig. S1).

3.5. Multivariable analysis

In the multivariable analysis, age > 70 years was independently associated with an increased risk of death, with age > 80 years associated with the highest odds ratio (OR 1.685, 95%CI 1.31–2.17, $p < .001$) (Table 3). Increasing SAPS II (without age), medical admission (compared to surgical), treatment with mechanical ventilation on admission, comorbid cancer, cirrhosis, heart failure and immunosuppression were also independently associated with an increased odds ratio of death. Being from a hospital with an ICU annual volume of patients >250 compared to <250 or from a country with a high compared to a low GNI (OR 0.643, 95%CI 0.43–0.97; $p = .04$) was associated with significantly lower odds ratios of mortality. After controlling for patient and hospital factors and GNI, there was significant between-hospital but not between-country variation (Table 3).

4. Discussion

In our cohort, mortality rates in patients with sepsis increased with advancing age and age was an independent risk factor for mortality even after adjusting for the higher severity of illness and other confounders. The probability of death increased consistently with age, with the maximum rate of increase occurring in patients aged between 71 and 77 years.

Studies assessing the effects of age in ICU patients, with or without sepsis, have used different cut-offs for stratification. Some authors used a broad "older" versus "younger" approach [9] and others used multiple different age categories [8,16,20-22]. We chose to use deciles because our database was sufficiently large to enable this analysis and it provided relatively equally-sized groups. We decided to gather patients >80 years into a single group (rather than dividing the group into those >80 and > 90 years), because of the limited number of patients in the older group.

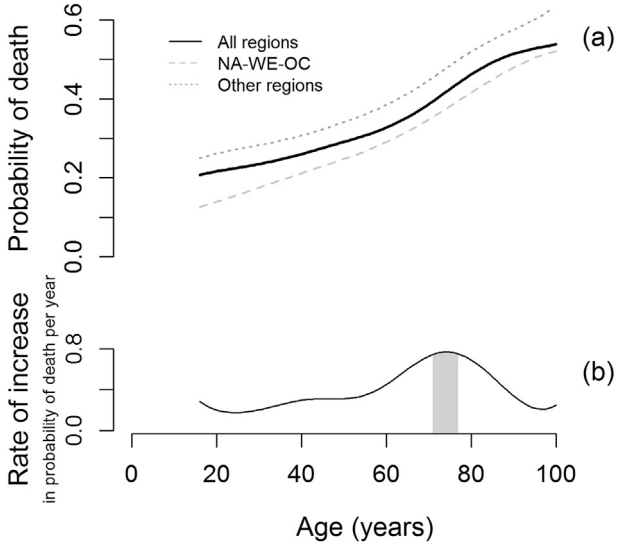

Fig. 2. Adjusted probability of death in patients with sepsis according to age (a) and rate of increase in adjusted probability of death per year (b). The probability of death increased consistently with age, with the maximum rate of increase of about 0.75% per year occurring in patients aged between 71 and 77 years. NA-WE-OC: North America-Western Europe-Oceania.

Interestingly, the proportion of patients with sepsis was similar across all age groups. This finding is in contrast to other studies that have shown an increase in the incidence of sepsis with advancing age [6,8,23,24]. The reasons for these differences are unclear but likely in part related to different study populations. Moreover, we only have data on sepsis in ICU patients and as some ICUs may deny admission of older patients (with frailty, comorbidities, etc) because of their likely poor prognosis, it is possible that we did not capture all patients with sepsis, perhaps particularly in the older age groups.

Considering only the population of patients older than 80 years of age, it is important to underline that although the incidence of sepsis was similar to other age groups, mortality was much higher in this group of patients. Indeed, the hospital mortality for those >80 years of age was almost twice that of patients ≤50 years. Other studies have reported similar findings. In 387 patients with sepsis, Nasa et al. reported ICU mortality rates of 45.6% in patients <60 years, 60.7% in those aged 60–80 years and 78.9% in those >80 years ($p = .035$) [25]. More recently, in 173 patients with sepsis, Brakenridge et al. reported hospital mortality rates of 15.9% for patients aged ≥55 years compared to just 2.1% for younger patients ($p = .016$) [9]. And in a study of >12,000 patients with sepsis in Australian/New Zealand ICUs in 2012, Kaukonen et al. [20] reported mortality rates of 30.4% in patients ≥85 year old compared to 7.3% in those ≤44 years.

Table 2
Outcomes in patient with sepsis, according to age groups.

	≤50	51–60	61–70	71–80	81+
	($n = 698$)	($n = 538$)	($n = 724$)	($n = 641$)	($n = 362$)
ICU stay, median (IQR)	6.0 [3.0–13.0]	7.0 [3.0–13.0]	6.0 [3.0–13.0]	6.0 [3.0–13.0]	5.0 [2.0–10.0]*
Survivors	7.0 [3.0–13.0]	7.0 [4.0–14.0]	6.0 [3.0–13.0]	6.0 [3.0–12.0]	5.0 [3.0–10.0]*
Non-survivors	5.5 [2.0–14.0]	5.0 [2.0–12.0]	6.5 [3.0–14.0]	6.0 [3.0–14.0]	6.0 [2.0–10.0]
Hospital stay, median (IQR)	15.0 [7.0–29.0]	16.5 [7.0–32.0]	16.0 [8.0–32.0]	16.0 [8.0–29.0]	11.0 [5.0–23.0]*
Survivors	17.5 [9.0–36.0]	21.0 [12.0–40.0]	21.0 [12.0–39.0]	21.0 [12.0–37.0]	17.0 [10.0–36.0]
Non-survivors	7.0 [3.0–16.0]	7.0 [3.0–15.0]	9.0 [4.0–19.0]	9.0 [4.0–21.0]*	8.0 [3.0–16.0]
ICU mortality n (%)	138 (20.0)	127 (24.0)	176 (24.7)*	183 (29.0)*	127 (36.2)*
Hospital mortality n (%)	169 (25.2)	160 (31.2)*	229 (33.1)*	271 (44.1)*	172 (49.3)*

ICU – intensive care unit; IQR – interquartile range.
Percentages are calculated after excluding missing data: ICU mortality: 54; hospital mortality: 129.
* $p < .05$ compared to patients ≤ 50 years of age.

Table 3
Results of multivariable analysis in the patients with sepsis.

Variables	OR	Lower	Upper	p-value
Fixed-effects, varying within clusters				
Age				
≤50	Ref			
51–60	1.049	0.825	1.334	0.695
61–70	0.922	0.754	1.128	0.432
71–80	1.379	1.095	1.737	0.006
81+	1.685	1.305	2.176	<0.001
Sex, male	1.053	0.893	1.242	0.54
SAPS II without age	1.05	1.041	1.059	<0.001
Type of admission (%)				
Surgical	Ref			
Medical	1.439	1.096	1.888	0.009
Trauma	1.329	0.761	2.321	0.317
Other	1.662	0.555	4.976	0.364
Source of admission				
OR/recovery	Ref			
Other hospital	1.177	0.8	1.732	0.407
ER/ambulance	0.976	0.69	1.38	0.891
Hospital floor	1.342	0.939	1.918	0.107
Other	1.157	0.771	1.738	0.481
Procedures (on admission)				
Mechanical ventilation	1.344	1.089	1.659	0.006
Renal replacement therapy	1.104	0.841	1.449	0.476
Comorbidities				
COPD	1.086	0.789	1.495	0.613
Cancer	1.488	1.084	2.043	0.014
Metastatic cancer	1.297	0.846	1.99	0.233
Hematologic cancer	1.607	1.033	2.501	0.035
Insulin	1.104	0.859	1.419	0.439
Heart failure, NYHA III/IV	1.363	1.033	1.8	0.029
Chronic renal failure	1.123	0.795	1.585	0.511
HIV infection	0.564	0.229	1.386	0.212
Cirrhosis	2.19	1.438	3.335	<0.001
Immunosuppression	1.305	1.007	1.692	0.044
Fixed-effects, constant within clusters				
Type of hospital				
Non-university	Ref			
University/Academic	0.901	0.686	1.183	0.453
ICU volume in 2011				
<250	Ref			
250–499	0.535	0.338	0.847	0.008
500–749	0.565	0.369	0.866	0.009
750+	0.47	0.293	0.755	0.002
ICU speciality				
Surgical	Ref			
Medical	0.561	0.33	0.951	0.032
Mixed	0.571	0.385	0.848	0.006
Others	0.685	0.41	1.143	0.146
Staffed ICU beds				
<15	Ref			
15+	1.172	0.89	1.544	0.257
GNI				
Low and lower middle	Ref			
Upper middle	1.175	0.717	1.926	0.516
High	0.643	0.425	0.97	0.036
Random-effects				
Country				
Variance (se) 0.06 (0.04)				
p-value 0.150				
Hospital within country				
Variance (se) 0.29 (0.09)				
p-value 0.001				

OR – odds ratio, SAPS - ER – emergency room, COPD – chronic obstructive pulmonary disease, NYHA – New York Heart Association, SOFA – sequential organ failure assessment, SAPS – simplified acute physiology score, GNI – gross national income.

Importantly, chronological age is not per se the sole reason for worse outcomes in older patients; the greater likelihood of comorbidity and greater degree of frailty also impact on outcomes in these patients [26,27]. Studies in non-sepsis populations have reported that the severity of acute illness and chronic comorbidities are predictors of ICU and hospital mortality in older patients [28,29]. Bagshaw and colleagues performed an analysis on over 15,000 patients aged >80 years and reported that patients with comorbid illness, a nonsurgical admission, higher acuity of illness, need for mechanical ventilation, and evidence of acute kidney injury had lower survival [16]. In trauma patients, Joseph et al. [26] reported that frail older (≥65 years) patients, i.e., those with a Trauma-Specific Frailty Index >0.27, had a greater odds ratio of death at 6 months than non-frail patients (OR 1.1; 95% CI, 1.04–4.7). In a population of older people (mean age 83.5 ± 5.4 years), Ferrante et al. [30] reported that patients with pre-ICU admission frailty had 180-day mortality rates more than twice as high as those without pre-admission frailty (54.5 vs 26.3%, $p < .001$). A recent study also reported that only one quarter of patients aged 80 years or above had returned to baseline levels of physical function at 1 year after ICU discharge [31]. Factors associated with survival and subsequent return to function included lower comorbidity, frailty and severity of illness scores. This underscores the need to consider physiological rather than chronological age in the decisions to prognosticate older patients who are critically ill. Importantly, Hamel and colleagues reported that age-related mortality was not related to the fact that older patients received less intensive therapy [32].

Our results showed that an abdominal site of infection was more common in older patients with sepsis than in younger patients. These findings are consistent with data from a one-day point prevalence study by Dimopoulos et al. [21], who showed that abdominal infections were more frequent in patients aged >85 years than those <45. Unlike our results, Dimopoulos et al. also reported other differences in patterns of infection, with those aged 85 and older having fewer bloodstream infections than those <75 and fewer central nervous system infections than those <65 years [21].

Microbiological culture results were positive in approximately 70% of our patients with sepsis, with slightly lower percentages in the ≤50 and > 80 age groups. The patterns of isolated microorganisms in our cohort were similar across the age groups, with Gram-negative organisms most frequently implicated in all patients. By contrast, Dimopoulos et al. reported that Gram-negative microorganisms were more frequently isolated in those aged 85 and older than in other groups [21]. In a large cohort of patients in Taiwan, Lee et al. [8] reported that systemic fungal infection was disproportionately higher in the oldest old (>80 years) and older (>65 years) patients than in younger groups. We were not able to confirm these findings.

The size of our study is a major strength, with nearly 3000 patients included prospectively. Moreover, the audit included many variables, allowing adjustment for a large number of factors. However, it also has limitations. Participation in the ICON audit was voluntary, thus many centers, especially non-academic ones, did not participate in data collection and the sample may not be representative of all ICU patients. For the same reason the epidemiologic data may not be a true representation of individual countries and, as a large proportion of the data was collected in Europe, generalizability of these results to other areas of the world may be limited. Although we adjusted for severity of illness, organ failures, and other variables, we cannot discount the possible influence of unmeasured factors, such as frailty and functional status prior to ICU admission. Similarly, although we controlled for the presence of comorbid conditions in our multivariable analysis we were not able to assess the severity of any comorbidity. We included patients with life-sustaining treatment limitation decisions, although these were more frequent in older patients and likely had some impact

on mortality rates. We have no data on actual reasons for death so cannot comment further on this aspect. We also did not have information on family or physician preferences surrounding the provision of care and therefore cannot discount selection bias. Because of the study design, we may have missed information regarding some processes of care in older patients, including but not limited to refusal of ICU admission, availability of geriatric care (consultations and facilities), more difficult diagnosis of sepsis in elderly patients who often have less typical presentation, possible increased occurrence of resistant organisms in elderly patients coming from care facilities or already treated with multiple antibiotics, and different choices of therapies because of age.

5. Conclusions

The majority of ICU patients with sepsis around the globe are over the age of 50 and 12% are >80 years of age. The risk of dying from sepsis increases considerably with age with the hospital mortality for patients >80 years of age almost twice that of patients ≤50 years of age.

Author contributions

KK, XW, UJ, JSV, RK, ML, RN, LEF, YS, JLV participated in the original ICON study. KK and JLV designed the current study. KK collected, analyzed and interpreted the data, and drafted the manuscript. XW, UJ, JSV, RK, ML, RN, LEF, YS, JLV reviewed the article for critical content. All authors read and approved the final text.

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Conflicts of interest

The authors have no conflicts of interest to declare related to this article.

Appendix A. 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); Gray'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).

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

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); 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); United Christian Hospital of Hong Kong SAR (K Lee).

Indonesia: Anestesi (M Wijanti); Pku Muhammadiyah Bantul, Yogyakarta (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 (O Nishida); 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 Anesthesiology and Critical Care Research Center (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-Medero).

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 (DJ Hawkins); 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 and Central 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); Hospital San Jose TEC Monterrey (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, México (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 110,062 (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); Kalinga 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).

Western 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 (P Gadisseux); 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 (H Spapen); 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, Limoges (B François); 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 (B Floccard); 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).

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Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.02.015.

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