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Association between timing of intubation and outcome in critically ill patients: A secondary analysis of the ICON audit

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ABSTRACT

Purpose: The optimal timing of endotracheal intubation in critically ill patients requiring invasive mechanical ventilation remains undefined.
Material and methods: In a secondary analysis of the large, prospective ICON database, we used a piecewise proportional hazards model to compare outcomes in patients who underwent intubation early (within two days after intensive care unit [ICU] admission) or later.
Results: After excluding 5340 patients already intubated on admission or with therapeutic limitation, 4729 patients were analyzed, of whom 4074 never underwent intubation. Of the remaining 655 patients, 449 underwent intubation early and 206 later. Despite similar severity scores on ICU admission, unadjusted ICU (27.6 vs. 18.2%) and hospital (33.3 vs. 23.4%) mortality rates were higher in patients intubated later than in those intubated earlier, as were ICU (9 [5–16] vs. 4 [2–9] days) and hospital (24 [9–35] vs. 13 [7–24] days) lengths-of-stay (all $p < 0.001$). After adjustment, the hazard for ICU and hospital death was significantly greater >10 days after ICU admission for patients intubated late.
Conclusions: In this large cohort of critically ill patients requiring intubation, intubation >2 days after admission was associated with increased mortality later in the hospital course.

1. Introduction

The optimal timing of endotracheal intubation in critically ill patients requiring invasive mechanical ventilation remains undefined. In a recent prospective multicenter study in patients with severe acute hypoxemic respiratory failure (ARF) [1], two thirds of the patients developed acute respiratory distress syndrome (ARDS), most of them (93%) on day 1 or 2 after intensive care unit (ICU) admission. Among the patients with ARDS, 11% never underwent intubation and were managed with non-invasive ventilation. Patients with ARDS who were initially treated with invasive mechanical ventilation (85%) had different degrees of severity of ARDS (mild, moderate, and severe). Disease severity may, therefore, not be the only factor involved in the decision to intubate. Indeed, endotracheal intubation has its own risks [2] and, aside from obvious emergent need for intubation, invasive ventilatory support is more commonly used in patients in whom non-invasive measures are not possible or fail [3-5], with a tendency to prefer high flow supplemental oxygen to non-invasive ventilation, especially in immunocompromised hosts [6].

Abbreviation: ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; COPD, chronic obstructive pulmonary disease; CNS, central nervous system; ICON, Intensive Care Over Nations audit; ICU, intensive care unit; IQR, interquartile range; NYHA, New York Heart Association; RRT, renal replacement therapy; SD, standard deviation; SOFA, sequential organ failure assessment score; SAPS II, Simplified Acute Physiology Score II.

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Whether or not delaying intubation could impact outcome in critically ill patients is not well defined. Delayed intubation can contribute to ARF in case of aspiration [7]. Failure of non-invasive ventilation is predictable, especially in patients with ARF combined with shock, marked metabolic acidosis, high illness severity scores, and greater degrees of hypoxemia [8]. A high expired tidal volume in patients receiving non-invasive ventilation has also been reported as a predictor of failure [9]. Notwithstanding the risk of intubation itself, which may include cardiac arrest, tracheal injury, ventilator-associated complications and the need for sedation [10], early intubation may exert a protective effect by controlling tidal volume, plateau pressure [11], loaded breathing [12,13] and by supporting myocardial function (decreased left ventricular afterload and better oxygen supply), while influencing body position, and limiting or preventing compression atelectasis especially in obese patients [14].

The goal of this study was to investigate the impact of the timing of endotracheal intubation on outcome, including survival and length of stay, in a large cohort of critically ill patients. Our hypothesis was that patients would have poorer outcomes if intubation was delayed.

2. Materials and methods

The Intensive Care Over Nations (ICON) audit prospectively collected data on 10,069 patients in 730 ICUS from 84 countries around the world (see Supplemental Appendix for list of participating centers). Institutional review board approval was obtained by the participating institutions according to local ethic committee regulations. All adult (>16 years) patients admitted to the ICU between May 8, 2012 and May 18, 2012 were included except for planned admissions for routine postoperative surveillance for <24 h after uncomplicated surgery. Data collected included epidemiological features and daily assessment of organ function and support [15]. Data were collected daily for a maximum of 28 days in the ICU. Patients were followed up for outcome until death, hospital discharge, or for 60 days.

In this secondary analysis of the ICON audit database, we compared patients who underwent endotracheal intubation early - within two calendar days of the ICU admission - to those who underwent intubation later. Patients who were already intubated on the day of ICU admission or who had a decision to withhold/withdraw life-sustaining measures at any time during their ICU stay were excluded. The primary outcomes of interest were ICU and hospital mortality. Secondary outcomes included ICU and hospital lengths of stay. We also performed a subgroup analysis of patients with sepsis, defined as the presence of infection with the concomitant occurrence of at least one sepsis-related organ failure.

3. Statistical methods

For population characteristics, results are expressed as means with standard deviations, medians with interquartile ranges, or numbers and percentages. Difference testing between groups was performed using ANOVA, Kruskal-Wallis test, Student's *t*-test, Mann-Whitney test, χ^2 test, or Fisher's exact test, as appropriate. We used Kaplan-Meier curves and the two-stage procedure test by Qiu and Sheng [16] to compare ICU and hospital survival rates in the two groups of patients who underwent intubation. We performed a sensitivity analysis by varying the timing of intubation from 2 to 1 calendar days in the whole population. To determine the adjusted risk of death according to early or later intubation during the ICU stay, we developed a piecewise proportional hazards model with intubation (early vs. late) and propensity score (linear term or in quartiles) to identify patients with a similar probability of early intubation as covariates in the model [17]. The optimal "change point" (approximate time at which the survival curves cross) for the hazard ratio was estimated as the time value that yielded the largest log partial likelihood of the fitted model [18,19]. The propensity score, that is the probability of undergoing intubation early, was calculated by multiple logistic regression using age, sex, Simplified Acute Physiology Score (SAPS) II and Sequential Organ Failure Assessment (SOFA) subscores, excluding the respiratory subscore, on admission to the ICU, hospital length of stay prior to ICU admission, type and sources of admission, the need for renal replacement therapy (RRT) on admission to the ICU, comorbidities, and the presence of sepsis on admission (see Supplemental Table 1). We also adjusted for ICU and hospital-related organizational factors including type of hospital, hospital bed capacity, ICU specialty, number of staffed ICU beds, and the gross national income (GNI). Data were analyzed using IBM SPSS statistics software, version 23 for windows (IBM, Armonk, NY) and R software, version 3.2.3 (CRAN project). All reported p-values are two-sided. A p value of <0.05 was considered to indicate statistical significance.

4. Results

Of the 10,069 patients included in ICON, we excluded 5340 patients who were already intubated on the day of admission or had a therapeutic limitation order during the ICU stay; these patients were admitted from various sources (emergency room 33.9%, floor 26.4%, operating room 22.7%, other hospital 10.2% and unknown 6.9%). This left 4729 patients for analysis, of whom 4074 never underwent intubation. Of the 655 patients who underwent intubation, this occurred within 2 days of the ICU admission in 449 and after 2 days in 206 (Fig. 1). Demographic and clinical data for the patients according to early or later intubation are shown in Table 1. Patients who underwent intubation late were more likely to be admitted from the hospital floor than those who underwent intubation earlier who were more likely to be admitted from the emergency room or by ambulance (Table 1).

Despite similar severity scores on ICU admission, ICU (27.6 vs. 18.2%) and hospital (33.3 vs. 23.4%) mortality rates were higher in patients who underwent intubation late than in those who underwent intubation earlier (both $p < 0.01$), as were ICU (9 [5–16] vs. 4 [2–9] days) and hospital (24 [9–35] vs. 13 [7–24] days) lengths of stay (both $p < 0.001$). In patients who underwent intubation late, the hazard of ICU and hospital death was significantly lower <10 days after ICU admission and significantly greater >10 days after ICU admission (Fig. 2A, B, Table 2). These results remained after adjustment (Table 2).

In a sensitivity analysis differentiating those intubated within one day and those intubated later, even though severity scores were slightly lower, there was a trend towards higher ICU (23.1 vs. 18.8%) and hospital (28.9 vs. 23.5%) mortality rates in those intubated later (Supplemental Table 2), and ICU (7 [4–13] vs. 4 [2–9] days) and hospital (15 [9–29] vs. 12 [6–24] days) lengths of stay were longer (both $p < 0.01$).

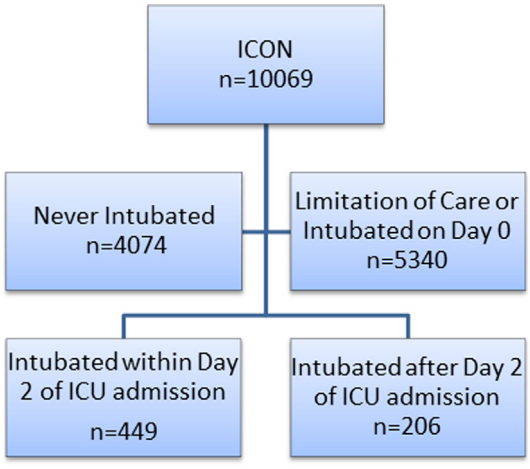

Fig. 1. Flow diagram of patients.

Table 1
Demographic and clinical characteristics of ICU patients according to intubation status.

Characteristic	Intubated within day 2 of ICU admission (n = 449)	Intubated after day 2 of ICU admission (n = 206)	p-Value
Age, year, mean ± SD	60.0 ± 17.2	61.2 ± 17.2	0.442
Sex, male (%)	257 (57.8)	120 (59.4)	0.693
SAPS II score, mean ± SD	41.3 ± 14.9	39.5 ± 14.9	0.153
SOFA score on admission, mean ± SD	5.9 ± 3.6	5.7 ± 3.5	0.485
LOS before ICU, day, median [IQR]	0 [0–2]	1 [0–5]	0.078
Type of admission, n (%)			0.456
Surgical (non-trauma)	122 (28.2)	49 (24.9)	
Medical	284 (65.7)	133 (67.5)	
Trauma	24 (5.6)	12 (6.1)	
Other	2 (0.5)	3 (1.5)	
Source of admission, n (%)			0.014
Other hospital	48 (10.7)	24 (11.7)	
ER/ambulance	183 (40.8)	63 (30.6)	
OR/recovery room	46 (10.2)	13 (6.3)	
Hospital floor	147 (32.7)	88 (42.7)	
Other	25 (5.6)	18 (8.7)	
Comorbidities, n (%)			
COPD	76 (16.9)	32 (15.5)	0.656
Cancer	54 (12)	21 (10.2)	0.494
Metastatic cancer	15 (3.3)	4 (1.9)	0.322
Hematologic cancer	11 (2.4)	6 (2.9)	0.729
Insulin-requiring diabetes mellitus	52 (11.6)	17 (8.3)	0.198
Heart failure (NYHA III/IV)	38 (8.5)	17 (8.3)	0.928
Chronic renal failure	48 (10.7)	28 (13.6)	0.282
HIV infection	3 (0.7)	2 (1.0)	0.652
Cirrhosis	12 (2.7)	9 (4.4)	0.253
Immunosuppression	15 (3.3)	12 (5.8)	0.138
Steroid therapy	15 (3.3)	6 (2.9)	0.773
Chemotherapy	16 (3.6)	6 (2.9)	0.668
Renal replacement therapy on admission	33 (7.3)	14 (6.8)	0.799
Sepsis on admission	18 (17.4)	39 (18.9)	0.628
Type of organ dysfunction, n (%) (alone or in combination)			
Respiratory	–	–	–
Coagulation	21 (4.7)	15 (7.3)	0.174
Hepatic	66 (14.7)	30 (14.6)	0.963
CNS	55 (12.2)	16 (7.8)	0.087
Renal	123 (27.4)	43 (20.9)	0.075
Cardiovascular	88 (19.6)	39 (18.9)	0.841
No. of organ dysfunctions, n (%)			0.499
0 organ	50 (11.1)	18 (8.7)	
1 organs	105 (23.4)	56 (27.2)	
2 organs	91 (20.3)	37 (18.0)	
3 organs	100 (22.3)	40 (19.4)	
>3 organs	103 (22.9)	55 (26.7)	
ICU LOS, day, median [IQR]	4 [2–9]	9 [5–16]	<0.001
Hospital LOS, day, median [IQR]	13 [7–24]	24 [9–35]	<0.001
ICU mortality, n (%)	80 (18.2)	56 (27.6)	0.007
Hospital mortality, n (%)	100 (23.4)	65 (33.3)	0.008

In the subgroup of patients with sepsis (Supplemental Table 3), there was a trend towards higher ICU (35.9 vs. 23.4%) and hospital (45.9 vs. 26.3%) mortality rates in patients intubated late.

5. Discussion

In this large, contemporary, prospective cohort of ICU patients, patients who underwent intubation late had higher ICU and hospital mortality rates and longer ICU and hospital lengths of stay than patients intubated early. After adjustment for their probability of being intubated early in the course of their critical illness, the hazard for ICU and hospital death was significantly lower before 10 days for patients who underwent intubation late and significantly greater after 10 days.

Intubation and invasive mechanical ventilation may impact on outcomes in critically ill patients. Advantages of intubation include airway protection and the ability to insure effective ventilation [20].

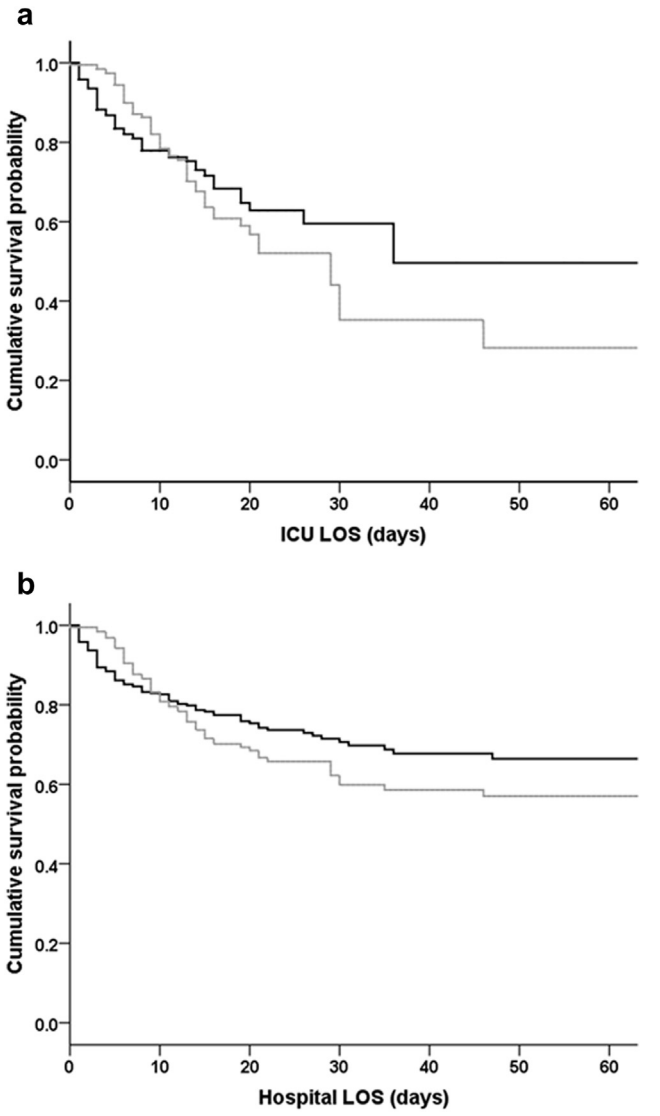

Fig. 2. Kaplan-Meier curves of ICU (A) and hospital (B) mortality according to the timing of intubation. Gray line: intubation performed >2 days after ICU admission; black line: intubation performed >2 days after ICU admission. Both p = 0.025 (two-stage procedure test).

Disadvantages include airway injury, hemodynamic instability and ventilation-associated complications [2]. Moreover, the optimal timing of intubation remains controversial. In the present study, the crossing of the Kaplan-Meier survival curves indicated non-proportional hazards suggestive of a heterogeneous population within each group [21,22]. Compared to earlier intubation, later intubation was associated with a lower hazard of death <10 days after ICU admission and a greater hazard of death >10 days after admission. Does this suggest earlier intubation is better than later intubation? The answer depends on the time scale. In this varied population, there were likely patients who benefited from late intubation and others who did not.

Our findings are consistent with those from a recent post hoc analysis of a large database of patients with septic shock [23]. In that study, early intubation (within 12 h) was more frequently performed in patients with more severe acute disease, a pulmonary site of infection, and no immunosuppression. Compared to patients intubated early, patients with delayed intubation had fewer days alive without organ support by day 28. Of note also, centers with the highest frequency of early intubation had higher mortality rates compared to ICUs with middle frequency of early intubation, suggesting that practice variation may also impact outcomes. In another recent study in patients with ARDS,

Table 2
Prediction model, using the timing of intubation as a cut-off.

Model		ICU mortality		Hospital mortality	
		HR (95% CI)	p-Value	HR (95% CI)	p-Value
Unadjusted	Before day 10	0.61 (0.39–0.96)	0.03	0.90 (0.59–1.37)	0.62
	After day 10	2.37 (1.23–4.59)	0.01	1.95 (1.19–3.20)	0.008
PS-adjusted (linear term)	Before day 10	0.65 (0.41–1.03)	0.07	0.92 (0.60–1.42)	0.71
	After day 10	2.57 (1.32–5.02)	0.006	1.99 (1.21–3.29)	0.00
PS-adjusted (quartiles)	Before day 10	0.65 (0.41–1.03)	0.06	0.94 (0.61–1.44)	0.78
	After day 10	2.53 (1.30–4.92)	0.006	2.03 (1.23–3.34)	0.005

HR: hazard ratio from the piecewise proportional hazards model for intubation after day 2 relative to intubation within day 2; PS: propensity score.

23% did not require intubation and mechanical ventilation on the first day of ARDS diagnosis. Among these patients, late intubation (after day 1) was also associated with worse outcome when compared to those intubated early or those who never required intubation [24].

Mechanistically, our results suggest that the timing of intubation in patients worldwide is apposite to clinical requirements [25]. When factors related to the use of early intubation were accounted for, the hazard for death was higher >10 days after ICU admission in those intubated late. The reason for this difference is not clear. Both groups, early and late intubation, were similar at admission, including in terms of severity and organ failure, with the exception that patients who underwent intubation late were more often admitted from the floor and less often from the emergency room than patients intubated early. It is, nevertheless, likely that the two groups were heterogeneous. The early group may have been composed of subgroups with higher mortality in the earlier course or lower mortality in the later course. One could also consider that the late group also included subgroups with lower earlier mortality (e.g., intubation for airway protection) or higher later mortality (e.g., ARDS with diffuse alveolar damage). Whether a failure to rescue with delayed diagnosis and/or delayed stabilization of a critically ill patient (e.g., with sepsis) may have contributed to the higher mortality is beyond the scope of the data collected in the ICON audit. Our results also suggest that endotracheal intubation and mechanical ventilation are performed frequently, with a large proportion of cases occurring within the first 24 to 48 h of ICU admission. Thus clinicians should be vigilant early in the course of critical illness and cognizant of rapid deterioration with the need to quickly move to invasive mechanical ventilation if required.

This study has several strengths. It uses data from a large, multicenter, prospective, observational study, increasing its generalizability. We used a piecewise proportional hazards model with intubation (early vs. late) and propensity score (linear term or in quartiles) to identify patients with a similar probability of early intubation as covariates in the model. Despite its strengths, we acknowledge several limitations to our study. The first is its observational nature. Even though we used robust modeling techniques, we cannot discount that unmeasured confounding may have biased our results and unbalanced our cohorts. Obviously, the decision to start invasive mechanical ventilation was left to the discretion of the ICU team, but we have no details regarding the indications for intubation. We are also unable to discern whether intubation was emergent or elective in anticipation of a deteriorating clinical course, or for a need of a diagnostic technique (e.g., bronchoscopy, computed tomography, esophagogastroduodenoscopy…). Knowledge about urgency would have allowed us to better control for confounding by indication. Second, the precision of the timing of intubation was limited to calendar days and a more refined distribution of the timeframe of intubation could not be established. Third, we have no details about the underlying ARF, such as respiratory rates, pattern and work of breathing, use and settings of non-invasive ventilation or high flow oxygen, use of adjuncts to respiratory support such as pulmonary vasodilators, depth of sedation or compliance with processes known to affect outcomes from ARF. These elements would have added to the robustness of our statistical models.

6. Conclusions

In this large cohort of critically ill patients, later intubation (after 2 days) was associated with a greater hazard of death after 10 days of ICU stay than early intubation. Although only hypothesis generating, this suggests that the timing of intubation may impact outcomes beyond the benefit of intubation itself. Intubation is usually performed when clinically indicated and is one of many therapies along a spectrum of modalities for respiratory support, which also includes high flow oxygen and non-invasive ventilation. Our data suggest that the timing of intubation may itself be a prognostic factor and close monitoring of critically ill patients with frequent reassessment for the need for intubation may be warranted, especially after the first 48 h of ICU admission.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2017.06.010.

Author contributions

PRB, RN, IML, YS, SJ, BF, XW, RW, JLV participated in the original ICON study. PRB design the current study, collected, analyzed and interpreted the data, and drafted the manuscript.

OG contributed to the design of the study and interpretation of the data. RK helped collect and interpret the data. RN, IML, YS, SJ, BF, XW, RW, JLV reviewed the article for critical content. All authors read and approved the final text.

Conflicts of interest

The authors have no conflicts of interest to declare relevant to the article.

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References

[1] Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016;315:788–800.
[2] Jaber S, Amraoui J, Lefrant JY, Arich C, Cohendy R, Landreau L, et al. Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. Crit Care Med 2006;34:2355–61.
[3] Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372:2185–96.
[4] Jaber S, Lescot T, Futier E, Paugam-Burtz C, Seguin P, Ferrandiere M, et al. Effect of noninvasive ventilation on tracheal reintubation among patients with hypoxemic respiratory failure following abdominal surgery: a randomized clinical trial. JAMA 2016;315:1345–53.
[5] Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA 2016;315:2435–41.
[6] Frat JP, Ragot S, Girault C, Perbet S, Prat G, Boulain T, et al. Effect of non-invasive oxygenation strategies in immunocompromised patients with severe acute respiratory failure: a post-hoc analysis of a randomised trial. Lancet Respir Med 2016;4:646–52.

[7] Gajic O, Dabbagh O, Park PK, Adesanya A, Chang SY, Hou P, et al. Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. Am J Respir Crit Care Med 2011;183:462–70.
[8] Rana S, Jenad H, Gay PC, Buck CF, Hubmayr RD, Gajic O. Failure of non-invasive ventilation in patients with acute lung injury: observational cohort study. Crit Care 2006;10:R79.
[9] Carteaux G, Millan-Guilarte T, de Prost N, Razazi K, Abid S, Thille AW, et al. Failure of noninvasive ventilation for de novo acute hypoxemic respiratory failure: role of tidal volume. Crit Care Med 2016;44:282–90.
[10] Curley GF, Laffy JG, Zhang H, Slutsky AS. Noninvasive respiratory support for acute respiratory failure-high flow nasal cannula oxygen or non-invasive ventilation? J Thorac Dis 2015;7:1092–7.
[11] Nieman GF, Gatto LA, Bates JH, Habashi NM. Mechanical ventilation as a therapeutic tool to reduce ARDS incidence. Chest 2015;148:1396–404.
[12] Vassilakopoulos T, Hussain SN. Ventilatory muscle activation and inflammation: cytokines, reactive oxygen species, and nitric oxide. J Appl Physiol (1985) 2007;102:1687–95.
[13] Nierat MC, Demiri S, Dupuis-Lozeron E, Allali G, Morelot-Panzini C, Similowski T, et al. When breathing interferes with cognition: experimental inspiratory loading alters timed up-and-go test in normal humans. PLoS One 2016;11:e0151625.
[14] Hibbert K, Rice M, Malhotra A. Obesity and ARDS. Chest 2012;142:785–90.
[15] Vincent JL, Marshall JC, Namendys-Silva SA, Francois B, Martin-Loeches I, Lipman J, et al. Assessment of the worldwide burden of critical illness: the Intensive Care Over Nations (ICON) audit. Lancet Respir Med 2014;2:380–6.
[16] Qiu P, Sheng J. A two-stage procedure for comparing hazard rate functions. J R Stat Soc B Methodol 2008;70:191–208.
[17] Kitsios GD, Dahabreh IJ, Callahan S, Paulus JK, Campagna AC, Dargin JM. Can we trust observational studies using propensity scores in the critical care literature? A systematic comparison with randomized clinical trials. Crit Care Med 2015;43:1870–9.
[18] Matthews DE, Farewell VT. On testing for a constant hazard against a change-point alternative. Biometrics 1982;38:463–8.
[19] Liang KY, Self SG, Liu XH. The Cox proportional hazards model with change point: an epidemiologic application. Biometrics 1990;46:783–93.
[20] Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372:747–55.
[21] Li H, Han D, Hou Y, Chen H, Chen Z. Statistical inference methods for two crossing survival curves: a comparison of methods. PLoS One 2015;10:e0116774.
[22] Logan BR, Klein JP, Zhang MJ. Comparing treatments in the presence of crossing survival curves: an application to bone marrow transplantation. Biometrics 2008;64:733–40.
[23] Delbove A, Darreau C, Hamel JF, Asfar P, Lerolle N. Impact of endotracheal intubation on septic shock outcome: a post hoc analysis of the SEPSISPAM trial. J Crit Care 2015;30:1174–8.
[24] Kangelaris KN, Ware LB, Wang CY, Janz DR, Zhuo H, Matthay MA, et al. Timing of intubation and clinical outcomes in adults with acute respiratory distress syndrome. Crit Care Med 2016;44:120–9.
[25] Bellani G, Laffey JG, Pham T, Madotto F, Fan E, Brochard L, et al. Non-invasive ventilation of patients with ARDS: insights from the LUNG SAFE Study. Am J Respir Crit Care Med 2016 (Epub ahead of print).

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

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

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

Diseases (D Filipescu); Fundeni Clinical Institute (G Droc); Galati Hospital (M Lupu); Inbi "Prof. Dr. Matei Bals" (A Nica); Institute of Pulmonology Marius Nasta (R Stoica); Institutul Clinic Fundeni (D Tomescu); Sfantul Pantelimon Hospital (D Constantinescu); Spitalul Cf 2 Bucuresti (G Valcoreanu Zbaganu); "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 (Y Shimomura); Japanese Red Cross Maebashi Hospital (D Miyazaki); Jichi Medical University Hospital (S Nunomiya); Jikei University School of Medicine (S Uchino); Kimitsu Chuo Hospital (N Kitamura); Kochi Medical School (K Yamashita); Kyoto Prefectural University of Medicine (S Hashimoto); Nara Medical University Hospital (H Fukushima)
Malaysia: Hospital Sultanah Nur Zahirah, Kuala Terengganu, Terengganu, (N Nik Adib); Kuala Lumpur Hospital (L Tai); Queen Elizabeth Hospital 2 (B Tony)
Philippines: Cebu Velez General Hospital (R Bigornia); Chong Hua Hospital (R Bigornia); Perpetual Succour Hospital (R Bigornia); The Medical City (J Palo)
Singapore: Alexandra Hospital (S Chatterjee); National University Health System (B Tan); Singapore General Hospital (A Kong); Tan Tock Seng Hospital (S Goh)
Taiwan: National Taiwan University Hospital (C Lee)
Thailand: Maharaj Nakorn Chiangmai Hospital, Chiaingmai University (C Pothirat); Prince of Songkla University (B Khwannimit); Ramathibodi Hospital (P Theerawit); Ramathibodi Hospital, Somdech Phra Debaratana Medical Centre (P Pornsuriyasak); Siriraj Hospital, Mahidol University (A Piriyapatsom)

Middle East
Egypt: Cairo University (A Mukhtar); Demerdash Surgical Intensive Care Unit (Dsicu); Ain Shams Faculty of Medicine (A Nabil Hamdy); Zaitoun Specialized Hospital (H Hosny)
Iran: Gums (A Ashraf); Imam Hossein Hospital, Sbums (M Mokhtari); Imamreza Hospital (S Nowruzinia); Laleh Hospital (A Lotfi); Shiraz University of Medical Sciences, SACRC (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 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 110062 (A Dewan); Bombay Hospital Institute of Medical Sciences (P Amin); Care Hospital (S Samavedam); Cims Hospital (B Shah); Columbiaasia Hospital, Mysore (D Gurupal); Dispur Hospitals (B Lahkar); Fortis Hospital (A Mandal); Fortis Hospital (Noida) (M Sircar); Fortis-Escorts Hospital, Faridabad, India (S Ghosh); Ganga Medical Centre & Hospital P Ltd. (V Balasubramani); Hinduja Hospital (F Kapadia); KDAH (S Vadi); Kerala Institute of Medical Sciences (Kims, RMCC) (K Nair); Kerala Institute of Medical Sciences (Kims, DTEM) (S Tripathy); Kovai Medical Centre and Hospital (S Nandakumar); Medanta The Medicity, Gurgaon (J Sharma); Medica Superspecialty Hospitals (A Kar); Metro Heart Institute with Multispeciality (S Jha); Ruby Hall Pune (K Zirpe/Gurav); Saifee Hospital (M Patel); Spandan Multispeciality Hospital (A Bhavsar); Tata Main Hospital (D Samaddar); Tata Memorial Hospital (A Kulkarni)
Pakistan: Aga Khan University (M Hashmi); Hearts International Hospital (W Ali); Liaquat National Hospital (S Nadeem)
Sri Lanka: Sri Jayewardenepura General Hospital (K Indraratna)

West Europe
Andorra: Hospital Nostra Senyora De Meritxell (A Margarit)
Austria: Akh Wien (P Urbanek); Allgemeines Und Orthopädisches Landeskrankenhaus Stolzalpe (J Schlieber); Barmherzige Schwestern Linz (J Reisinger); General Hospital Braunau (J Auer); Krankenhaus D. Barmherzigen Schwestern Ried I.I. (A Hartjes); Krankenhaus Floridsdorf (A Lerche); LK Gmünd-Waidhofen/Thaya-Zwettl, Standort Zwettl (T Janous); LKH Hörgas-Enzenbach (E Kink); LKH West (W Krahulec); University Hospital (K Smolle)
Belgium: AZ Groeninge Kortrijk (M Van Der Schueren); AZ Jan Palfijn Gent (P Thibo); AZ Turnhout (M Vanhoof); Bracops Anderlecht (I Ahmet); Centre Hospitalier Mouscron (G Philippe); CH Peltzer La Tourelle (P Dufaye); Chirec Edith Cavell (O Jacobs); CHR Citadelle (V Fraipont); CHU Charleroi (P Biston); Chu Mont-Godinne (A Dive); CHU Tivoli (Y Bouckaert); Chwapi (E Gilbert); Clinique Saint-Pierre Ottignies (B Gressens); Clinique-Maternité Sainte Elisabeth (E Pinck); Cliniques De L'Europe - St-Michel (V Collin); Erasme University Hospital (JL Vincent); Ghent University Hospital (J De Waele); Moliere Hospital (R Rimachi); Notre Dame (D Gusu); Onze Lieve Vrouw Ziekenhuis, Aalst (K De Decker); Ixelles Hospital (K Mandianga); Sint-Augustinus (L Heytens); St Luc University Hospital (UCL) (X Wittebole); UZ

Brussel (S Herbert); Vivalia Site De Libramont (V Olivier); VZW Gezondheidszorg Oostkust Knokke-Heist (W Vandenheede); ZNA Middelheim (P Rogiers)
Denmark: Herning Hospital (P Kolodzeike); Hjoerring Hospital (M Kruse); Vejle Hospital (T Andersen)
Finland: Helsinki University Central Hospital (V Harjola); Seinäjoki Central Hospital (K Saarinen)
France: Aix Marseille Univ, Hôpital Nord (M Leone); Calmette Hospital, Lille (A Durocher); Centre Hospitalier de Dunkerque (S Moulront); Centre Hospitalier Lyon Sud (A Lepape); Centre Hospitalo-Universitaire Nancy-Brabois (M Losser); CH Saint Philibert, Ghicl, Lille (P Cabaret); CHR De Dax (E Kalaitzis); CHU Amiens (E Zogheib); CHU Dijon (P Charve); CHU Dupuytren (B Francois); CHU Nîmes (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)
Iceland: Landspitali University Hospital (A Moller); Landspitali University Hospital Fossvogur (S Stefansson)

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

Hospital Novo Mesto (L Kosec); Oncological Institute (M Kerin Povšic); Ukc Maribor (I Osojnik); University Clinic of Respiratory and Allergic Diseases (V Tomic); University Clinical Centre Maribor (A Sinkovic)
Spain: CH Salamanca (J González); Clinic Hospital (E Zavala); Complejo Hospitalario De Jaén (J Pérez Valenzuela); Complejo Hospitalario De Toledo (L Marina); Complexo Hospitalario Universitario De Ourense (P Vidal-Cortés); Complexo Hospitalario Universitario De Vigo (P Posada); Corporación Sanitaria Parc Tauli (A Ignacio Martin-Loeches); Cruz Roja Hospital (N Muñoz Guillén); H Vall Hebron (M Palomar); HGGC Dr Negrín (J Sole-Violan); Hospital Clinic (A Torres); Hospital Clinico San Carlos (M Gonzalez Gallego); Hospital Clínico Universitario De Valencia (G Aguilar); Hospital Clínico Universitario Lozano Blesa (R Montoiro Allué); Hospital Clinico Valencia (M Argüeso); Hospital De La Ribera (M Parejo); Hospital De Sagunto (M Palomo Navarro); Hospital De San Juan De Alicante (A Jose); Hospital De Torrejon De Ardoz (N Nin); Hospital Del Mar (F Alvarez Lerma); Hospital Del Tajo (O Martinez); Hospital General Universitario De Elche (E Tenza Lozano); Hospital General Universitario Gregorio Marañon (S Arenal López); Hospital General Universitario Gregorio Marañon (M Perez Granda); Hospital General Universitario Santa Lucía (S Moreno); Hospital Germans Trias I Pujol (C Llubia); Hospital Infanta Margarita (C De La Fuente Martos); Hospital Infanta Sofia (P Gonzalez-Arenas); Hospital J.M. Morales Meseguer (N Llamas Fernández); Hospital J.M. Morales Meseguer (B Gil Rueda); Hospital Marina Salu. Denia. Alicante. (I Estruch Pons); Hospital Nuestra Señora Del Prado, Talavera De La Reina, Toledo. España (N Cruza); Hospital San Juan De Dios Aljarafe (F Maroto); Hospital Sas of Jerez (A Estella); Hospital Son Llatzer (A Ferrer); Hospital Universitario Central De Asturias (L Iglesias Fraile); Hospital Universitario Central De Asturias (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)