

## Supplementary Appendix

### **Patient characteristics, clinical course and factors associated to ICU mortality in critically ill patients infected with SARS-CoV-2 in Spain: a prospective, cohort, multicentre study.**

#### **METHODS**

##### **Outcome definitions**

Medical and infectious complications followed standard definition

##### -Medical complications:

1. Acute respiratory distress syndrome. According to Berlin definition.<sup>1</sup>

Mild: PaO<sub>2</sub>/FiO<sub>2</sub> between 200-300

Moderate: PaO<sub>2</sub>/FiO<sub>2</sub> between 100-200

Severe: PaO<sub>2</sub>/FiO<sub>2</sub> > 100

A PEEP level of at least 5 cm of water was not required to allow classifying patients receiving HFNC or conventional facemask.

2. Shock.<sup>3</sup>

Shock is best defined as a life-threatening, generalized form of acute circulatory failure associated with inadequate oxygen utilization by the cells. It is a state in which the circulation is unable to deliver sufficient oxygen to meet the demands of the tissues, resulting in cellular dysfunction. The result is cellular dysoxia, i.e. the loss of the physiological independence between oxygen delivery and oxygen consumption, associated with increased lactate levels. Some clinical symptoms suggest an impaired microcirculation, including mottled skin, acrocyanosis, slow capillary refill time and an increased central-to-toe temperature gradient.

3. Bleeding.<sup>4</sup>

Clinical suspicion of haemorrhage plus either haemoglobin drop  $> 3$  g/dL or need for any transfusion.

4. Pulmonary embolism.<sup>5</sup>

Clinical probability + imaging + laboratory variables.

5. Cardiac arrest.

Pulseless electrical activity or ventricular fibrillation /pulseless ventricular tachycardia.

6. Heart failure.<sup>6</sup>

Clinical signs and symptoms with or without preserved left ventricular ejection fraction. Abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures

7. Arrhythmias.

New onset:

- Atrial fibrillation, atrial flutter.
- other supraventricular tachycardia
- Ventricular tachycardia/ Torsade de Pointes
- Atrioventricular block  $\geq 2$  degree.

8. Stroke.<sup>7</sup>

Neurological dysfunction caused by focal cerebral, spinal or retinal infarction  $\pm$  imaging (caused by ischemia or haemorrhage)

9. Acute kidney injury. According to Kidney Disease Improving Global Outcomes definitions<sup>8</sup>

**Stage 1:** one of the following:

- Serum creatinine increased 1.5–1.9 times baseline
- Serum creatinine increase  $>0.3$  mg/dl (26.5  $\mu$ mol/l)

- Urinary output  $< 0.5$  ml/kg/h during a 6 hours block

**Stage 2:** one of the following

- Serum creatinine increase 2.0–2.9 times baseline
- Urinary output  $< 0.5$  ml/kg/h during two 6 hours blocks

**Stage 3:** one of the following:

- Serum creatinine increase  $> 3$  times baseline
- Serum creatinine increases to  $> 4.0$  mg/dl (353  $\mu$ mol/l)
- Initiation of renal replacement therapy
- Urinary output  $< 0.3$  ml/kg/h during more than 24 hours
- Anuria for more than 12 hours

On the tables presented on the main text and supplementary material, only AKI stages II and III were considered.

#### 10. Elevated liver enzymes

Defined by elevation  $\times 2$  times normal values of bilirubin and/or GPT

#### - Infectious complications

##### 1. Respiratory super-infection.<sup>9</sup>

Presence of infectious signs/symptoms of respiratory origin without radiological criteria defining the presence of a pneumonia.

##### 2. Pneumonia.<sup>9</sup>

Defined by the presence of a new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin, which include the new onset of fever, purulent sputum, leucocytosis, and decline in oxygenation.

3. Bloodstream infection.<sup>10</sup>

As defined by the positivity of blood cultures. For common skin colonizing agents (coagulase-negative staphylococci), two cultures were required for the complication to be present. Primary vascular source was not required (could be secondary bloodstream infection).

4. Urinary infection<sup>11</sup>

Positive urine culture plus signs and symptoms of infection.

5. Septic shock.<sup>12</sup>

Sepsis with vasopressors required to maintain a mean arterial pressure  $\geq 65$  mmHg and serum lactate level  $> 2$  mmol l<sup>-1</sup> in the absence of hypovolemia.<sup>12</sup>

## RESULTS

Table S1. Severity scores, vital signs and laboratory markers during ICU stay.

	All (n=663)	Survivors (n=460)	Non-survivors (n=203)	P value
<b>Scores</b>				
SOFA maximum	8 [5-11] /583	7 [5-9] /424	11 [9-13] /159	<10 <sup>-28</sup>
<b>Vital Signs</b>				
Temperature maximum, °C	37.8 [37.0-38.5] /648	37.7 [37.0-38.4] /453	38.0 [37.0-38.6] /195	<b>0.014</b>
Mean arterial pressure minimum, mmHg	70.0 [62.3-78.3] /646	73.3 [65.0-79.7] /451	65.0 [56.7-72.7] /195	<10 <sup>-8</sup>
Heart rate maximum, bpm	100 [88-118] /649	98 [85-110] /454	113 [100-126] /195	<10 <sup>-14</sup>
SpO <sub>2</sub> , minimum, %	86 [75-90] /646	87 [80-90] /449	80 [65-87] /197	<10 <sup>-10</sup>
<b>Arterial blood gas</b>				
PaO <sub>2</sub> /FiO <sub>2</sub> minimum	90 [69-121] /621	99 [77-132] /438	72 [59-91] /183	<10 <sup>-18</sup>
PaCO <sub>2</sub> maximum, mmHg	55 [44-67] /663	51 [42-61] /442	66 [57-79] /191	<10 <sup>-21</sup>
<b>Laboratory findings</b>				
Ferritin maximum, ng/mL	1569 [804-2729] /538	1463 [747-2545] /386	1814 [1119-3353] /152	<0.001
D-dimer maximum, ng/mL	4600 [2047-7492] /619	3972 [1800-7330] /438	5550 [3224-7840] /181	<0.001
RCP maximum, mg/dL	30.1 [15.9-193.4] /648	27.3 [13.6-171.0] /454	39.1 [23.0-256.0] /194	<10 <sup>-4</sup>
Lymphocyte count, minimum, μL	0.40 [0.23-0.60] /649	0.41 [0.30-0.60] /454	0.30 [0.20-0.50] /195	<10 <sup>-7</sup>
CRP/ lymphocyte ratio maximum	65.5 [24.6-300.0] /647	57.2 [20.3-244.6] /453	92.7 [40.7-480.7] /194	<10 <sup>-5</sup>
IL-6 maximum, pg/mL	179 [40-1057] /191	128 [31-484] /129	1036 [131-2421] /62	<10 <sup>-6</sup>
LDH maximum, U/L	524 [412-695] /633	482 [391-619] /447	646 [496-879] /186	<10 <sup>-12</sup>
Leukocytes maximum, 10 <sup>3</sup> / μL	11.2 [7.2-16.5] /642	10.6 [6.9-15.3] /451	13.1 [8.5-20.3] /191	<10 <sup>-4</sup>
Procalcitonin maximum, ng/mL	0.53 [0.19-2.12] /601	0.36 [0.15-0.98] /426	2.00 [0.60-7.85] /175	<10 <sup>-20</sup>
Platelets maximum, 1000/mm <sup>3</sup>	359 [265-455] /650	381 [284-473] /455	311 [228-409] /195	<10 <sup>-6</sup>
Bilirubin, maximum, mg/dL	1.20 [0.80-2.30] /622	1.19 [0.76-1.92] /441	1.60 [0.90-3.20] /181	<0.001
GPT maximum, U/L	99 [57-180] /647	100 [58-171] /455	95 [51.5-193.5] /192	0.762

Creatinine maximum, mg/dL	1.10 [0.82-1.88] /648	1.00 [0.78-1.42] /455	1.74 [1.12-3.59] /193	<b>&lt;10<sup>-17</sup></b>
Urea maximum, mg/dL	84 [53-126.5] /564	72 [45-105] /389	117 [79-183] /175	<b>&lt;10<sup>-16</sup></b>
Troponin maximum, ng/mL	22.5 [6.6-100.0] /503	14.5 [5.0-59.0] /358	62.2 [22.9-263.3] /145	<b>&lt;10<sup>-10</sup></b>
NT-ProBNP, maximum pg/mL	390 [121-1415] /191	274 [91-896] /117	833 [195-2767] /74	<b>&lt;0.001</b>
Haematocrit minimum, %	39.0 [35.1-42.0] /633	39.0 [36.0-42.3] /446	38.2 [34.0-42.0] /187	0.050
Lactate maximum, mmol/L	1.49 [1.14-2.00] /476	1.42 [1.10-1.90] /335	1.61 [1.20-2.20] /141	<b>0.009</b>

Table S1. Worst (highest or lowest) values are shown. Data are expressed as median [interquartile range] or count (percentage). For numeric variables, total counts are presented for each cell. P values were calculated with Mann-Whitney test for numerical variables, and Fisher exact test for categorical variables. SOFA: sequential organ failure assessment; SpO<sub>2</sub>: peripheral oxyhaemoglobin saturation; PaO<sub>2</sub>/FiO<sub>2</sub>: partial pressure of arterial oxygen to inspiratory oxygen fraction ratio; PaCO<sub>2</sub>: partial pressure of carbon dioxide; CRP: C-reactive protein; IL-6: interleukin 6; LDH: lactate dehydrogenase; GPT: pyruvic glutamic transaminase; NT-proBNP: N-terminal pro-brain natriuretic peptide.

**Table S2. Risk factors during admission associated with in-ICU death**

<b>Risk factors associated with ICU death during the clinical course (N=231)</b>		
<b>Variables</b>	<b>OR (95% CI)</b>	<b>P value</b>
Age, years	1.036 (0.983, 1.092)	0.117
SOFA maximum	1.364 (1.132, 1.645)	<b>0.001</b>
APACHE II per 5-point increase*	1.611 (1.044, 2.487)	<b>0.031</b>
Minimum mean arterial pressure, mmHg	0.991 (0.952, 1.031)	0.651
Heart rate maximum, bpm	1.012 (0.982, 1.044)	0.433
Respiratory rate, maximum, rpm	0.947 (0.876, 1.024)	0.174
PaO <sub>2</sub> /FiO <sub>2</sub> , minimum	0.949 (0.924, 0.974)	<b>&lt;0.0001</b>
CRP, maximum, mg/dL	1.001 (0.997, 1.005)	0.558
Ferritin, maximum, per 100 ng/mL increase	0.992 (0.964, 1.021)	0.605
D-dimer, maximum, per 100 ng/mL	1.009 (0.991, 1.027)	0.323
Lactate, maximum, mmol/L	1.200 (0.753, 1.912)	0.442
Leukocytes, maximum, 10 <sup>3</sup> /mL	1.004 (0.952, 1.060)	0.969
Procalcitonin, maximum	1.06 (1.01, 1.11)	<b>0.030</b>
Platelets, maximum, 1000/mm <sup>3</sup>	0.997 (0.993, 1.000)	<b>0,045</b>
Bilirubin, maximum, mg/dL	0.987 (0.849, 1.147)	0,863
Creatinine, maximum, mg/dL	1.007 (0.718, 1.411)	0.097
Urea maximum, mg/dL	1.004 (0.997, 1.011)	0.215
Troponin maximum, per 100 ng/mL	1.011 (0.999, 1.023)	0.071
Haematocrit, minimum, %	0.967 (0.887, 1.055)	0.454
Overall Pseudo-R <sup>2</sup> 0.542		

Table S2. Worst values during admission to predict the mortality risk. Number of subjects where the model was run (those without any missing data). OD: odds ratio; SOFA: sequential organ failure assessment; SpO<sub>2</sub>: peripheral oxyhaemoglobin saturation; PaO<sub>2</sub>/FiO<sub>2</sub>: partial pressure of arterial oxygen to inspiratory oxygen fraction ratio; PaCO<sub>2</sub>: partial pressure of carbon dioxide; CPR: C-reactive protein; IL-6: interleukin 6; LDH: lactate dehydrogenase. \* APACHE II was calculated at admission.

**Table S3. Chronology of ICU complications**

	All (n=663)	Survivors (n=460)	Non- survivors (n=203)	P value
<b>Chronology of medical complications: days from</b>				
Symptoms to ARDS	10 [7-14] /590	10 [7-14] /402	10 [8-14.5] /188	0.251
ICU admission to ARDS	0 [0-1] /597	0 [0-1] /407	0 [0-2] /190	<b>0.021</b>
Symptoms to shock	13 [10-20] /145	12 [8-17] /63	16 [11-23] /82	<b>0.009</b>
ICU admission to shock	4 [1-11] /147	3 [1-7] /64	5 [2-13] /83	<b>0.027</b>
Symptoms to bleeding	20 [15-26] /21	20.5 [17- 28] /10	16 [13-26] /11	0.398
ICU admission to bleeding	9.5 [4-18] /22	11 [6-18] /11	8 [4-18] /11	0.552
Symptoms to thromboembolism	19 [13-28] /61	18 [13-27] /42	24 [12-28] /19	0.370
ICU admission to thromboembolism	8 [3-18] /64	7 [2.50-18] /44	14 [4-20] /20	0.206
Symptoms to cardiac arrest	16 [12-25] /23	21 [15-34] /3	15 [12- 24.5] /20	0.234
ICU admission to cardiac arrest	6 [2-13] /23	13 [4-33] /3	6 [2-12] /20	0.234
Symptoms to myocardial ischemia	13 [8-20] /21	17.5 [11- 21.5] /8	11 [8-16] /13	0.231
ICU admission to myocardial ischemia	2 [0-5] /21	1.5 [0-3] /8	3 [0-6] /13	0.706
Symptoms to arrhythmias	16 [11-23] /82	15 [8-22] /39	16 [11-24] /43	0.223
ICU admission to arrhythmias	5.5 [1-13] /82	5 [0-12] /39	7 [2-13] /43	0.166
Symptoms to ischemic stroke	16 [12.5- 22.5] /8	14 [9-14] /3	22 [18-23] /5	0.099
ICU admission to ischemic stroke	7 [1-12.5] /8	6 [0-8] /3	12 [2-13] /5	0.368
Symptoms to acute renal failure	13 [8-19] /220	12 [8-18] /108	13.5 [9-19] /112	0.096
ICU admission to acute renal failure	3 [0-8] /221	2 [0-7] /109	3.5 [0-8] /112	0.352
Symptoms to acute liver failure	15 [11-21] /318	14 [11-18] /224	17.5 [12- 26] /94	0.003
ICU admission to elevated liver enzymes	5 [2-10] /322	5 [2-8] /226	7 [3-14] /94	0.005
<b>Chronology of infectious complications</b>				



Symptoms to respiratory co-infection	20 [14-31] /174	19 [14-30] /109	22 [14-33] /65	0.336
ICU admission to respiratory co-infection	11 [6-18] /176	11 [5-18] /111	12 [6-19] /65	0.554
Symptoms to pneumonia	25 [17-36] /41	23.5 [16-37] /26	28 [21-36] /15	0.448
ICU admission to pneumonia	15 [8-22] /41	16.5 [6-25] /26	15 [9-21] /15	0.881
Symptoms to bacteraemia	22 [16-30] /171	20 [15-28] /106	24 [18-30] /65	0.161
ICU admission to bacteraemia	11 [7.5-18.5] /172	10 [7-18] /106	12 [8-19] /66	0.306
Symptoms to urinary infection	26 [19-35] /77	24 [17-30] /53	30 [22-40] /24	0.020
ICU admission to urinary infection	14.5 [7-21] /78	13 [6-20] /53	15 [9-24] /25	0.506
Symptoms to septic shock	20 [13-25] /41	14.5 [6-20] /12	21 [15-25] /29	0.039
ICU admission to septic shock	9 [3-16] /41	3 [0-8.5] /12	10 [6-17] /29	0.027

Table S3. Data are expressed as median [interquartile range]. For numeric variables, total counts are presented for each cell. P values were calculated with Student t-test or Mann-Whitney test. ARDS: acute respiratory distress syndrome; ICU: intensive care unit.

**Table S4. Demographic, comorbidities, pharmacological treatment, symptoms, scores, vital signs and laboratory markers on admission: active patients**

	Active patients (n=138)
Age, years	64.00[55.00-69.00]
Female	30 (22.06%)
Body mass index, kg/m <sup>2</sup>	27.24[25.66-31.13]
Arterial Hypertension	42 (30.43%)
Diabetes Mellitus	23 (16.67%)
Chronic heart failure	0 (0.00%)
Chronic renal failure	6 (4.35%)
Asthma	2 (1.45%)
COPD	8 (5.80%)
Obese	18 (29.03%)
Dyslipidaemia	16 (11.59%)
Malignancy	2 (1.45%)
Antihypertensives	40 (28.99%)
Hypoglycaemic agents	21 (15.22%)

Antiplatelet agents	11 (7.97%)
Anticoagulants	9 (6.52%)
Bronchodilators	28 (20.29%)
Lipid lowering agents	4 (2.90%)
Thyroid hormone replacement	6 (4.35%)
Immunosupresors	4 (2.90%)
Corticosteroids	7 (5.07%)
to hospital admission	7 [4-10]
to ICU admission	10 [7-15]
Fever	88 (63.77%)
Cough	54 (39.13%)
Dyspnoea	76 (55.07%)
Myalgia	20 (14.49%)
Headache	9 (6.52%)
Rhinorrhoea	0 (0.00%)
Vomiting	3 (2.17%)
Arthralgia	6 (4.35%)
Chest pain	5 (3.62%)
Sputum	7 (5.07%)
Anosmia	6 (4.35%)
Pharyngodynia	2 (1.45%)
Diarrhoea	15 (10.87%)
Fatigue	4 (2.90%)
APACHE II	15 [10-17]
SOFA	6 [4-8]
Temperature, °C	36.9 [36.4-37.6]
Mean arterial pressure, mmHg	86.3 [77.3-96]
Heart rate, bpm	89 [75-105]
SpO <sub>2</sub> , %	88 [80-91]
Respiratory rate, bpm	25 [22-30]
PaO <sub>2</sub> /FiO <sub>2</sub> <100	21 (38.2%)
PaO <sub>2</sub> /FiO <sub>2</sub> 100-200	22 (40.0%)
PaO <sub>2</sub> /FiO <sub>2</sub> >200	12 (21.8%)
Ventilatory ratio	2.31 [1.63-3.53]
Ferritin, ng/mL	1359 [942-2180]
D-dimer, ng/mL	1036 [578-2350]
RCP, mg/dL	115.5 [24.1-179.5]
Lymphocytes, $\mu$ L	0.62 [0.43-0.99]
CPR/lymphocyte ratio	147.8 [42.0-337.3]
IL-6, pg/mL	61.3 [36.7-418]
LDH, U/L	482 [367-653]

Leukocytes, 10 <sup>3</sup> / μL	8.52 [6.10-13.00]
Procalcitonin, ng/mL	0.22 [0.10-0.62]
Platelets, 1000/mm <sup>3</sup>	201 [149.5-280]
Bilirubin, mg/dL	0.63 [0.47-0.90]
GPT, U/L	32 [21-55]
Creatinine, mg/dL	0.88 [0.77-1.10]
Urea, mg/dL	44 [28-59]
Troponin, ng/mL	3.35[0-14.00]
NT-proBNP, pg/mL	388 [37.5-572.5]
Haematocrit, %	39.7 [34.0-42.5]
Lactate, mmol/L	1.20 [1.00-1.72]

Table S4. Data are expressed as median [interquartile range] or count (percentage). P values were calculated with Mann-Whitney test for numerical variables, and Fisher exact test for categorical variables. COPD: Chronic obstructive pulmonary disease; SOFA: sequential organ failure assessment; SpO<sub>2</sub>: peripheral oxyhaemoglobin saturation; PaO<sub>2</sub>/FiO<sub>2</sub>: partial pressure of arterial oxygen to inspiratory oxygen fraction ratio; PaCO<sub>2</sub>: partial pressure of carbon dioxide; CPR: C-reactive protein; IL-6: interleukin 6; LDH: lactate dehydrogenase; GPT: pyruvic glutamic transaminase; NT-proBNP: N-terminal pro-brain natriuretic peptide.

**Figure S1. Chronology of ICU complications.**

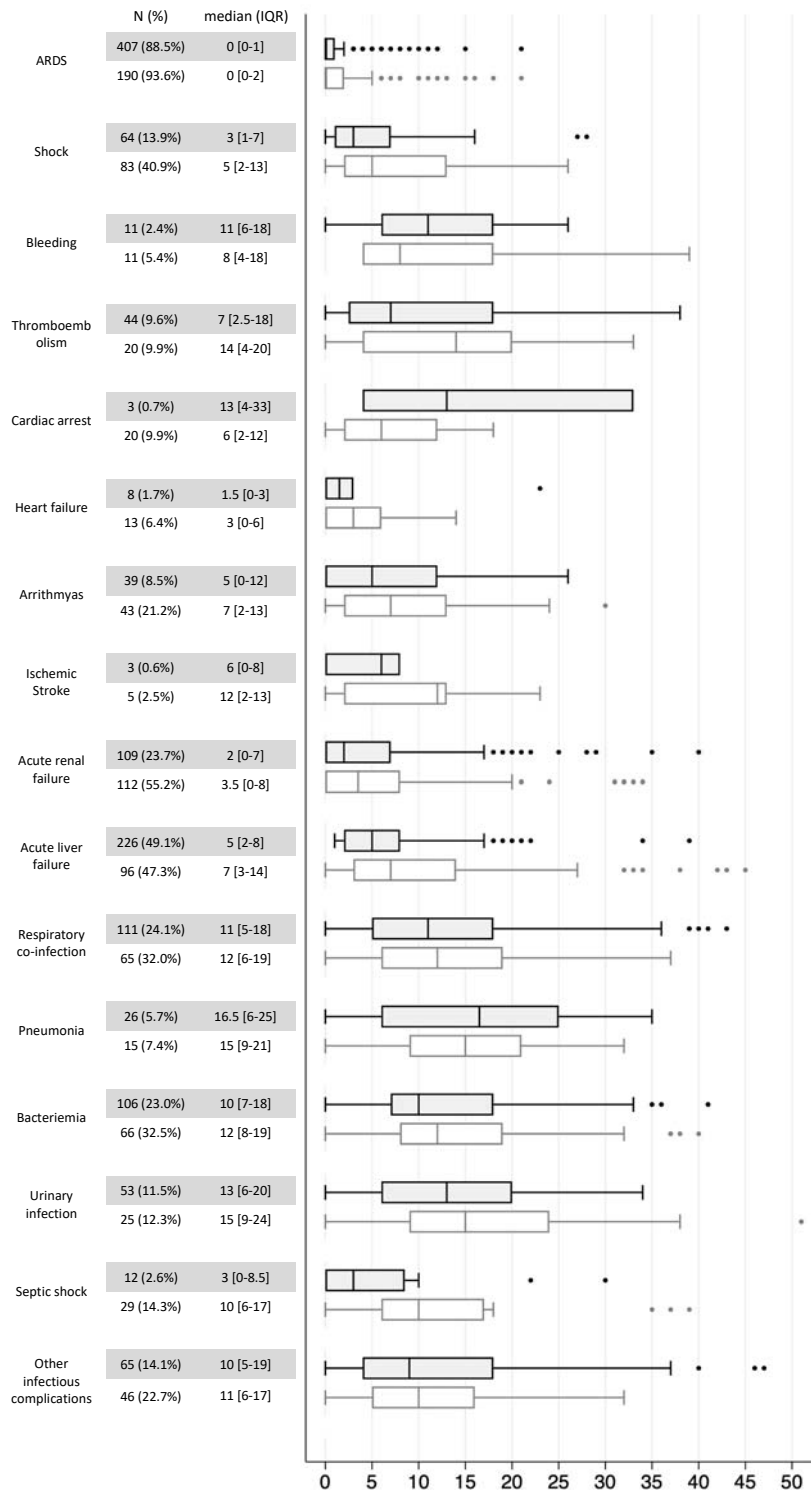


Figure S1. Medical and infectious complication are described across discharged (grey) and deceased (white) patients. For each complication and outcome, we described count and % of patients with the complication, median and interquartile range of day of onset, and a boxplot of days from ICU admission.

## REFERENCES

1. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: The Berlin Definition. *JAMA* 2012; 307:2526-33.
2. Barberà JA, Román A, Gómez-Sánchez MA, et al. Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Summary of Recommendations. *Arch Bronconeumol*. 2017.
3. Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European society of intensive care medicine. *Intensive Care Med* 2014; 40:1795-815.
4. Mehran R, Rao S, Bhatt D, et al. Standardized bleeding definitions for cardiovascular clinical trials. A consensus report from the bleeding academic research consortium. *Circulation* 2011; 123:2736-47.
5. Konstantinides S, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European respiratory society (ERS). *E Respir J* 2019, 1901647.
6. McMurray J, Adamopoulos S, Anker S, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European society of cardiology. Developed in collaboration with the heart failure association (HFA) of the ESC. *Eur J Heart Fail* 2012; 14:803-69.
7. An update definition of the stroke for the 21st century: a statement for healthcare professionals from the American heart association/American stroke. *Stroke* 2013; 44:2064-89.
8. A European renal best practice (ERBP= position on the kidney disease improving global outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy. *Nephrol Dial Transplant* 2012; 27:4263-72.
9. Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by

- the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis.* 2016;63(5):e61-e111. doi:10.1093/cid/ciw353
10. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;49(1):1-45. doi:10.1086/599376
  11. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis.* 2010;50(5):625-663. doi:10.1086/650482
  12. Singer M, Deutschman CS, Seymour CW, et al. The third consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; 23:801-10.