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eTable 1. List of participating centers

Site
Hospital Universitario Marqués de Valdecilla
Hospital Germans Trias i Pujol
Hospital Universitario de Torrejón
Hospital Universitario de Basurto
Hospital Universitari Joan XXIII de Tarragona
Hospital Universitario de Cruces
Hospital Universitario de la Princesa
Hospital Universitario Reina Sofia, Córdoba
Hospital Universitario de Gran Canaria Doctor Negrín
Hospital General de Segovia
Hospital Universitari Son Espases
HM Hospitales Madrid
Hospital Virgen del Rocío
Hospital Virgen Macarena
Hospital San Juan de Dios
Hospital General Universitario Gregorio Marañón
Hospital Universitario de Getafe
Hospital Universitario Ramón y Cajal
Hospital Universitario Río Hortega
Hospital Universitario Príncipe de Asturias
Hospital Punta de Europa-Algeciras
Hospital Universitario 12 de Octubre
Hospital Universitario Sant Joan d'Alacant
Hospital Universitario Lucus Augusti
Hospital Nuestra Señora de Gracia
Hospital Universitario de Móstoles
Hospital Universitari Bellvitge
Hospital Clinic Barcelona
Clínica Sagrada Familia
Hospital Universitario Vall d'Hebron
Hospital Clínico Universitario de Valladolid
Hospital de León
Hospital Universitari Arnau de Vilanova
Hospital San Pedro de Alcántara
Hospital Sagrat Cor
Hospital Infanta Leonor de Madrid
Hospital La Fe de Valencia

Site
Hospital Universitari Mútua Terrassa
Hospital del Mar
Hospital Universitario Central de Asturias
Hospital de Mataró
Hospital Virgen De Valme
Complexo Hospitalario Universitario de Ourense
Hospital General Río Carrión
Hospital Universitario La Paz
Hospital Álvaro Cunqueiro
Hospital Universitario de Salamanca
Hospital de Tortosa Verge de la Cinta
Hospital Clínic Universitari de València
Hospital Son Llàtzer
Hospital de Santa Maria
Hospital Universitario de Jerez de la Frontera
Hospital Universitario San Agustín
Hospital Parc Taulí
Hospital Clínico Universitario de Santiago

eTable 2. Missing data map of variables including in the multivariable analyses

	No bacterial coinfection (N = 3,943)			Bacterial coinfection (N = 133)		
		N			N	
Variables	**N Valid**	**Missing**	**% Missing**	**N Valid**	**Missing**	**% Missing**
Age	3,943	0	0%	133	0	0%
Sex	3,940	3	0%	133	0	0%
BMI	3,518	425	11%	124	9	7%
Comorbidities	3,943	0	0%	133	0	0%
SOFA (without respiratory system component)	2,750	1,193	30%	93	40	30%
PaO_2/FiO_2 ratio at hospital admission	2,874	1,069	27%	119	14	11%
Procalcitonin at hospital admission	2,800	1,143	29%	101	32	24%
C-reactive protein at hospital admission	3,903	40	1%	133	0	0%
Leucocyte count at hospital admission	3,921	22	1%	132	1	1%
Respiratory support at hospital admission	3,913	30	1%	133	0	0%
Septic shock at hospital admission	3,858	85	2%	116	17	13%

Abbreviations: BMI indicates body mass index; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen. We used the multiple imputation method (Sterne JAC et al, BMJ 2009; 338:b2393)(Omar R, E. W. Biometrics 2010) for missing data to generate 30 datasets in which missing values are replaced with plausible estimates. The model for multiple imputation included all covariates of the multivariable analyses. We used the AUTO method which scans the data to determine the best imputation method (monotone or FCS). The monotone method is an efficient method for data that have a monotone pattern of missingness. Fully conditional specification (FCS) is an iterative Markov Chain Monte Carlo (MCMC) method that is appropriate when the data have an arbitrary (monotone or nonmonotone) missing pattern.

eTable 3. Timing of antibiotics administration in the overall population

Variables	No bacterial coinfection (N = 3,943)	Bacterial coinfection (N = 133)	Total (N=4076)
	N	N	N
≤48h from hospital admission	2906 (74)	118 (89)	3024 (74)
>48h from hospital admission	747 (19)	11 (8)	758 (19)
No antibiotics	261 (6)	1 (<1)	262 (6)
Data missing	29 (<1)	3 (<1)	32 (<1)

Variables are expressed as n (%). The percentages are related to the number of patients.

eTable 4. Microorganisms of bacterial coinfection

Aetiology	Bacterial coinfection (N = 133)
Staphylococcus aureus	44 (33)
Streptococcus pneumoniae	40 (30)
Haemophilus influenzae	15 (11)
Pseudomonas aeruginosa	9 (7)
Escherichia coli	8 (6)
Klebsiella species	6 (5)
Legionella species	3 (2)
Methicillin Resistant Staphylococcus aureus	3 (2)
Streptococcus species	3 (2)
ESBL Klebsiella pneumoniae	2 (2)
Moraxella catarrhalis	2 (2)
Stenotrophomonas maltophilia	2 (2)
Enterobacter species	1 (1)
Mycoplasma pneumoniae	1 (1)
Serratia species	1 (1)
Other	1 (1)

Variables are expressed as n (%). The percentages of pathogens are related to the number of patients.

6 patients have 2 microorganisms and 1 patient has 3 microorganisms.

eTable 5. Sample of bacterial coinfection

Sample	Intubated patients[a] (N = 99)	Non intubated patients[a] (N = 34)	Total (N = 133)
Tracheal aspirate	64 (64)	2 (6)	67 (50)
Bronchoalveolar lavage	4 (4)	0 (0)	4 (3)
Sputum	6 (6)	19 (56)	24 (18)
Nasopharyngeal / oropharyngeal swabs	4 (4)	4 (12)	8 (6)
Hemoculture	3 (3)	2 (6)	5 (4)
Urine	14 (14)	11 (32)	25 (19)
Other	7 (7)	1 (3)	8 (6)

Variables are expressed as n (%). The percentages of samples are related to the number of patients. 6 patients have 2 samples and 1 patient has 3 samples. [a] During the first 48 hours from hospital admission.

eTable 6. ICU outcome

Variables	No bacterial coinfection (N = 3,943)	Bacterial coinfection (N = 133)	P-value
In-hospital mortality, n (%)	1,125 (29)	43 (32)	0.346
15-day mortality, n (%)[a]	420 (11)	19 (15)	0.194
30-day mortality, n (%)[b]	839 (22)	33 (26)	0.321
90-day mortality, n (%)[c]	1,128 (31)	44 (37)	0.160
Length of ICU stay, median (Q1; Q3), days			
All patients	13 (7; 27)	17 (9; 33)	**0.017**
Surviving patients	12 (7; 27)	17.5 (9; 34)	**0.002**
Length of hospital stay, median (Q1; Q3), days			
All patients	24 (15; 41)	24 (14; 43)	0.923
Surviving patients	25 (16; 45)	29.5 (17; 49)	0.193
Ventilator-free days, median (Q1; Q3)	0 (0; 17)	0 (0; 16)	0.764
Invasive mechanical ventilation length, median (Q1; Q3), days[d]			
All patients	15 (8; 27)	16.5 (8; 27)	0.452
Surviving patients	14 (8; 26)	15 (8; 28)	0.310
ICU-free days, median (Q1; Q3)	5 (0; 19)	0 (0; 16)	**0.006**

Abbreviations: ICU indicates intensive care unit; Q1, first quartile; Q3, third quartile. Percentages calculated on non-missing data. P-values marked in bold indicate numbers that are statistically significant on the 95% confidence limit. [a] Calculated only for patients with 15-day follow-up (3,826 in the no bacterial coinfection group and 130 in the bacterial coinfection group). [b] Calculated only for patients with 30-day follow-up (3,740 in the no bacterial coinfection group and 126 in the bacterial coinfection group). [c] Calculated only for patients with 90-day follow-up (3,648 in the no bacterial coinfection group and 119 in the bacterial coinfection group). [d] Duration of invasive mechanical ventilation was measured from initiation of ventilation until either successful extubation, successful permanent disconnection or death.

eTable 7. Multivariable models assessing predictors of 30-day mortality, using cut-off values of procalcitonin and C-reactive protein (N = 4,076)

Variables	Adjusted HR (95% CI)[a]	P-value
Procalcitonin at hospital admission ≥0.12 ng/mL[b]	1.17 (0.97 to 1.40)	0.094
C-reactive protein at hospital admission ≥97 mg/L[b]	1.02 (0.87 to 1.19)	0.839

Abbreviations: HR indicates hazard ratio; CI, confidence interval; BMI, body mass index. Cox regression model stratified on the center variable and adjusted by COVID-19 wave. Data are shown as estimated HRs (95% CIs) of the explanatory variables in the 30-day mortality group. The P-value is based on the null hypothesis that all ORs relating to an explanatory variable equal unity (no effect). P-values marked in bold indicate numbers that are statistically significant on the 95% confidence limit. [a] Adjusted for variables (age, sex, BMI, comorbidities, SOFA (without respiratory system component), PaO_2/FiO_2 ratio at hospital admission, respiratory support at hospital admission, leucocyte count ≥11 $x10^9$/L, septic shock, bacterial coinfection, and COVID-19 wave). [b] Cut-off value obtained from ROC curve for bacterial coinfection (value with a sensitivity of 80%).

eTable 8. Multivariable models assessing predictors of 90-day mortality, using cut-off values of procalcitonin and C-reactive protein (N = 4,076)

Variables	Adjusted HR (95% CI)[a]	P-value
Procalcitonin at hospital admission ≥0.12 ng/mL[b]	1.20 (1.03 to 1.40)	**0.022**
C-reactive protein at hospital admission ≥97 mg/L[b]	1.00 (0.88 to 1.15)	0.942

Abbreviations: HR indicates hazard ratio; CI, confidence interval; BMI, body mass index. Cox regression model stratified on the center variable and adjusted by COVID-19 wave. Data are shown as estimated HRs (95% CIs) of the explanatory variables in the 30-day mortality group. The P-value is based on the null hypothesis that all ORs relating to an explanatory variable equal unity (no effect). P-values marked in bold indicate numbers that are statistically significant on the 95% confidence limit. [a] Adjusted for variables (age, sex, BMI, comorbidities, SOFA (without respiratory system component), PaO_2/FiO_2 ratio at hospital admission, respiratory support at hospital admission, leucocyte count ≥11 $x10^9$/L, septic shock, bacterial coinfection, and COVID-19 wave). [b] Cut-off value obtained from ROC curve for bacterial coinfection (value with a sensitivity of 80%).

eTable 9. Association of procalcitonin and C-reactive protein with bacterial coinfection, using cut-off values of procalcitonin and C-reactive protein, by septic shock

Variables	Adjusted OR (95% CI)[a]	P-value
No septic shock (N = 3,880)		
Procalcitonin at hospital admission ≥0.10 ng/mL[b]	0.91 (0.54 to 1.56)	0.738
C-reactive protein at hospital admission ≥92.5 mg/L[b]	2.08 (1.24 to 3.51)	**0.006**
Septic shock (N = 94)		
Procalcitonin at hospital admission ≥0.11 ng/mL[b]	81.10 (1.71 to 3,850.77)	**0.026**
C-reactive protein at hospital admission ≥100 mg/L[b]	1.41 (0.01 to 197.54)	0.892

Abbreviations: OR indicates odds ratio; CI, confidence interval; BMI, body mass index; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen. Mixed-effects models with center variable as a random effect. Data are shown as estimated ORs (95% CIs) of the explanatory variables in the bacterial coinfection group. The P-value is based on the null hypothesis that all ORs relating to an explanatory variable equal unity (no effect). P-values marked in bold indicate numbers that are statistically significant on the 95% confidence limit. Area under the ROC curve, AUC for no septic shock model = 0.76 (95% CI 0.72 to 0.80); AUC for septic shock model = 0.98 (95% CI 0.94 to 1.00). [a] Adjusted for variables (age, sex, BMI, comorbidities, SOFA (without respiratory system component), PaO_2/FiO_2 ratio at hospital admission, leucocyte count ≥11 $x10^9$/L, and COVID-19 wave). [b] Cut-off value obtained from ROC curve for bacterial coinfection (value with a sensitivity of 80%).

eTable 10. Association of procalcitonin and C-reactive protein with bacterial coinfection, using cut-off values of procalcitonin and C-reactive protein, by non-respiratory SOFA score

Variables	Adjusted OR (95% CI)[a]	P-value
Non-respiratory SOFA score <2 (N = 1,518)		
Procalcitonin at hospital admission ≥0.09 ng/mL[b]	0.82 (0.34 to 1.98)	0.655
C-reactive protein at hospital admission ≥104 mg/L[b]	3.18 (1.32 to 7.62)	**0.010**
Non-respiratory SOFA score ≥2 (N = 1, 325)		
Procalcitonin at hospital admission ≥0.12 ng/mL[b]	0.92 (0.44 to 1.93)	0.828
C-reactive protein at hospital admission ≥107 mg/L[b]	2.27 (1.08 to 4.75)	**0.030**

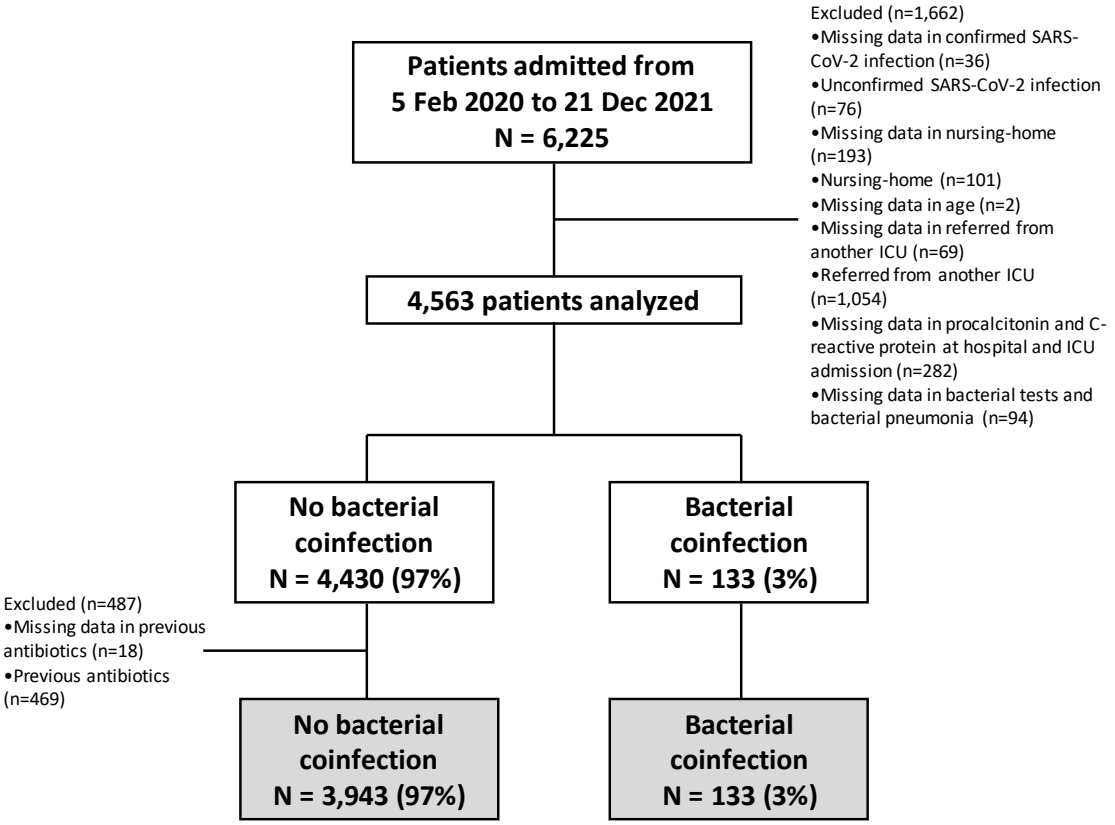
Abbreviations: SOFA, indicates sequential organ failure assessment; OR, odds ratio; CI, confidence interval; BMI, body mass index; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen. Mixed-effects models with center variable as a random effect. Data are shown as estimated ORs (95% CIs) of the explanatory variables in the bacterial coinfection group. The P-value is based on the null hypothesis that all ORs relating to an explanatory variable equal unity (no effect). P-values marked in bold indicate numbers that are statistically significant on the 95% confidence limit. Area under the ROC curve, AUC for no septic shock model = 0.71 (95% CI 0.62 to 0.80); AUC for septic shock model = 0.76 (95% CI 0.70 to 0.82). [a] Adjusted for variables (age, sex, BMI, comorbidities, PaO_2/FiO_2 ratio at hospital admission, leucocyte count ≥11 x10^9/L, septic shock, and COVID-19 wave). [b] Cut-off value obtained from ROC curve for bacterial coinfection (value with a sensitivity of 80%).

eTable 11. Association of procalcitonin and C-reactive protein with bacterial coinfection, using cut-off values of procalcitonin and C-reactive protein, by symptoms timing

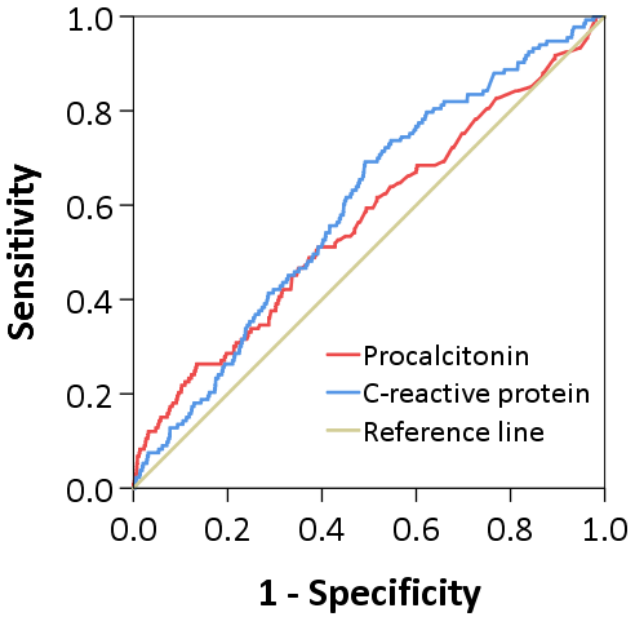
Variables	Adjusted OR (95% CI)[a]	P-value
Early symptoms (<3 days) (N = 371)		
Procalcitonin ≥0.44 ng/mL[b]	14.97 (0.96 to 234.03)	0.054
C-reactive protein ≥58 mg/L[b]	1.62 (0.08 to 31.51)	0.750
Late symptoms (≥3 days) (N = 3,667)		
Procalcitonin ≥0.11 ng/mL[b]	1.08 (0.62 to 1.87)	0.783
C-reactive protein ≥100 mg/L[b]	1.98 (0.90 to 4.36)	0.092

Abbreviations: OR indicates odds ratio; CI, confidence interval; BMI, body mass index; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen. Mixed-effects models with center variable as a random effect. Data are shown as estimated ORs (95% CIs) of the explanatory variables in the bacterial coinfection group. The P-value is based on the null hypothesis that all ORs relating to an explanatory variable equal unity (no effect). P-values marked in bold indicate numbers that are statistically significant on the 95% confidence limit. Area under the ROC curve, AUC for early symptoms model = 1.00 (95% CI 0.99 to 1.00); AUC for late symptoms model = 0.79 (95% CI 0.75 to 0.83). [a] Adjusted for variables (age, sex, BMI, comorbidities, SOFA (without respiratory system component), PaO_2/FiO_2 ratio at hospital admission, leucocyte count ≥11 $x10^9$/L, septic shock, and COVID-19 wave). [b] Cut-off value obtained from ROC curve for bacterial coinfection (value with a sensitivity of 80%).

eFigure 1. Flow diagram of the study population



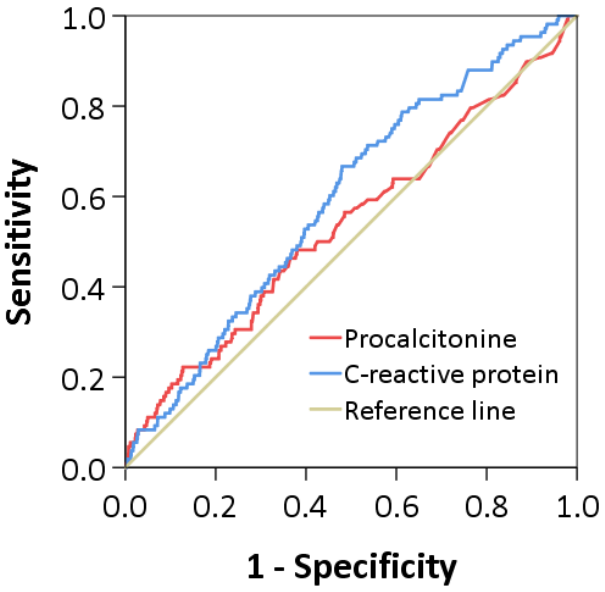
eFigure 2. Receiver operating characteristic curve of procalcitonin and C-reactive protein for identification of bacterial coinfection



AUC=0.57 (95% CI 0.51 to 0.62) for procalcitonin and AUC=0.60 (95% CI 0.55 to 0.64) for C-reactive protein.

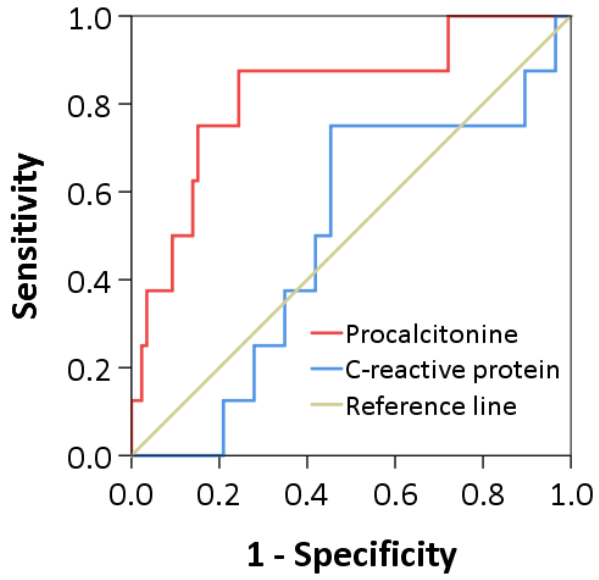
eFigure 3. Receiver operating characteristic curve of procalcitonin and C-reactive protein for identification of bacterial coinfection according to septic shock (No septic shock - Panel A, Septic shock - Panel B)

Panel A



AUC=0.54 (95% CI 0.48 to 0.60) for procalcitonin and AUC=0.59 (95% CI 0.54 to 0.64) for C-reactive protein.

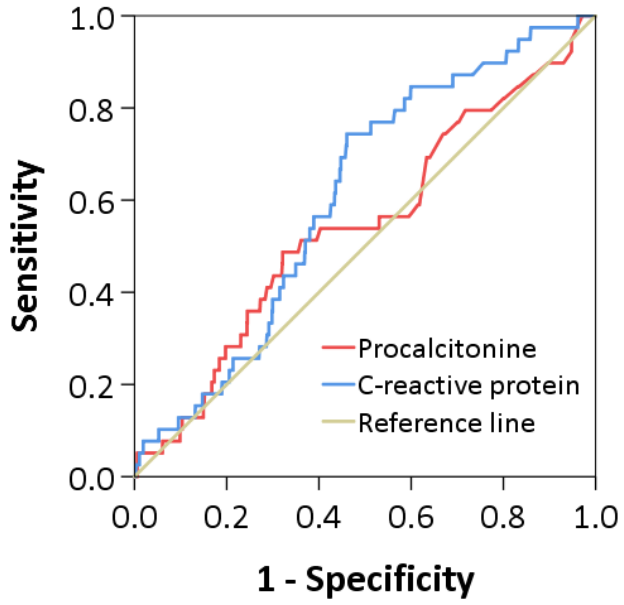
Panel B



AUC=0.82 (95% CI 0.67 to 0.98) for procalcitonin and AUC=0.50 (95% CI 0.30 to 0.69) for C-reactive protein.

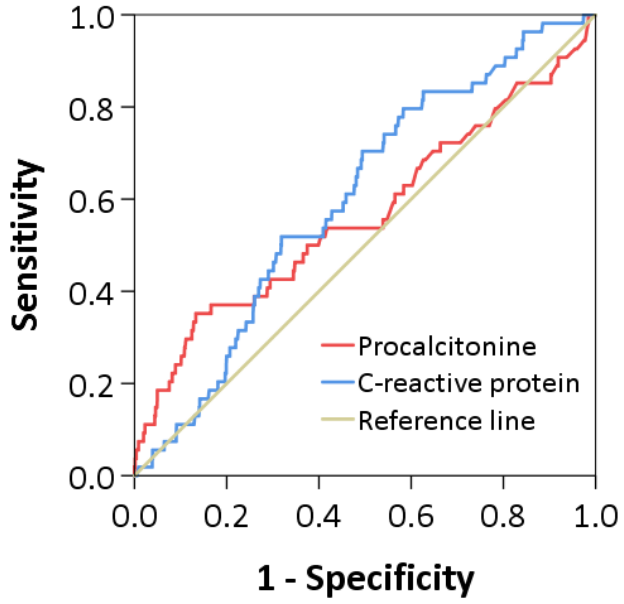
eFigure 4. Receiver operating characteristic curve of procalcitonin and C-reactive protein for identification of bacterial coinfection according to SOFA (without respiratory system component) (<2 - Panel A, ≥2 - Panel B)

Panel A



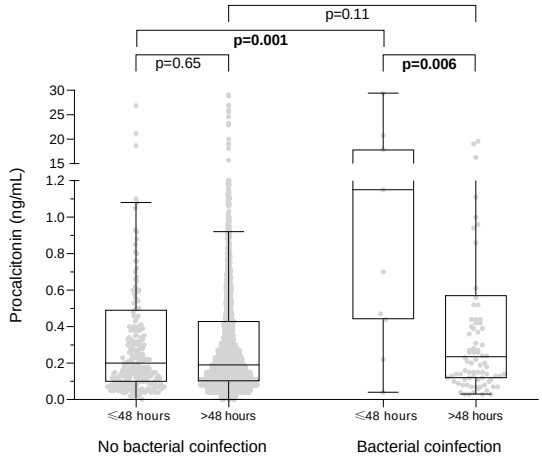
AUC=0.54 (95% CI 0.45 to 0.64) for procalcitonin and AUC=0.61 (95% CI 0.53 to 0.68) for C-reactive protein.

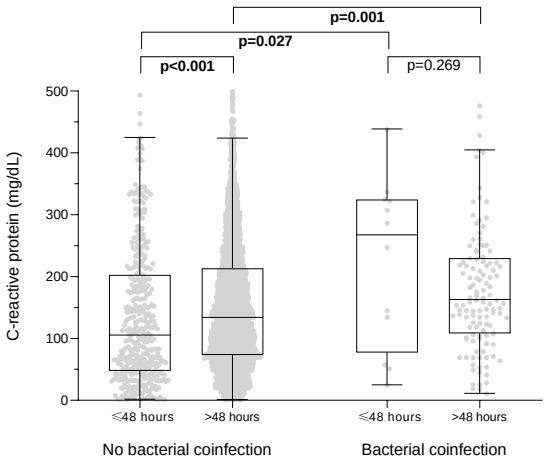
Panel B



AUC=0.57 (95% CI 0.48 to 0.66) for procalcitonin and AUC=0.60 (95% CI 0.53 to 0.67) for C-reactive protein.

eFigure 5. Procalcitonin (Panel A) and C-reactive protein (Panel B) according to time from first symptoms to hospital admission and bacterial coinfection

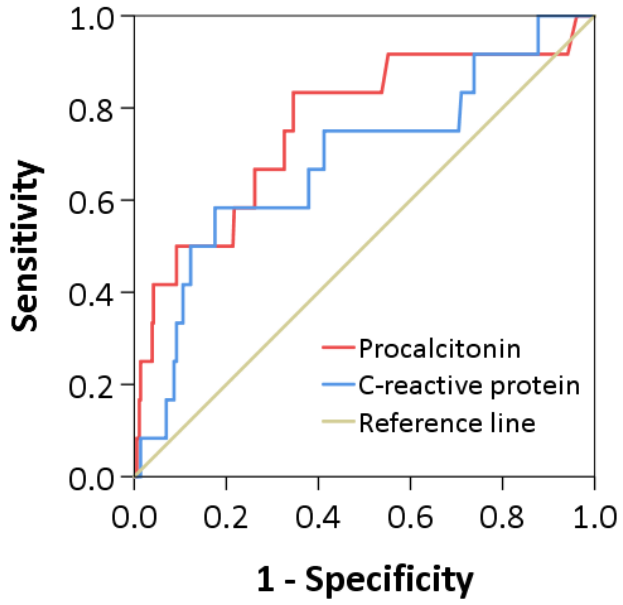




Mann-Whitney test indicated a statistically significant difference between groups (≤ 48 vs > 48 hours) in the no bacterial coinfection group for C-reactive protein (p<0.001), but not for procalcitonin (p=0.65), and a statistically significant difference between groups (≤ 48 vs > 48 hours) in the bacterial coinfection group for procalcitonin (p=0.006), but not for C-reactive protein (p=0.269). Mann-Whitney test indicated a statistically significant difference between groups (no bacterial coinfection vs bacterial coinfection) in the ≤ 48hours group for C-reactive protein (p=0.027), and for procalcitonin (p=0.001), and a statistically significant difference between both groups (no bacterial coinfection vs bacterial coinfection) in the > 48 hours group for C-reactive protein (p=0.001), but not for procalcitonin (p=0.11).

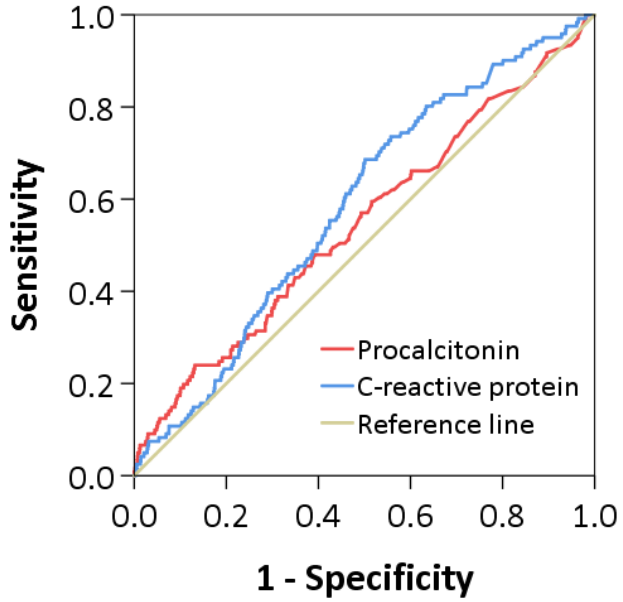
eFigure 6. Receiver operating characteristic curve of procalcitonin and C-reactive protein for identification of bacterial coinfection according to time from first symptoms to hospital admission (<3 days - Panel A, ≥3 days - Panel B)

Panel A



AUC=0.76 (95% CI 0.61 to 0.92) for procalcitonin and AUC=0.69 (95% CI 0.52 to 0.85) for C-reactive protein.

Panel B



AUC=0.55 (95% CI 0.49 to 0.60) for procalcitonin and AUC=0.59 (95% CI 0.54 to 0.63) for C-reactive protein.