Supplementary

Prediction of ventilator-associated pneumonia outcomes according to the early microbiological response: a retrospective observational study.

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METHODS

Procedures and definitions

VAP was clinically suspected in ICU patients if they had been mechanically ventilated for at least 48 hours and developed new or progressive radiological pulmonary infiltrates together with either or both of the following:

- at least two signs from among a temperature >38°C or <36°C, leukocytosis >12,000/mm^3 or leukopenia <4,000/mm^3, and purulent respiratory secretions [1, 2];
- A Simplified Clinical Pulmonary Infectious Score (sCPIS) of >6 points [3, 4].

Early-onset VAP was defined if these occurred within the first 4 days of mechanical ventilation [1].

Initial empiric antimicrobial treatment was administered at the discretion of the attending physician, based on local adaptation of current guidelines, the most frequently isolated pathogens, and patterns of antimicrobial sensitivity. When cultures

results became available, appropriate modifications were made to antibiotic therapy based on pathogen identification and sensitivity testing.

Data collection, evaluation, and microbiological diagnosis

Demographic data included age, gender, weight, height, body surface area, reason for ICU admission, alcohol and smoking use, and comorbidities. We also recorded any empirical antimicrobial treatments and subsequent changes.

Statistical analysis

We report numbers and percentages for categorical variables, and the median and first and third quartiles for continuous variables (not normally distributed data). Categorical variables were compared using the chi-square test. Two continuous variables were compared using the Mann_whitney test. Three continuous variables were compared using the Kruskal–Wallis test, and if significant overall, post-hoc pairwise comparisons were conducted via the Bonferroni test to control for the experiment-wise error rate.

Logistic regression analyses [5] were used to examine the association between superinfection and risk factors. Each risk factor was first tested individually (age, sex, smoking habit, alcohol abuse, previous corticosteroids use, previous antibiotic use, ≥5 days of previous hospitalization, previous respiratory isolation, diabetes mellitus, chronic renal failure, solid cancer, chronic heart diseases, chronic lung diseases, chronic liver diseases, APACHE II score at ICU admission, SAPS II score at ICU admission, SOFA score at ICU admission, causes of ICU admission, days of MV before VAP, Late onset VAP, CPIS at VAP diagnosis, SOFA score at VAP diagnosis, temperature at VAP diagnosis, multilobar at VAP diagnosis, ARDS at VAP diagnosis, pleural effusion at VAP diagnosis, shock at VAP diagnosis, fever at VAP diagnosis, creatinine at VAP

diagnosis, hemoglobin at VAP diagnosis, white blood cell count at VAP diagnosis, lymphocytes at VAP diagnosis, C-reactive protein at VAP diagnosis, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella spp.*, *Enterobacter spp.*, *Proteus spp.*, *Serratia spp.*, *Aspergillus spp.*, *Streptococcus pneumoniae*, *Escherichia coli*, *Stenotrophomonas maltophilia*, virus, and initial appropriate treatment), before all risk factors that showed associations in the univariate model ($p<0.10$) were added to the multivariable model. Finally, a backward stepwise selection (likelihood ratio) ($p_{in}<0.05$, $p_{out}>0.10$) was used to determine factors associated with superinfection [6]. We then calculated the odds ratios (ORs) and their 95% confidence intervals (CIs). Multicollinearity was confirmed by calculating the variance inflation factor. The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the final model. The area under the receiver operating characteristic curve (AUC) of the multivariable model was calculated.

Cox proportional hazards regression analyses [7] were performed to determine the effect of superinfection on 28-day mortality, both crude and adjusted for potential confounders (i.e., APACHE II score at ICU admission, change in SOFA score from VAP diagnosis to day 3, C-reactive protein at VAP diagnosis, and initial appropriate treatment). We calculated the hazard ratios and their 95% CIs. Proportional hazards assumptions were tested with log-minus-log plots. Any lack of fit of our final model was evaluated by deviance residuals.

To measure possible overfitting and instability of selection variables in the final models, we performed internal validation using ordinary non-parametric bootstrapping with 1,000 bootstrap samples and bias-corrected, accelerated 95% CIs

[8].

A two-sided p value <0.05 was considered statistically significant. All analyses were performed with IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

eTable 1. Demographic and baseline characteristics of patients at ICU admission					
	Group 1	**Group 2**	**Group 3**	***Group 4***	
Variable	**Persistence (n = 67)**	**Superinfection (n = 25)**	**Eradication (n = 65)**	***Non-microbiologic assessed* (n = 93)**	***p* value**
Age (years), median (Q1; Q3)	65 (53; 72)	56 (48; 74)	61 (45; 74)	63 (55; 74)	0.416
Male sex, n (%)	50 (75)	15 (60)	46 (71)	63 (68)	0.555
Current or former smoking habit, n (%)	30 (46)	13 (52)	40 (62)	46 (49)	0.291
Current or former alcohol abuse, n (%)	18 (27)	5 (20)	17 (26)	17 (18)	0.503
Previous corticosteroids use, n (%)	3 (5)	4 (17)	5 (8)	9 (11)	0.385
Previous antibiotic use, n (%)	52 (78)	18 (72)	55 (85)	76 (82)	0.515
≥ 5 days of previous hospitalization, n (%)	44 (66)	13 (52)	47 (72)	64 (69)	0.312
Previous respiratory isolation, n (%)	28 (42)	8 (32)	34 (52)	32 (34)	0.113
Comorbidities, n (%)					
Diabetes mellitus	16 (24)	1 (4)	14 (22)	23 (25)	0.150
Chronic renal failure	6 (9)	0 (0)	3 (5)	12 (13)	0.113
Solid cancer	13 (19)	3 (12)	4 (6)	9 (10)	0.102
Chronic heart diseases	21 (31)	6 (24)	16 (25)	36 (39)	0.230
Chronic lung diseases	19 (28)	7 (28)	26 (40)	23 (25)	0.216
COPD	13 (19)	6 (24)	17 (26)	14 (15)	0.358
Chronic liver diseases	9 (13)	2 (8)	9 (14)	18 (20)	0.474
APACHE II score, median (Q1; Q3)	16 (12; 21)	17 (13; 19)	16 (12; 21)	17 (14; 24)	0.307
SAPS II score, median (Q1; Q3)	43 (36; 52)	40 (34; 51)	38 (28; 46)	40 (31; 51)	0.413
SOFA score, median (Q1; Q3)	7 (5; 10)	7 (5; 9)	7 (6; 10)	8 (6; 10)	0.279
Causes of ICU admission, n (%)					
Hypercapnic respiratory failure	3 (5)	4 (16)	8 (13)	10 (11)	0.282
Hypoxemic respiratory failure	6 (9)	2 (8)	3 (5)	9 (10)	0.706
Acute coronary syndrome	1 (2)	0 (0)	5 (8)	4 (5)	0.200
Polytrauma	9 (13)	0 (0)	11 (18)	5 (5)	**0.024**
Postoperative	13 (19)	4 (16)	12 (19)	21 (23)	0.846
Cardiac arrest	3 (5)	5 (20)	4 (6)	8 (9)	0.101
Decreased consciousness	14 (21)	4 (16)	14 (22)	15 (16)	0.778

eTable 1. Demographic and baseline characteristics of patients at ICU admission					
	Group 1	**Group 2**	**Group 3**	***Group 4***	
Variable	**Persistence (n = 67)**	**Superinfection (n = 25)**	**Eradication (n = 65)**	***Non-microbiologic assessed* (n = 93)**	***p* value**
Shock	8 (12)	3 (12)	3 (5)	11 (12)	0.439
Nonsurgical abdominal disease	2 (3)	2 (8)	0 (0)	5 (6)	0.196
Others	8 (12)	1 (4)	3 (5)	3 (4)	0.131

Abbreviations: APACHE II score = Acute Physiology And Chronic Health Evaluation II score; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; Q1 = first quartile; Q3 = third quartile; SAPSII = simplified acute physiology score II; SOFA = sequential organ failure assessment.

[a] p <0.05 for comparison between the persistence group and the superinfection group.

[b] p <0.05 for comparison between the persistence group and the eradication group.

[c] p <0.05 for comparison between the persistence group and the non-microbiologic assessed group.

[d] p <0.05 for comparison between the superinfection group and the eradication group.

[e] p <0.05 for comparison between the superinfection group and the non-microbiologic assessed group.

[f] p <0.05 for comparison between the eradication group and the non-microbiologic assessed group.

e**Table 2. Patients characteristics at VAP diagnosis**					
	Group 1	**Group 2**	**Group 3**	***Group 4***	
Variable	**Persistence (n = 67)**	**Superinfection (n = 25)**	**Eradication (n = 65)**	***Non-microbiologic assessed* (n = 93)**	***p* value**
Days of MV before VAP, median (Q1; Q3)	5 (3; 10)	5 (3; 9)	6 (4; 13)	5 (3; 8)	0.181
Late onset VAP, n (%)	51 (77)	18 (72)	54 (83)	60 (68)	0.191
Severity assessment of pneumonia					
CPIS, median (Q1; Q3)	6 (5; 7)	6 (6; 7)	6 (6; 8)	7 (6; 7)	0.365
SOFA score, median (Q1; Q3)	7 (5; 10)	9 (7; 11)	7 (5; 9)	8 (5; 11)	0.184
Temperature (˚C), median (Q1; Q3)	37.7 (36.2; 38.0)	36.0 (35.4; 37.6)	37.6 (36.2; 38.2)	37.0 (35.4; 38.0)	**0.033**
Temperature < 36˚C, n (%)	15 (23)	12 (48)	13 (20)	31 (34)	**0.023**[d]
Multilobar pneumonia, n (%)	24 (36)	11 (44)	24 (37)	46 (49)	0.272
Presence of ARDS, n (%)	5 (8)	4 (16)	9 (14)	18 (20)	0.211
Pleural effusion, n (%)	17 (26)	6 (27)	17 (27)	31 (34)	0.690
Shock at pneumonia diagnosis, n (%)	28 (42)	18 (72)	27 (42)	45 (49)	0.053
Laboratory variables, median (Q1; Q3)					
Creatinine (mg/dL)	0.9 (0.7; 1.2)	0.7 (0.6; 1.7)	1.0 (0.7; 1.5)	1.0 (0.7; 1.9)	0.329
Hemoglobin (g/dL)	10.1 (9.5; 11.2)	10.6 (9.7; 12.0)	10.5 (9.2; 11.7)	9.8 (9.0; 11.5)	0.301
White blood cell count (10^9 cells/L)	10.7 (8.5; 16.3)	12.6 (8.9; 16.0)	12.0 (9.2; 17.2)	13.2 (9.4; 17.8)	0.461
Lymphocytes (n/mm^3)	827 (609; 1177)	743 (410; 1061)	963 (718; 1306)	851 (586; 1376)	0.497
C-reactive protein (mg/L)	11.8 (6.6; 19.5)	14.1 (4.9; 20.0)	13.2 (5.2; 23.7)	11.9 (6.4; 19.3)	0.966
Procalcitonin (ng/mL)	0.3 (0.1; 0.7)	0.5 (0.1; 4.7)	0.3 (0.1; 0.9)	0.4 (0.1; 1.5)	0.479
PaO_2/FiO_2 (mmHg)	233 (178; 283)	176 (147; 265)	176 (140; 236)	200 (152; 256)	**0.017**[b]

Abbreviations: ARDS = acute respiratory distress syndrome; CPIS = clinical pulmonary infection score; Q1 = first quartile; Q3 = third quartile; MV = mechanical ventilation; PaO_2/FiO_2 = ratio of arterial oxygen tension to inspired oxygen fraction; SOFA = sequential organ failure assessment; VAP = ventilator-associated pneumonia.

[a] p <0.05 for comparison between the persistence group and the superinfection group.

[b] p <0.05 for comparison between the persistence group and the eradication group.

[c] p <0.05 for comparison between the persistence group and the non-microbiologic assessed group.

[d] p <0.05 for comparison between the superinfection group and the eradication group.

[e] p <0.05 for comparison between the superinfection group and the non-microbiologic assessed group.

[f] $p < 0.05$ for comparison between the eradication group and the non-microbiologic assessed group.

e**Table 3. Patients characteristics 3 days after VAP diagnosis**					
	Group 1	**Group 2**	**Group 3**	***Group 4***	
Variable	**Persistence (n = 67)**	**Superinfection (n = 25)**	**Eradication (n = 65)**	***Non-microbiologic assessed* (n = 93)**	***p* value**
Severity assessment, median (Q1; Q3)					
CPIS	6 (4; 7)	6 (6; 7)	6 (4; 7)	6 (4; 7)	0.543
SOFA score	6 (4; 9)	8 (7; 10)	7 (4; 9)	7 (4; 10)	0.079
SOFA changes from day 1 at day 3	0 (-2; 0)	0 (-1; 1)	0 (-1; 0)	0 (-2; 1)	0.833
Temperature (˚C)	37.1 (36.0; 38.0)	35.7 (35.2; 37.1)	37.2 (36.3; 37.8)	37.0 (36.0; 37.5)	**0.003**[ad]
Temperature < 36˚C, n (%)	14 (22)	14 (56)	11 (17)	20 (23)	**0.001**[adf]
Laboratory variables, median (Q1; Q3)					
C-reactive protein (mg/L)	10.4 (5.3; 16.9)	12.8 (5.4; 26.1)	10.9 (2.8; 19.0)	11.3 (5.4; 19.8)	0.740
Procalcitonin (ng/mL)	0.2 (0.1; 0.6)	0.5 (0.1; 2.8)	0.1 (0.1; 0.6)	0.6 (0.1; 1.2)	0.096
PaO_2/FiO_2 (mmHg)	255 (176; 306)	225 (188; 272)	221 (151; 285)	222 (156; 266)	0.223

Abbreviations: CPIS = clinical pulmonary infection score; Q1 = first quartile; Q3 = third quartile; SOFA = sequential organ failure assessment; PaO_2/FiO_2 = ratio of arterial oxygen tension to inspired oxygen fraction; VAP = ventilator-associated pneumonia.

[a] p <0.05 for comparison between the persistence group and the superinfection group.

[b] p <0.05 for comparison between the persistence group and the eradication group.

[c] p <0.05 for comparison between the persistence group and the non-microbiologic assessed group.

[d] p <0.05 for comparison between the superinfection group and the eradication group.

[e] p <0.05 for comparison between the superinfection group and the non-microbiologic assessed group.

[f] p <0.05 for comparison between the eradication group and the non-microbiologic assessed group.

eTable 4. Outcomes					
	Group 1	**Group 2**	**Group 3**	***Group 4***	
Variable	**Persistence (n = 67)**	**Superinfection (n = 25)**	**Eradication (n = 65)**	***Non-microbiologic assessed* (n = 93)**	***p* value**
ERS/ESICM/ESCMID/ALAT guidelines adherence, n (%)	44 (70)	12 (50)	40 (67)	33 (61)	0.339
Initial appropriate treatment, n (%)	54 (83)	18 (75)	54 (90)	47 (87)	0.326
Treatment failure on day 3, n (%)	44 (66)	18 (72)	37 (57)	39 (42)	**0.006**[ce]
Days of MV, median (Q1; Q3)	14 (9; 24)	22 (13; 43)	18 (13; 27)	10 (6; 16)	**<0.001**[cef]
Ventilator-free-days, median (Q1; Q3)	9 (0; 22)	0 (0; 12)	7 (0; 20)	18 (0; 24)	**0.001**[ae]
ICU length of stay, median (Q1; Q3)	20 (13; 32)	24 (17; 44)	24 (15; 35)	15 (10; 23)	**<0.001**[cef]
ICU mortality, n (%)	14 (21)	13 (52)	20 (31)	28 (30)	**0.038**[a]
28-days mortality, n (%)	16 (24)	11 (44)	18 (28)	19 (20)	0.111
90-days mortality, n (%)	23 (34)	16 (64)	25 (40)	33 (37)	0.062

Abbreviations: ERS = European Respiratory Society; Q1 = first quartile; Q3 = third quartile; ICU = intensive care unit; MV = mechanical ventilation.

[a] p <0.05 for comparison between the persistence group and the superinfection group.

[b] p <0.05 for comparison between the persistence group and the eradication group.

[c] p <0.05 for comparison between the persistence group and the non-microbiologic assessed group.

[d] p <0.05 for comparison between the superinfection group and the eradication group.

[e] p <0.05 for comparison between the superinfection group and the non-microbiologic assessed group.

[f] p <0.05 for comparison between the eradication group and the non-microbiologic assessed group.

eTable 5. Significant univariate and multivariable regression analyses for superinfection (n = 147)

Variable	Univariate			Multivariable [a]		
	OR	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Diabetes mellitus	0.14	0.02 to 1.09	0.061	-	-	-
SOFA score at VAP diagnosis (+1 point)	1.13	0.99 to 1.28	0.060	-	-	-
Temperature at VAP diagnosis (+1°C)	0.65	0.46 to 0.91	0.011	0.67	0.48 to 0.95	0.025
Shock at VAP diagnosis	3.55	1.39 to 9.09	0.008	3.43	1.25 to 9.40	0.017
S. aureus	2.36	0.95 to 5.88	0.064	2.87	1.06 to 7.75	0.038
Aspergillus	5.81	1.10 to 30.74	0.038	-	-	-

Abbreviations: CI = confidence interval; OR = Odds Ratio; SOFA = sequential organ failure assessment.

[a] Hosmer–Lemeshow goodness-of-fit test, p=0.52.

eTable 6. Internal validation of the multivariable regression model for superinfection using non-parametric bootstrap technique

Variable	Original	Bias	SE	95% BCa CI	*p* value
Temperature at VAP diagnosis (°C)	-0.397	-0.012	0.190	-0.774 to 0.700	0.021
Shock at VAP diagnosis	1.232	0.108	0.839	0.220 to 2.909	0.008
S. aureus	1.054	0.016	0.571	-0.087 to 2.250	0.041

Abbreviations: BCa = adjusted bootstrap confidence interval; CI = confidence interval; SE = standard error; SOFA = sequential organ failure assessment.

eTable 7. Causes of treatment failure

	Group 1	Group 2	Group 3
Variable n (%)	**Persistence (n = 67)**	**Superinfection (n = 25)**	**Eradication (n = 65)**
No treatment failure	23 (34)	7 (28)	28 (43)
No improvement of Pao2/Fio2	12 (18)	6(24)	8 (13)
Persistence of fever or hypothermia with purulent respiratory secretions	11 (17)	6 (24)	7 (11)
Greater than or equal to 50% increase in radiographic infiltrates.	2 (3)	1 (4)	2 (3)
Occurrence of septic shock or multiple organ dysfunction syndrome	2 (3)	0	4 (6)
No improvement of Pao2/Fio2 plus Persistence of fever or hypothermia with purulent respiratory secretions	10 (15)	4 (16)	7 (11)
No improvement of Pao2/Fio2 plus greater than or equal to 50% increase in radiographic infiltrates.	2 (3)	7 (28)	1 (2)
No improvement of Pao2/Fio2 plus occurrence of septic shock or multiple organ dysfunction syndrome	1 (2)	0	2 (3)
Persistence of fever or hypothermia with purulent respiratory secretions plus greater than or equal to 50% increase in radiographic infiltrates.	1 (2)	1 (4)	0
More than two causes	2 (3)	0	4 (6)
Death	1 (2)	0	1 (2)

eTable 8. Univariate and multivariable Cox regression analyses for 28-day mortality (n = 136)

Variable	Univariate			Multivariable		
	HR	**95% CI**	***p* value**	HR	**95% CI**	***p* value**
Superinfection at day 3	1.92	0.97 to 3.79	0.061	2.39	1.16 to 4.92	0.018
APACHE II score at ICU admission (+1 point)	0.98	0.94 to 1.03	0.492	0.99	0.94 to 1.04	0.612
Change in SOFA score from VAP diagnosis to day 3 (+1 point)	1.17	1.01 to 1.35	0.041	1.15	0.97 to 1.37	0.110
C-reactive protein at VAP diagnosis (+1 mg/L)	1.02	0.99 to 1.05	0.213	1.03	0.99 to 1.06	0.132
Initial appropriate antibiotic therapy	0.80	0.37 to 1.73	0.577	1.21	0.50 to 2.95	0.674

Abbreviations: APACHE II score = Acute Physiology And Chronic Health Evaluation II score; CI = confidence interval; HR = hazard ratio; SOFA = sequential organ failure assessment; VAP = ventilator-associated pneumonia.

eTable 9. Internal validation of the multivariable Cox regression model for 28-day mortality using non-parametric bootstrap technique

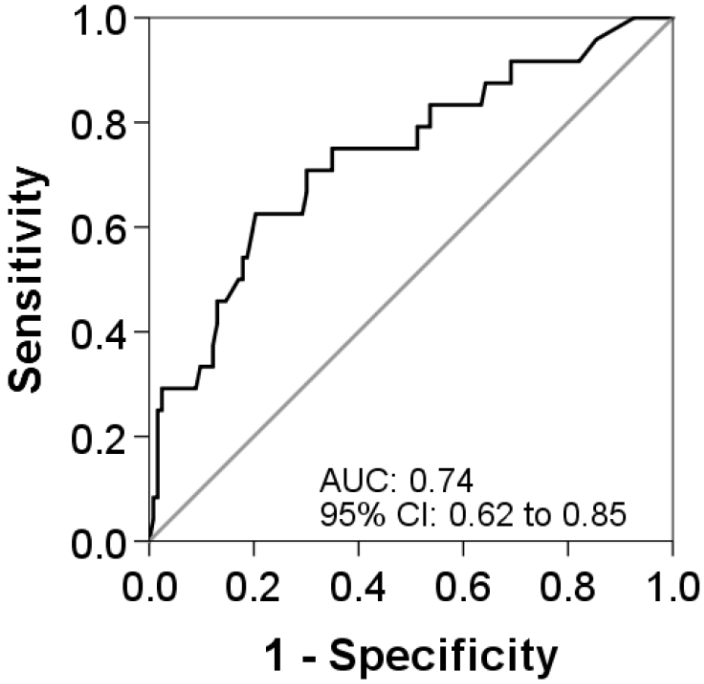
Variable	Original	Bias	SE	95% BCa CI	*p* value
Superinfection at day 3	0.871	0.016	0.389	0.046 to 1.674	0.011
APACHE II score at ICU admission	-0.013	0.000	0.022	-0.060 to 0.030	0.530
Change in SOFA score from VAP diagnosis to day 3	0.141	-0.007	0.084	-0.015 to 0.291	0.079
C-reactive protein at VAP diagnosis (mg/L)	0.026	-0.002	0.018	-0.008 to 0.056	0.127
Initial appropriate antibiotic therapy	0.191	0.051	0.670	-1.053 to 1.940	0.677

Abbreviations: APACHE II score = Acute Physiology And Chronic Health Evaluation II score; BCa = adjusted bootstrap confidence interval; CI = confidence interval; ICU = intensive care unit; SE = standard error; SOFA = sequential organ failure assessment; VAP = ventilator-associated pneumonia.

eTable 10 Comparisons of outcomes between patients with eradication and without eradication.

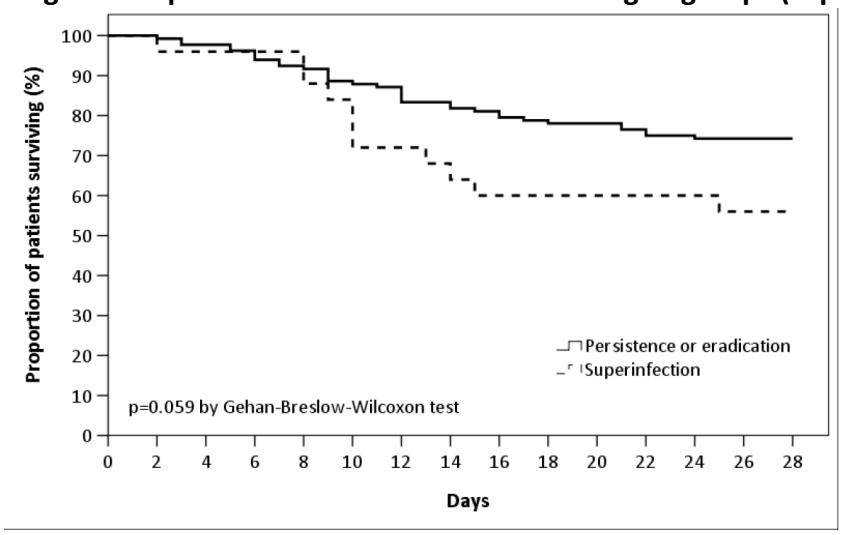
	Group 2	**Group 3**	
Variable	**Superinfection + Persistence + *Non-microbiologic assessed*** **(n = 185)**	**Eradication (n = 65)**	***p* value**
ERS/ESICM/ESCMID/ALAT guidelines adherence, n (%)	89 (63)	40 (67)	0.631
Initial appropriate treatment, n (%)	119 (83)	54 (90)	0.214
Treatment failure on day 3, n (%)	101 (55)	37 (57)	0.745
Days of MV, median (Q1; Q3)	12 (8; 22)	18 (13; 27)	**0.003**
Ventilator-free-days, median (Q1; Q3)	13 (8; 22)	7 (0; 20)	0.221
ICU length of stay, median (Q1; Q3)	17 (12; 29)	24 (15; 35)	**0.009**
ICU mortality, n (%)	55 (30)	20 (31)	0.875
28-days mortality, n (%)	46 (25)	18 (28)	0.653
90-days mortality, n (%)	72 (40)	25 (40)	0.916

eFigure 1. ROC curve analysis of the multivariable regression model for superinfection



Abbreviations: AUC = area under the curve; CI = confidence interval; ROC = receiver operating characteristic.

eFigure 2 Kaplan Maier survival curve according to groups (superinfection vs others)



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