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Hospital-Acquired Infections in Critically Ill Patients With COVID-19

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e-Appendix 1.

e-Methods

Partecipating Centers

This work is a retrospective analysis of prospectively collected data of all consecutive COVID-19 patients admitted to the ICUs of 8 Italian hub hospitals (in brackets the number of patients admitted per center):

- Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan, (n=117);
- IRCCS Istituto Clinico Humanitas, Milan, (n=103);
- ASST Grande Ospedale Metropolitano Niguarda, Milan (n=152);
- Azienda Ospedaliera S. Gerardo, Monza, (n=137);
- Presidio Ospedaliero "Alessandro Manzoni", Lecco, (n=90);
- Azienda Ospedaliero-Universitaria di Modena, Modena, (n=87);
- Policlinico Universitario S. Orsola Malpighi, Bologna, (n=44);
- Policlinico Universitario A. Gemelli, Roma, (n=44)

The overall participating centers totaled 36 COVID-19 ICUs with a peak of 520 ICU beds. It is worth considering that the peak ICU beds utilization in Lombardy during the March-April Italian COVID-19 pandemic was 1571 beds.

Additional Statistical Analysis

Descriptive statistics were produced for demographic, clinical and laboratory characteristics of cases. Data were presented as median and interquartile range (IQR) or number and percentages for categorical variables.

The crude incidence rate per 1000 patient-days (pd) of ICU (IR/ 1000 ICU pd) and relative 95% confidence intervals (CIs) was calculated. All the infectious episodes, including also multiple infectious episodes for each patient, during ICU stay were considered. The analysis time scale was the time since ICU admission until the date of ICU discharge.

The distributions of microorganisms identified in HAIs, as well as descriptive statistics of the total number of days of ICU, and mechanical ventilation were calculated by type of infection.

Time at risk of ICU HAIs was from ICU admission to HAIs, death, or discharge from ICU.

Competing risk analysis was used to estimate the cumulative incidence of HAIs, with death as competing event; patients were censored at discharge from ICU (i.e. we considered discharge as noninformative censoring, since patients were no longer at risk of ICU infection once discharged from ICU).

Fine and Gray competing risk regression models were used to assess independent risk factors associated to HAI; SubHazard Ratios (SHRs) and their corresponding 95% CI are reported. Death was considered competing event for developing infection. Univariable and multivariable models were fitted; variable selection strategy for multivariable models was: clinically relevant variables, not colinear, <10% missing data, with no further selection. Collinearity was assessed by calculation of the correlation matrix of coefficients of Fine and Gray model, and considered not relevant if rho <0.30. Proportionality of subhazards assumption was tested by adding a term for interaction with time of each predictor.

In secondary analyses, to assess risk factors for HAIs, infection-specific hazards ratios were employed in univariable and multivariable Cox proportional hazard models, with censoring at discharge, and considering death as a competing event. In these analyses, all infections were included, and the conditional risk set model Prentice, Williams and Peterson Total Time (time from entry) was applied to take into account multiple HAIs per patient (stratifying for order of infections); robust standard errors with clustering by patient were calculated.

Variable selection strategy for multivariable models was: clinically relevant variables, not colinear, <10% missing data, with no further selection. Collinearity was assessed by calculation of the correlation matrix of coefficients of Cox model, and considered not relevant if rho <0.30. Proportional hazard assumption was tested on the basis of Schoenfeld residuals and with visual models.

As a sensitivity analysis, multiple imputation with 10 replications with multivariable normal regression via MCMC data augmentation, for those variables with <20% missing data was performed, and the same analyses repeated on the imputed datasets.

Proportional hazard subdistribution hypothesis was tested by adding interaction with time of the effect of each variable included in the model.

All tests were two-sided, and $p<0.05$ was chose to indicate statistical significance. JMP 11 statistical (SAS, Cary, NC, USA) and Stata computer software version 16.1 (Stata Corporation, 4905 Lakeway Drive, College Station, Texas 77845, USA) were used for statistical analysis.

e-Table 1. Diagnostic criteria for infections.

Infection	Site of Culture	Bacterial Load	Clinical Signs	Also
Blood Stream Infection	2 percutaneous blood samples + eventual blood from catheters	---	Fever/tachycardia/hypotension + No further sign of localized infection	No differential time to positivity between percutaneous and catheters
	If Common Commensal organisms (i.e., diphtheroids (*Corynebacterium* spp. not *C. diphtheria*), *Bacillus* spp. (not *B. anthracis*), *Propionibacterium* spp., coagulase-negative staphylococci (including *S. epidermidis*), viridans group streptococci, *Aerococcus* spp. *Micrococcus* spp. and *Rhodococcus* spp.): necessary two or more blood specimens collected from different sites or at different times			
Catheter-related Blood Stream Infection[1]	2 percutaneous + catheter blood or catheter tip	---	Fever/tachycardia/hypotension + No further sign of localized infection. Eventual erythema, swelling, purulent drainage from catheter insertion-site.	Differential time to positivity > 2 hours or catheter CFU > 3-fold percutaneous CFU or positive catheter tip
	If Common Commensal organisms (i.e., diphtheroids (*Corynebacterium* spp. not *C. diphtheria*), *Bacillus* spp. (not *B. anthracis*), *Propionibacterium* spp., coagulase-negative staphylococci (including *S. epidermidis*), viridans group streptococci, *Aerococcus* spp. *Micrococcus* spp. and *Rhodococcus* spp.): necessary two or more blood specimens collected from different sites or at different times			
Candidemia/ Invasive Candidiasis	**Proven**: *Candida* spp identified from one or more blood specimens obtained by culture or non-culture microbiologic testing methods (for example, T2 Magnetic Resonance)			
	Presumptive: 1) risk factors (i.e., Candida score, Candida Colonization Index); 2) biomarkers (i.e., 1,3-beta-d-glucan BDG); 3) exclusion of alternative diagnoses			

Ventilator-Associated Pneumonia[2]	Bronchoalveolar lavage	≥ 10^4 CFU/mL	2 of: fever, leukocytosis/leucopenia, purulent secretions + New/progressive radiographic infiltrate + Worsening oxygenation	
	Endotracheal Aspirate	≥ 10^5 CFU/mL		
	Excluded organisms: "Normal respiratory flora", "normal oral flora", "mixed respiratory flora", and, unless identified from lung tissue or pleural fluid (with specimen obtained during thoracentesis or initial placement of chest tube and NOT from an indwelling chest tube), *Candida* spp, coagulase-negative staphylococci, *Enterococcus* spp			
Invasive Pulmonary Aspergillosis	**Proven**: 1) microscopic analysis of needle aspiration/biopsy showing histopatologic/cytopatologic/direct microscopic evidence of hyphae and tissue damage or 2) positive culture of lung biopsy for Aspergillus spp.			
	Putative: 1) bronchoalveolar lavage positive for Aspergillus spp. without bacterial growth; 2) one of: refractory/recrudescent fever despite appropriate antibiotic therapy, pleuritic chest pain, dyspnea, hemophtysis, worsening oxygenation; 3) abnormal imaging by chest X-ray or computed tomography; 4) host risk factors (i.e. neutropenia, hematological malignancy, glucocorticoid treatment, congenital/acquired immunodeficiency).			
Catheter-associated Urinary Tract Infection[3]	2 consecutive urine specimens[4]	≥ 10^5 CFU/mL	Fever/tachycardia/hypotension	
	Excluded organisms: "mixed flora", *Candida* spp, yeast, mold, dimorphic fungi, parasites			
Clostridium Difficile Colitis	Unformed stool culture	---	Fever/tachycardia/hypotension + Unformed stool	Enzyme immunoassay positive for C. difficile GDH + toxins A/B or positive NAAT
Any relevant culture sample which caused antibiotic therapy initiation or changing (obtained within 72 hours before or 24 hours after antibiotic starting/modification.				

Colony forming units, CFU; [1]) At least 48 hours after catheter positioning. [2]) At least 48 hours after intubation. [3]) At least 48 hours after catheterization. All the patients had urinary indwelling catheters. [4]) Urinary catheter is removed after finding of a positive specimen, a new catheter is repositioned and a second specimen is collected.

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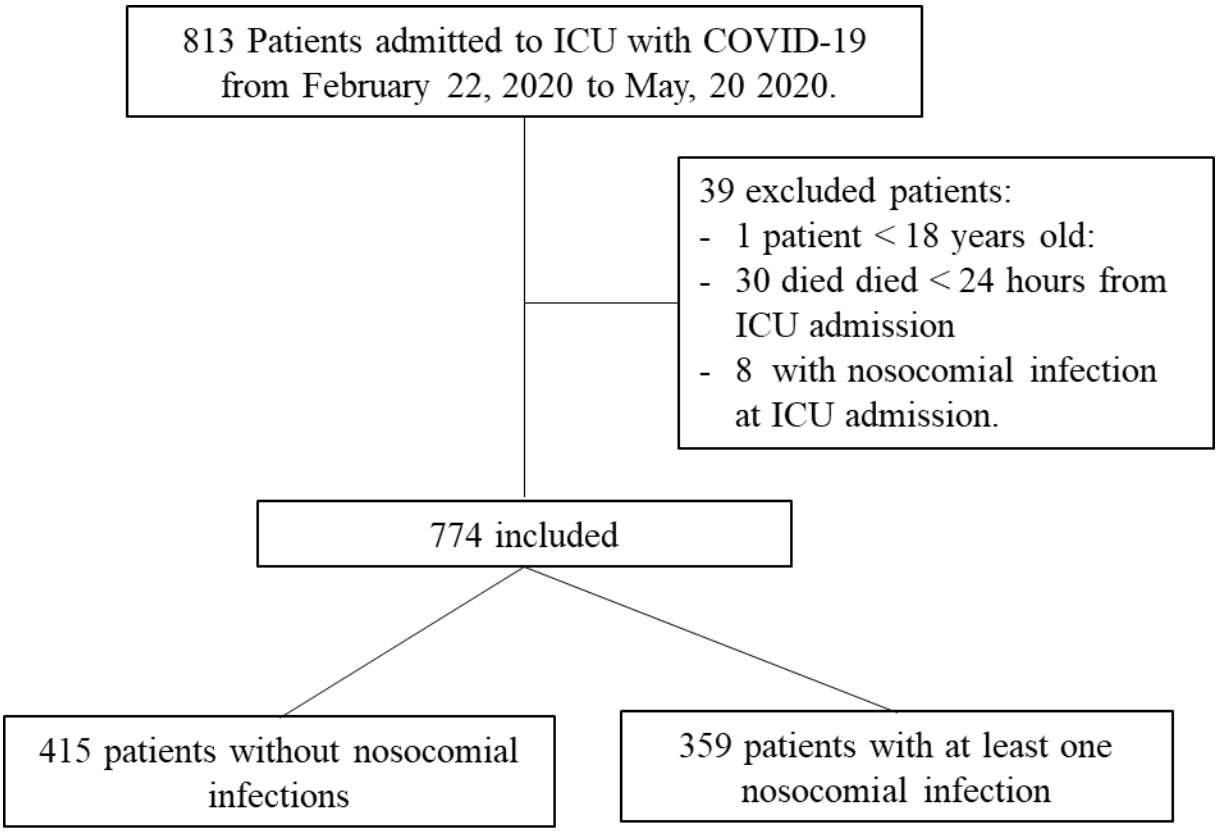
Additional Results

e-Figure 1. Patients Flowchart.



ICU, Intensive Care Unit

e-Table 2. Results of the Fine and Gray analysis (table 1) following multiple imputations.

	Total (n = 774)	Infected (n=359, 46%)	Not infected (n=415, 54%)	*p*-value	HR (95%CI)
Gender (female)	177 (23%)	74 (21%)	103 (25%)	0.679	1.12 (0.66 – 1.91)
Age (years)	62 [54 – 68]	62 [54 – 68]	62 [54 – 69]	0.094	0.98 (0.96 – 1.00)
Non-respiratory SOFA Score	1 [1 - 2]	1 [1 - 2]	1 [1 - 2]	**0.023**	**0.78 (0.64 – 0.97)**
PaO_2/FiO_2					
$PaO_2/FiO_2 > 200$	118 (15%)	46 (13%)	72 (17%)		
$200 \leq PaO_2/FiO_2 < 100$[a]	382 (49%)	180 (50%)	202 (49%)	0.420	1.29 (0.70 – 2.39)
$PaO_2/FiO_2 \leq 100$[a]	250 (32%)	122 (34%)	128 (31%)	0.115	1.74 (0.87 – 3.47)
PEEP (cmH_2O)	12 [10 -14]	12 [10 -14]	10 [10 -14]	**0.019**	**1.11 (1.02 - 1.20)**
pH					
$7.35 \leq pH < 7.45$	301 (39%)	137 (38%)	164 (40%)		
$pH < 7.25$[b]	41 (5%)	25 (7%)	16 (4%)	0.895	1.05 (0.51 – 2.18)
$7.25 \leq pH < 7.35$[b]	188 (24%)	102 (28%)	86 (21%)	0.955	0.99 (0.61 - 1.59)
$pH \geq 7.45$[b]	225 (29%)	89 (25%)	136 (33%)	**0.017**	**0.49 (0.28 – 0.88)**
Antibiotic Therapy[c]					
No antibiotic	240 (31%)	130 (36%)	110 (27%)		
Narrow spectrum[d]	294 (38%)	130 (36%)	164 (40%)	0.254	0.69 (0.36 - 1.31)
Broad spectrum[d]	240 (31%)	99 (28%)	141 (34%)	0.060	0.51 (0.25 –- 1.03)
Anakinra[e]	89 (12%)	52 (14%)	37 (9%)	0.926	0.96 (0.42 – 2.21)
Tocilizumab[e]	187 (24%)	85 (24%)	102 (25%)	0.968	0.97 (0.26 - 3.61)
High-dose Corticosteroids[e]	36 (5%)	17 (5%)	19 (5%)	0.137	2.27 (0.77 – 6.69)
Low-dose Corticosteroids[e]	171 (22%)	80 (22%)	91 (22%)	0.682	0.89 (0.52 - 1.53)

Data are presented as absolute frequency (% of the included patients) or as median and interquartile range. HR, Hazard ratio. SOFA, Sequential Organ Failure Assessment; PaO_2, arterial oxygen partial pressure; FiO_2, inspiratory fraction of oxygen; PEEP, positive end expiratory pressure.

[a] vs $PaO_2/FiO_2 > 200$; [b] vs $7.35 \leq pH < 7.45$; [c] At ICU admission; [d] vs No Antibiotic; [e] At least 24 hours prior to infection.

e-Table 3. Patients' characteristics at ICU admission, comorbidities, and employed therapies divided for different treatment.

	Total (n = 774)	High-dose corticosteroids (n=36)	Low-dose corticosteroids (n=171)	Anakinra (n=89)	Tocilizumab (n=187)
Time from hospital admission (days)		21 [12-28]	12 [5-21]	6 [3-11]	4 [2-7]
Time from ICU admission		16 [7-22]	7 [1-16]	3 [0-6]	0 [1-2]
Gender (female)	177 (23%)	8 (20%)	41 (24%)	19 (21%)	37 (20%)
Age (years)	62 [54 - 68]	67 [61 - 72]	60 [53 - 66]	60 [51 - 65]	61 [54 - 68]
BMI (kg/m2)	28 [25 - 31]	28 [26 - 29]	28 [26 - 31]	28 [25 - 31]	28 [25 - 30]
Charlson's Comorbidity Index	2 [1 - 3]	3 [2 - 3]	2 [1 - 3]	2 [1 - 3]	2 [1 - 3]
Immunologic comorbidity[1]	91 (12%)	3 (10%)	20 (12%)	8 (9%)	18 (10%9
Hypertension	350 (45%)	16 (40%)	76 (44%)	34 (38%)	92 (49%)
Diabetes	130 (17%)	6 (20%)	31 (18%)	15 (17%)	28 (15%)
SOFA Score	4 [3 - 5]	4 [3 - 5]	4 [3 - 4]	4 [3 - 5]	4 [3 - 4]
SAPS II Score	37 [30 - 44]	46 [39 - 51]	39 [30 - 45]	40 [34 - 46]	39 [33 - 46]
PaO_2/FiO_2 (mmHg)	123 [90 - 174]	112 [82 - 148]	112 [83 - 156]	118 [87 - 152]	123 [88 - 167]
Respiratory Rate (bpm)	22 [18 - 28]	22 [16 - 26]	22 [18 - 25]	20 [16 - 25]	22 [20 - 29]
TV/PBW (mL/kg)	6.8 [6.2 - 7.7]	7.9 [6.4 - 9.4]	7.1 [6.4 - 7.9]	7.5 [6.6 - 7.9]	6.9 [6.4 - 8]
PEEP (cmH_2O)	12 [10 - 14]	10 [8 - 14]	10 [10 - 14]	12 [10 - 14]	10 [10 - 14]
Plateau Pressure (cmH_2O)	24 [22 - 26]	27 [25 - 30]	24 [22 - 27]	25 [23 - 27]	24 [22 - 28]
pH	7.41 [7.34 - 7.46]	7.39 [7.3 - 7.43]	7.42 [7.34 - 7.46]	7.39 [7.3 - 7.44]	7.42 [7.34 - 7]
$PaCO_2$ (mmHg)	42 [36 - 51]	44 [38 - 54]	43 [37 - 51]	46 [38 - 56]	41 [36 - 50]
White Blood Cells	8.68 [6.24 - 11.7]	7.5 [6.2 - 11.7]	9.1 [6.5 - 12.7]	8.6 [6.2 - 12]	7.9 [5.9 - 11]
Neutrophilis (10^3/mm3)	7.26 [5.02 - 10.33]	6.5 [5.2 - 9]	8 [5.3 - 11.2]	7 [5 - 10.4]	6.7 [4.8 - 10]
Lymphocytes (10^3/mm3)	0.7 [0.47 - 1]	0.5 [0.4 - 1]	0.7 [0.4 - 1]	0.6 [0.4 - 1]	0.7 [0.4 - 1]
Neutroph/Lympho Ratio	10 [5.9 - 17.1]	11.5 [7.3 - 23.6]	10.5 [6.1 - 18.8]	10.2 [6 - 17.9]	9.6 [5.8 - 16]

Platelets (10^3/mm3)	241 [180 - 314]	227 [159 - 280]	248 [186 - 322]	242 [181 - 317]	261 [193 - 315]
Serum Bilirubin (mg/dL)	0.7 [0.5 - 1]	0.6 [0.44 - 0.8]	0.6 [0.4 - 0.8]	0.7 [0.5 - 1]	0.6 [0.4 - 1]
INR	1.19 [1.1 - 1.29]	1.09 [1.03 - 1.21]	1.18 [1.1 - 1.28]	1.19 [1.11 - 1.3]	1.15 [1.06 - 1]
Creatinine (mg/dL)	0.86 [0.69 - 1.08]	0.79 [0.66 - 0.99]	0.78 [0.6 - 1]	0.85 [0.67 - 1.05]	0.8 [0.65 - 1]
LDH (units/L)	458 [356 - 600]	793 [424 - 1084]	451 [337 - 586]	465 [354 - 644]	493 [371 - 652]
D-dimer (ng/mL)	1201 [517 - 4215]	2280 [995 - 23353]	1598 [760 - 6118]	1289 [428 - 3848]	1796 [764 - 8283]
C-reactive protein (mg/dL)	14.3 [6 - 23]	16.6 [7.6 - 24.9]	9.3 [3.3 - 18.9]	15.9 [8.6 - 23.1]	11.5 [3.6 - 21]
Procalcitonin (ng/mL)	0.4 [0.2 - 1.1]	0.6 [0.21 - 1.3]	0.23 [0.1 - 0.7]	0.39 [0.15 - 1.4]	0.24 [0.1 - 1]
Ferritine (ng/mL)	1437 [822 - 2472]	960 [677 - 1681]	1385 [869 - 2466]	1723 [1194 - 2980]	1359 [691 - 2261]
Interleukin 6 (ng/L)	200 [82 - 755]	256 [93 - 1233]	177 [31 - 983]	122 [58 - 269]	457 [165 - 1888]
Hydroxychloroquine	698 (90%)	34 (90%)	146 (85%)	86 (97%)	167 (89%)
Remdesivir	103 (13%)	5 (10%)	24 (14%)	22 (25%)	18 (10%)
Lopinavir/Ritonavir	455 (59%)	5 (10%)	57 (33%)	33 (37%)	89 (48%)
Anakinra	89 (12%)	8 (20%)	32 (19%)	-	0 (0%)
Tocilizumab	187 (24%)	15 (40%)	51 (30%)	0 (0%)	-
Corticosteioids	171 (22%)	-	-	32 (36%)	51 (27%)
Pronation	379 (49%)	27 (80%)	94 (55%)	44 (49%)	101 (54%)
Renal Replacement Therapy	45 (6%)	3 (10%)	11 (6%)	2 (2%)	13 (7%)
Extracorporeal lung support	10 (1%)	0 (0%)	5 (3%)	0 (0%)	4 (2%)

Data are presented as absolute frequency (% of the included patients) or as median and interquartile range. BMI, Body Mass Index; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score; PaO_2, arterial oxygen partial pressure; FiO_2, inspiratory fraction of oxygen; TV, Tidal Volume; PBW, Predicted Body Weight; PEEP, positive end expiratory pressure; $PaCO_2$, arterial carbon dioxide partial pressure; INR, international normalized ratio; LDH, lactate dehydrogenase. [1] Including chronic immunosuppressive therapies, active hematological malignancies, neoplastic diseases, autoimmune diseases.

e-Table 4. Use of antibiotics at ICU admission

	Overall (n=774)
Overall use of antibiotics	534 (69%)
Antibiotic Class	
β-lactam/ β-lactamase inhibitors	88 (24%)
Cephalosporins (III-IV generation)	188 (51%)
Antipseudomonal carbapenems	9 (2%)
Linezolid	10 (3%)
Glycopeptides	10 (3%)
Antipseudomonal fluoroquinolones	81 (22%)
Cephalosporins (V generation)	1 (0%)
Daptomycin	1 (0%)
Aminoglycosides	1 (0%)
Oxacillin/Methicillin	1 (0%)
Others[1]	79 (22%)

[1] Including metronidazole, anti-tuberculosis agents, lincosamides, rifampicin.

e-Table 5. Use of antibiotics for the first nosocomial infection.

	Ongoing at time of sample collection	Introduced as empiric therapy	Introduced after cultures results
	No. (%) of infected patients		
Overall use of antibiotics	272 (36%)	280 (37%)	588 (78%)
Antibiotic Class			
β-lactam/ β-lactamase inhibitors	73 (10%)	87 (12%)	105 (14%)
Cephalosporins (III-IV generation)	55 (7%)	52 (7%)	75 (10%)
Antipseudomonal carbapenems	46 (6%)	64 (9%)	88 (12%)
Linezolid	43 (6%)	70 (9%)	80 (11%)
Glycopeptides	27 (4%)	57 (8%)	65 (9%)
Antipseudomonal fluoroquinolones	24 (3%)	12 (2%)	43 (6%)
Cephalosporins (V generation)	19 (3%)	6 (1%)	31 (4%)
Penicillins	17 (2%)	4 (1%)	31 (4%)
Daptomycin	13 (2%)	5 (1%)	24 (3%)
Aminoglycosides	11 (1%)	24 (3%)	49 (7%)
Oxacillin/Methicillin	10 (1%)	4 (1%)	25 (3%)
Cephalosporins/β-lactamase inhibitors	9 (1%)	16 (2%)	40 (5%)
Colistin	7 (1%)	7 (1%)	24 (3%)
Fosfomycin	0 (0%)	2 (0%)	17 (2%)
Others[1]	22 (3%)	8 (1%)	39 (5%)

[1] Including metronidazole, anti-tuberculosis agents, lincosamides, rifampicin

e-Table 6. Gram-negative antibiotic susceptibility tests

Microorganism	Penicillin*	Amoxicillin Clavulanate	Piperacillin Tazobactam	Cephalosporin III	Cephalosporin IV*	ESBL +	Antipseudomonal carbapenems	Aminoglycosides	Antipseudomonal fluoroquinolones
Pseudomonas aeruginosa	7	4	20	24	9	8	13	8	9
Enterobacterales (other)	16	26	23	28	13	3	11	3	14
Klebsiella spp	11	18	16	21	15	5	12	8	18
Eschirichia coli	6	12	1	14	11	11	0	16	16
Acinetobacter baumannii	-	-	-	19	19	n/a	19	19	19

*) please note that not all isolates were tested for penicillin and cephalosporin IV antibiotic classes. Moreover, 2 isolates of Stenotropomonas maltophilia and one isolate of Hafni alvei and Bacteroides spp were documented. Their mechanism of resistance is not shown in the table.

e-Table 7. Univariable risk factors for MDR infections.

	Total (n = 359)	MDR Infected (n=133, 37%)	Not MDR infected (n=226, 63%)	p-value	HR (95%CI)
Gender (female)	74 (20%)	26 (20%)	48 (21%)	0.785	1.04 [0.78 - 1.38]
Age (years)	63 [57 - 67]	61 [53 - 68]	62 [54 - 68]	0.902	1.00 [0.99 - 1.01]
BMI (kg/m2)	28 [25 - 31]	28 [25 - 31]	28 [25 - 31]	0.240	1.01 [0.99 - 1.03]
Charlson's Comorbidity Index	2 [1 - 3]	2 [1 - 3]	2 [1 - 3]	0.436	0.97 [0.90 - 1.05]
Immunologic comorbidity[a]	34 (9%)	16 (12%)	18 (8%)	0.836	0.96 [0.64 - 1.44]
Hypertension	167 (47%)	65 (49%)	102 (45%)	0.484	1.09 [0.86 - 1.38]
Diabetes	57 (16%)	18 (14%)	39 (17%)	0.902	1.02 [0.73 - 1.44]
SOFA Score	4 [3 - 4]	4 [3 - 5]	4 [3 - 5]	**0.003**	**0.86 [0.78 - 0.95]**
Non-respiratory SOFA Score	1 [0 - 1]	0 [0 - 1]	1 [0 - 2]	**0.034**	**0.80 [0.64 - 0.98]**
SAPS II Score	39 [32 - 45]	37 [32 - 44]	38 [32 - 44]	0.744	1.00 [0.98 - 1.01]
APACHE II Score	9 [7 - 12]	10 [7 - 12]	9 [7 - 12]	0.490	0.99 [0.96 - 1.02]
PaO_2/FiO_2 (mmHg)	117 [89 - 151]	123 [86 - 173]	119 [87 - 162]	0.413	1.00 [0.99 - 1.01]
$PaO_2/FiO_2 > 200$[b]	46 (13%)	16 (12%)	30 (14%)		
$200 \leq PaO_2/FiO_2 < 100$[b]	180 (52%)	165 (50%)	115 (52%)	0.449	0.87 [0.60 - 1.25]
$PaO_2/FiO_2 \leq 100$[b]	122 (35%)	48 (37%)	74 (34%)	0.656	0.92 [0.62 - 1.35]
Respiratory Rate (bpm)	23 [18 - 28]	22 [18 - 28]	22 [18 - 28]	0.083	1.02 [1.00 - 1.04]
TV/PBW (mL/kg)	6.9 [6.2 - 7.7]	7 [6.3 - 7.7]	6.9 [6.2 - 7.7]	0.473	1.05 [0.92 - 1.20]
PEEP (cmH_2O)	12 [10 - 14]	12 [10 - 14]	12 [10 - 14]	0.432	0.98 [0.93 - 1.03]
Plateau Pressure (cmH_2O)	24 [22.5 - 27]	24 [22 - 27]	24 [22 - 27]	0.106	1.03 [0.99 - 1.07]
pH (units)	7.40 [7.31 - 7.46]	7.39 [7.33 - 7.46]	7.40 [7.32 - 7.46]	0.356	0.53 [0.14 - 2.03]
$7.35 \leq pH < 7.45$	137 (39%)	48 (37%)	89 (40%)		
$pH < 7.25$[c]	25 (7%)	14 (11%)	11 (5%)	**0.049**	**1.53 [1.00 - 2.35]**
$7.25 \leq pH < 7.35$[c]	102 (29%)	36 (27%)	66 (30%)	0.947	0.99 [0.72 - 1.35]
$pH \geq 7.45$[c]	89 (25%)	33 (25%)	56 (25%)	0.487	1.12 [0.82 - 1.52]
$PaCO_2$ (mmHg)	44 [37 - 56]	44 [36 - 52]	44 [36 - 53]	0.213	1.01 [0.99 - 1.02]

White Blood Cells	8.75 [6.14 - 12.86]	9.25 [6.95 - 12.09]	9.1 [6.6 - 12.48]	0.364	1.00 [0.99 - 1.02]
Neutrophilis (10^3/mm3)	7.63 [5.11 - 11.72]	8.02 [5.9 - 10.66]	7.91 [5.63 - 11]	**0.023**	**1.03 [1.00 - 1.05]**
Lymphocytes (10^3/mm3)	0.66 [0.48 - 0.98]	0.71 [0.48 - 1]	0.7 [0.48 - 1]	0.621	0.98 [0.88 - 1.08]
Neutroph/Lympho Ratio	10.9 [6.6 - 18]	10.2 [5.6 - 16.6]	10.6 [6 - 17.4]	0.114	1.01 [1.00 - 1.02]
Platelets (10^3/mm3)	229 [184 - 300]	243 [176 - 315]	232 [180 - 308]	0.216	1.00 [0.99 - 1.01]
Serum Bilirubin (mg/dL)	0.7 [0.5 - 1.1]	0.7 [0.5 - 1.1]	0.7 [0.5 - 1.1]	0.342	0.92 [0.78 - 1.09]
INR	1.16 [1.06 - 1.25]	1.20 [1.12 - 1.3]	1.19 [1.09 - 1.29]	0.199	0.59 [0.26 - 1.32]
Creatinine (mg/dL)	0.8 [0.67 – 1.00]	0.84 [0.70 - 1.10]	0.82 [0.70 - 1.06]	**0.026**	**0.74 [0.57 - 0.97]**
LDH (units/L)	485 [384 - 679]	465 [357 - 578]	469 [368 - 598]	**0.042**	**1.00 [0.99 - 1.01]**
D-dimer (ng/mL)	1710 [761 - 5952]	1550 [558 - 6360]	1663 [610 - 6160]	0.613	NC
C-reactive protein (mg/dL)	14.4 [7.0 - 22.8]	15.0 [7.1 - 26.1]	14.9 [7.1 - 24.6]	0.863	1.00 [0.99 - 1.01]
Procalcitonin (ng/mL)	0.4 [0.19 - 1.2]	0.45 [0.2 - 1.22]	0.4 [0.2 - 1.2]	0.584	1.01 [0.98 - 1.03]
Ferritine (ng/mL)	1595 [1035 - 2542]	1552 [1008 - 2560]	1573 [1026 - 2553]	0.849	NC
Interleukin 6 (ng/L)	156 [60 - 330]	177 [88 - 293]	166 [72 - 305]	0.106	1.00 [0.99 - 1.01]
Antibiotic therapy	229 (64%9	93 (70%)	136 (60%)	0.918	1.01 [0.77 - 1.32]
No antibiotic	130 (36%)	40 (30%)	90 (40%)	-	-
Narrow spectrum[c]	130 (36%)	51 (39%)	79 (35%)	0.927	1.02 [0.71 - 1.45]
Broad spectrum[c]	99 (28%)	42 (31%)	57 (25%)	0.935	1.01 [0.75 - 1.37]
Mechanical ventilation	359 (9%)	133 (100%)	226 (100%)	NC	NC
High dosage corticosteroids[d]	17 (5%)	11 (8%)	6 (3%)	**0.020**	**0.54 [0.32 - 0.90]**
Low dosage corticosteroids[d]	80 (22%)	33 (25%)	47 (21%)	0.852	0.96 [0.67 - 1.40]
Anakinra[d]	52 (14%)	18 (14%)	34 (15%)	0.175	0.62 [0.31 - 1.24]
Tocilizumab[d]	85 (24%)	32 (24%)	53 (23%)	0.375	1.89 [0.46 - 7.75]

Data are presented as absolute frequency (% of the included patients) or as median and interquartile range. ICU, Intensive Care Unit; HR, Hazard ratio; BMI, Body Mass Index; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score; PaO_2, arterial oxygen partial pressure; FiO_2, inspiratory fraction of oxygen; TV, Tidal Volume; PBW, Predicted Body Weight; PEEP, positive end expiratory pressure; $PaCO_2$, arterial carbon dioxide partial pressure; INR, international normalized ratio; LDH, lactate dehydrogenase; NC, not calculable. [a] Including chronic immunosuppressive therapies, active hematological malignancies, neoplastic diseases, autoimmundiseases. [b] vs $PaO_2/FiO_2 > 200$; [c] vs $7.35 \leq pH < 7$.

e-Table 8. Microorganism of early vs. late ventilator associated pneumonia

		Overall	EO VAP	LO VAP
No. (% of the included VAP)		389	35 (9%)	354 (91%)
MDR			12 (34%)	122 (34%)
Gram Staining	**Microorganism**			
G +		140 (36%)	20 (57%)	120 (34%)
	Staphylococcus aureus	110 (28%)	18 (51%)	92 (26%)
	Enterococcus spp	21 (5%)	1 (3%)	20 (6%)
	Coagulase-negative staphylococci			
	Streptococcus Pneumoniae	3 (1%)		3 (1%)
	Other	6 (2%)	1 (3%)	5 (1%)
G -		249 (64%)	15 (43%)	234 (66%)
	P. aeruginosa	85 (21%)	3 (9%)	82 (23%)
	Enterobacterales (other)	53 (14%)	3 (9%)	50 (14%)
	Klebsiella spp	43 (11%)	5 (13%)	38 (11%)
	E. Coli	31 (8%)	2 (6%)	29 (8%)
	A. baumanii	6 (2%)		6 (2%)
	Other	31 (8%)	2 (6%)	29 (8%)

VAP: Ventilator Associated Pneumonia; *EO*: Early Onset (<5 days after intubation); *LO*: Late Onset (=> 5 days after intubation); *MDR*: Multi-Drug Resistant bacteria.

e-Table 9. Infection onset times.

	VAP	BSI	CRBSI	UTI	P
Days from Hospital Admission	17 (10 - 27)	19 (11 - 29)	18 (11 - 28)	19 (11 - 26)	0.537
Days from ICU admission	12 (7 - 22)	15 (8 - 25)	14 (8 - 23)	14 (6 - 22)	0.564
Days from intubation	12 (7 - 21)	---	---	---	---

Data are presented as median and interquartile range. VAP, Ventilator-Associated Pneumonia; BSI, Blood Stream Infection; CRBSI, Catheter-Related Blood Stream Infection; UTI, Urinary Tract Infection; ICU, intensive care unit.

e-Table 10. Onset times of MDR and non-MDR bacterial infections.

	MDR	non-MDR	P
Days from Hospital Admission	18 (11 - 28)	18 (11 - 28)	0.849
Days from ICU admission	14 (7 - 23)	13 (7 - 77)	0.963
Days from intubation*	18 (11 - 22)	18 (11 - 21)	0.593

Data are presented as median and interquartile range. MDR, multi-drug resistant; ICU, intensive care unit. *) only for Ventilator-Associated Pneumonia.