Supplemental Online Material

Validation of IDSA/ATS guidelines for ICU admission in adults over 80 years old with community-acquired pneumonia

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Methods

Data collection and evaluation

Demographic variables, comorbidities, and physiological parameters were collected in the emergency department within 24 hours of admission. The Pneumonia Severity Index (PSI) at admission was calculated(1). During hospitalization, we recorded whether the patients had specific complications, including multilobar infiltration, pleural effusions, acute respiratory distress syndrome (ARDS), septic shock, and acute renal failure. The decisions for endotracheal intubation and initiation of invasive mechanical ventilation were made by attending physicians. Further details are reported elsewhere(2). All surviving patients were visited or contacted by telephone within 30 days of discharge.

Microbiological diagnosis

Microbiological diagnosis was performed on respiratory, blood and urine samples, which were collected before the initiation of empirical antibiotic therapy in the emergency department. Bacterial testing included blood and sputum cultures, as well as urine samples for *Streptococcus pneumoniae* and *Legionella pneumophila* antigen detection. Pleural fluid, tracheobronchial aspirates (TBAS) and bronchoalveolar lavage (BAL) fluid samples were collected, when available, for Gram and Ziehl-Neelsen staining. They were then processed for the detection of bacterial, fungal and mycobacterial pathogens. Blood samples for atypical pathogen serology were collected at admission and between the third and sixth week thereafter. Respiratory viruses were diagnosed by serology, immunofluorescence assay (IFA), and isolation in cell cultures between 2005 and 2007. However, from 2008 to 2019, diagnosis was performed with polymerase chain reaction (PCR) testing and/or cultures of nasopharyngeal swab samples. Two independent, nested and multiplex real-time PCR tests were used to detect human

influenza viruses (A, B and C), respiratory syncytial virus, adenoviruses, parainfluenza viruses (1–4), coronaviruses (229E and OC43), enteroviruses and rhinoviruses (A, B and C).

Routine antimicrobial susceptibility testing included the Phoenix system (Becton Dickinson, MD, USA) and disk diffusion method or E-test. Results of susceptibility testing were interpreted according to EUCAST guidelines (http://www.eucast.org). Detailed criteria for etiological diagnosis are described elsewhere(3, 4).

Statistical analysis

We reported the number and percentage of patients as categorical variables, the median (first quartile [Q1]; third quartile [Q3]) as continuous variables with non-normal distributions, and the mean (standard deviation [SD]) as continuous variables with normal distributions. Categorical variables were compared using the chi-squared test or Fisher's exact test, whereas continuous variables were compared using the t-test or nonparametric Mann-Whitney U test.

We also performed univariable and multivariable logistic regression analyses to identify variables predictive of ICU admission. Factors showing an association in the univariate analyses ($p<0.10$) were incorporated into the multivariable regression model including two predefined covariates (i.e., the period of admission and the center). Final variable selection was performed using the backward stepwise selection method (likelihood ratio) ($p_{in}<0.05$, $p_{out}>0.10$). Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. Single collinearity was evaluated using the Pearson correlation (r), i.e., $r>|\pm 0.30|$, while multicollinearity was examined by means of the variance inflation factor (VIF), i.e., VIF>10. We assessed the model's performance by studying calibration and discrimination We evaluated calibration with the Hosmer-Lemeshow goodness-of-

fit test. The discriminative ability refers to the score's ability to distinguish patients admitted to the ICU from those admitted to the general ward. It was expressed as the area under the receiver operating characteristic curve (AUC) ranging between 0.5 (no discriminative ability) and 1.0 (perfect discriminative ability) (6). Possible overfitting and instability of the selection variables in the prediction model were assessed by internal validation using ordinary nonparametric bootstrapping with 1,000 bootstrap samples and bias-corrected, accelerated 95% Cis (7). We used the multiple imputation method (8) for missing data in the multivariable analysis (Supplementary Table 2).

To determine the predictive capacity of IDSA/ATS severe CAP criteria for ICU admission, we determined sensitivity, specificity and positive and negative likelihood ratios(9), along with 95% CIs. The coincidence between the predictive rule and clinical decision for ICU admission was assessed with the *kappa* coefficient of agreement(10).The univariate association of the predictive rule and severity criteria with ICU admission is expressed as the relative risk and a 95% CI.

The level of significance was set at 0.05 (two-tailed). and all analyses were performed using IBM SPSS Version 26.0 (IBM Corp., Armonk, NY, USA).

Supplementary Table 1. Criteria for severe CAP according to the IDSA/ATS guidelines (adapted from (12))

Minor criteria
• Respiratory rate ≥30 breaths/min *
• PaO_2/FiO_2 ≤250 *
• Multilobar infiltrates
• Confusion-disorientation
• Uremia (BUN level ≥20 mg/dL)
• Leukopenia (WBC count $<4x10^9$/L)
• Thrombocytopenia (platelet count $<100x10^9$/L)
• Hypothermia (core temperature <36ºC)
• Hypotension (SBP <90 mmHg) requiring aggressive fluid resuscitation
Major criteria
• Invasive mechanical ventilation
• Septic shock with the need for vasopressors †

Abbreviations: FiO_2 indicates fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; BUN, blood urea nitrogen; WBC, white blood cell; SBP, systolic blood pressure. * The need for non-invasive ventilation can substitute either respiratory rate ≥30 breaths/min or PaO_2/FiO_2 ≤250. † Septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid replacement alongside hypoperfusion abnormalities (12).

Supplementary Table 2. Missing data map of variables including in the univariable and multivariable analyses to identify variables predictive of ICU admission

	N	
Variable	**Valid**	**Missing**
Sex	2,006	0
Antibiotic use in the last week	1,954	52
Chronic pulmonary disease	1,981	25
Chronic cardiovascular disease	1,994	12
Chronic renal disease	1,997	9
Chronic liver disease	1,991	15
Diabetes mellitus	1,993	13
Neurological disease	1,982	24
Confusion	1,997	9
Respiratory rate	1,899	107
Heart rate	1,935	71
Systolic blood pressure	1,965	41
Diastolic blood pressure	1,961	45
Temperature	1,958	48
Serum creatinine	2,000	6
C-reactive protein	1,649	357
White blood cell count	2,002	4
Lymphocytes	1,099	907
Glucose level	1,980	26
Platelet count	1,313	693
PaO_2/FiO_2	1,590	416
Pleural effusion	1,992	14
Multilobar	2,002	4
Septic shock	2,006	0

Abbreviations: FiO_2 indicates fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen.

Supplementary Table 3. Etiology of microorganisms by site of care

Variable	Patients not in the ICU (N = 1,802)	Patients in the ICU (N = 204)	P-value
Patients with defined etiology, n (%)	592 (33)	104 (51)	**<0.001**
Streptococcus pneumoniae	313 (53)	60 (58)	0.363
Respiratory virus	70 (12)	7 (7)	0.127
Legionella pneumophila	28 (5)	6 (6)	0.650
Haemophilus influenzae	24 (4)	4 (4)	>0.999
Atypical bacterial	38 (6)	3 (3)	0.158
Coxiella burnetii	12 (2)	1 (1)	0.704
Mycoplasma pneumoniae	15 (3)	0 (0)	0.145
Chlamydophila pneumoniae	11 (2)	2 (2)	>0.999
Pseudomonas aeruginosa	11 (2)	0 (0)	0.385
Staphylococcus aureus	12 (2)	5 (5)	0.156
GNEB	11 (2)	1 (1)	>0.999
Escherichia coli	11 (2)	1 (1)	>0.999
Moraxella catarrhalis	3 (1)	0 (0)	>0.999
Other	20 (3)	4 (4)	0.771
Polymicrobial	61 (10)	14 (13)	0.338
PES pathogens	46 (8)	9 (9)	0.758

Abbreviations: ICU indicates intensive care unit; GNEB, gram-negative enteric bacteria; PES, *Pseudomonas aeruginosa*, Enterobacteriaceae ESBL+ and *Staphylococcus aureus* methicillin resistant. The percentages of pathogens are related to the number of patients with etiologic diagnosis in each group (592 in the ward group and 104 in the ICU group). P-values marked in

bold indicate numbers that are statistically significant within the 95% confidence limit.

Supplementary Table 4. Internal validation of the prediction model for ICU admission using nonparametric bootstrap technique

Variable	Original	Bias	SE	95% BCa CI
Male sex	0.466	0.007	0.181	0.102 to 0.825
Neurological disease	-0.975	-0.014	0.267	-1.515 to -0.521
Respiratory rate ≥30 breaths/min	1.022	0.000	0.190	0.647 to 1.406
Systolic blood pressure <90 mmHg	0.759	-0.024	0.320	0.114 to 1.319
Serum creatinine ≥1.5 mg/dL	0.409	-0.005	0.182	0.038 to 0.758
Glucose level ≥200 mg/dL	0.777	-0.005	0.196	0.398 to 1.132
PaO_2/FiO_2 <250	0.836	0.013	0.182	0.452 to 1.232
Pleural effusion	0.581	-0.008	0.234	0.137 to 1.007
Multilobar	0.956	0.015	0.194	0.557 to 1.404
Septic shock	2.226	0.050	0.295	1.678 to 2.954

Abbreviations: BCa indicates adjusted bootstrap; CI, confidence interval; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; SE, standard error.

Supplementary Table 5. Characteristics of the study population by severe CAP

Variable	Patients with non-severe CAP (N = 1, 487)	Patients with severe CAP (N =519)	P-value
Age, years, median (Q1; Q3)	84 (82; 87)	85 (82; 89)	**<0.001**
Male sex, n (%)	854 (57)	333 (64)	**0.007**
Current smoker, n (%)	86 (6)	35 (7)	0.398
Current alcohol consumer, n (%)	85 (6)	35 (7)	0.344
Previous antibiotic, n (%)	307 (21)	111 (22)	0.535
Influenza vaccine, n (%)	871 (68)	217 (60)	**0.008**
Pneumococcal vaccine, n (%)	300 (23)	85 (23)	0.940
Previous inhaled corticosteroids, n (%)	234 (22)	74 (16)	**0.008**
Previous systemic corticosteroids, n (%)	43 (5)	15 (4)	0.776
Previous episode of pneumonia (last year), n (%)	197 (19)	81 (19)	0.864
Comorbidities, n (%) [a]	1,133 (76)	431 (83)	**0.001**
Chronic respiratory disease	605 (41)	219 (43)	0.422
Chronic cardiovascular disease	404 (27)	152 (30)	0.322
Diabetes mellitus	353 (24)	149 (29)	**0.020**
Chronic neurological disease	254 (17)	144 (28)	**<0.001**
Chronic renal disease	155 (10)	112 (22)	**<0.001**
Chronic liver disease	33 (2)	9 (2)	0.507
Nursing-home, n (%)	96 (6)	58 (11)	**<0.001**
Confusion, n (%)	165 (11)	264 (51)	**<0.001**
Respiratory rate, breaths/min, median (Q1; Q3)	22 (18; 28)	32 (24; 36)	**<0.001**
Heart rate, beats/min, median (Q1; Q3)	92 (80; 104)	97 (83; 110)	**<0.001**
Systolic blood pressure, mmHg, median (Q1; Q3)	137 (120; 155)	124 (100; 148.5)	**<0.001**
Diastolic blood pressure, mmHg, median (Q1; Q3)	70 (62; 80)	66.5 (57; 80)	**<0.001**
Temperature, ºC, median (Q1; Q3)	37.3 (36.7; 38.0)	37.1 (36.2; 38.0)	**<0.001**
Serum creatinine, mg/dL, median (Q1; Q3)	1.1 (0.9; 1.4)	1.6 (1.2; 2.1)	**<0.001**
C-reactive protein, mg/dL, median (Q1; Q3)	15.4 (7.7; 25.0)	19.3 (8.4; 28.8)	**0.002**

Variable	Patients with non-severe CAP (N = 1, 487)	Patients with severe CAP (N =519)	P-value
White blood cell count, cells/mm^3, median (Q1; Q3)	12,900 (9,400; 17,200)	12,750 (8,400; 18,570)	0.429
Lymphocytes, cells/mm^3, median (Q1; Q3)	950 (610; 1,365)	795 (374.5; 1,337)	**<0.001**
Glucose level, mg/dL, median (Q1; Q3)	132 (111; 168)	141 (111; 199)	**0.003**
Platelet count, platelets/mm^3, median (Q1; Q3)	263 (192; 1,250)	236 (167; 309)	**<0.001**
PaO_2/FiO_2, median (Q1; Q3)	286 (257; 319)	233 (200; 267)	**<0.001**
PSI score, median (Q1; Q3)	103 (91; 121)	145 (130; 162)	**<0.001**
Severe CAP, n (%)	-	519 (100)	-
Only ≥1 major criterion	-	58 (11)	-
≥1 major criterion and ≥3 minor criteria	-	84 (16)	-
Only ≥3 minor criteria	-	377 (73)	-
Bacteremia, n (%) [b]	85 (8)	66 (19)	**<0.001**
Pleural effusion, n (%)	161 (11)	68 (13)	0.117
Multilobar, n (%)	199 (13)	263 (51)	**<0.001**
ARDS, n (%)	16 (1)	63 (13)	**<0.001**
Acute renal failure, n (%)	332 (24)	341 (67)	**<0.001**
Septic shock, n (%)	0 (0)	102 (20)	**<0.001**
Appropriate empiric treatment, n (%)	1,261 (92)	383 (90)	0.104
Length of hospital stay, days, median (Q1; Q3)	6 (5; 9)	9 (6; 15)	**<0.001**
Invasive mechanical ventilation, n (%) [c]	0 (0)	70 (13)	**<0.001**
ICU admission, n (%)	50 (3)	154 (30)	**<0.001**
30-day mortality, n (%) [d]	53 (4)	128 (25)	**<0.001**

Abbreviations: ARDS indicates acute respiratory distress syndrome; CAP, community-acquired pneumonia; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; PaO_2, partial pressure of arterial oxygen; PSI, pneumonia severity index; Q1, first quartile; Q3, third quartile. Percentages calculated on non-missing data. P-values marked in bold indicate numbers that they are statistically significant within the 95% confidence limit. [a] Possibly >1 comorbidity. [b] Calculated only for patients with blood samples (1,127 in the non-severe CAP group and 355 in the severe CAP group). [c] Patients who initially received non-invasive ventilation but subsequently needed intubation were included in the invasive mechanical ventilation group. [d] Calculated only for

patients with 30-day follow-up (1,461 in the non-severe CAP group and 517 in the severe CAP group).

Supplementary Table 6. Etiology of microorganisms by severe CAP

Variable	Patients with non-severe CAP (N = 1, 487)	Patients with severe CAP (N =519)	P-value
Patients with defined etiology, n (%)	505 (34)	191 (37)	0.242
Streptococcus pneumoniae	278 (55)	95 (50)	0.210
Respiratory virus	62 (12)	15 (8)	0.097
Legionella pneumophila	25 (5)	9 (5)	0.896
Haemophilus influenzae	19 (4)	9 (5)	0.569
Atypical bacterial	36 (7)	5 (3)	**0.024**
Coxiella burnetii	11 (2)	2 (1)	0.531
Mycoplasma pneumoniae	13 (3)	2 (1)	0.378
Chlamydophila pneumoniae	12 (2)	1 (1)	0.128
Pseudomonas aeruginosa	3 (1)	8 (4)	**0.002**
Staphylococcus aureus	11 (2)	6 (3)	0.424
GNEB	3 (1)	9 (5)	**0.001**
Escherichia coli	3 (1)	9 (5)	**0.001**
Moraxella catarrhalis	3 (1)	0 (0)	0.566
Other	17 (4)	7 (4)	0.847
Polymicrobial	47 (9)	28 (15)	**0.042**
PES pathogens	21 (4)	34 (18)	**<0.001**

Abbreviations: CAP indicates community-acquired pneumonia; GNEB, gram-negative enteric bacteria; PES, *Pseudomonas aeruginosa*, Enterobacteriaceae ESBL+ and *Staphylococcus aureus* methicillin resistant. Percentages of pathogens are related to the number of patients with etiological diagnosis in each group (505 in the non-severe CAP group and 191 in the severe CAP group). P-values marked in bold indicate numbers that are statistically significant within the 95% confidence limit.

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