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TITLE PAGE

The SIS NET ICU Study:**Characteristics of patients with severe community acquired pneumonia admitted to Italian ICUs, a multicentre prospective observational study**

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ABSTRACT

Background: The SIS-NET ICU study aimed to describe the epidemiology of severe community-acquired pneumonia (CAP) among patients admitted to Italian intensive care units (ICUs). This study also aimed to describe the clinical and microbiological characteristics, outcomes, and treatments received by the included patients.

Methods: We conducted a prospective, observational, multicenter, study. We included patients consecutively admitted to the ICUs of 13 participating centers during the study period for acute respiratory failure due to CAP. The study period spanned from January to November 2025. The analyses aimed to describe the epidemiological and clinical characteristics, diagnostic pathways, factors associated with ICU mortality, and type of respiratory support during the ICU stay.

Results: We included a cohort of 150 patients with a mean age of 63 years and a male predominance (61%). The occurrence rate of CAP in the participating ICUs was 2.5%. Influenza A, respiratory syncytial virus, streptococcus pneumoniae and haemophilus influenzae were the predominant isolated microorganisms. The average APACHE II score was 17 (SD: 7.9) and the median SOFA score was 7 (SD: 3.9). The comorbidity burden was substantial. A high proportion of patients was managed with non-invasive respiratory supports. Rapid microbiological testing methods were early adopted in 63% of patients, with substantial impact on antimicrobial therapy decisions. Each 10-year increase in age was associated with a 54% increase in the odds of death (aOR 1.54, 95% CI 1.06–2.35; $p = 0.02$) and immunosuppressed status was associated with higher odds of death (aOR 3.13, 95% CI 1.04–9.63; $p = 0.04$). Polymicrobial infection showed a trend towards higher mortality (aOR 2.47, 95% CI 0.94–6.89; $p = 0.06$), although this association did not reach conventional statistical significance.

Conclusions: Our study demonstrated the predominance of common pathogens as microbiological isolates in patients with severe CAP in Italy. Comorbidities, age and immunosuppressed status were independently associated with a higher odds of mortality.

Clinical trial number: not applicable.

Keywords: ICU, CAP, infections, microbiology, mechanical ventilation

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INTRODUCTION

Community acquired pneumonia (CAP) affects million of patients worldwide annually and the severe cases burden healthcare systems, both in term of mortality and morbidity and healthcare resources (1). CAP has a spectrum of clinical severities. Severe CAP has been defined by Infectious Diseases Society of America/American Thoracic Society Criteria on the basis of major criteria, including septic shock with the need for vasopressors or respiratory failure requiring mechanical ventilation and minor criteria, including thresholds of respiratory rate, $\text{PaO}_2/\text{FiO}_2$ ratio, radiological findings and laboratory criteria (2).

A recent clinical practice guideline by the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Latin American Thoracic Association (ALAT) considered severe CAP as a CAP requiring intensive care unit (ICU) admission, even in the absence of shock or need for mechanical ventilation (1). Thus, clinical suspicion and diagnosis remain pivotal for the identification of severe CAP. Furthermore, ICUs are the settings where these patients may be admitted and managed from their early clinical presentation.

Current knowledge on etiological epidemiology has been challenged by pandemic periods and the introduction of rapid microbiological testing methods (e.g. PCR molecular techniques), which increased the proportion of identified viral or mixed bacterial-viral infections (3).

Geographical differences in epidemiology, along with the need for monitoring emerging viral etiologies, have recently issued the need for the creation of a network within the “Severe Infections and Sepsis clinical NEtwork for identification of clinical and diagnostic markers, immunological monitoring and Target and tailored therapies for adults, children and patients admitted to intensive care units (SIS-NET)” (4), a national project in Italy that

is composed of three clinical pillars, among which critical care. In the context of this project, the present study was developed to describe the epidemiology of severe CAP among patients admitted to Italian ICUs. This study also aimed to describe the clinical characteristics, outcomes, and treatments received by patients affected by these infections.

METHODS

We conducted a prospective, observational, multicenter, national, and non-profit study. We included patients consecutively admitted to the ICUs of the 13 participating centers during the study period. The entire period of study spanned from January to November 2025. Three ICUs included patients for a limited period due to authorizative issues. The study was approved by the EC of the participating centres (first approval by Comitato Etico Locale Palermo 1, 19/09/2024, n°23, Clinical trial number: not applicable.) and conducted in accordance with the Declaration of Helsinki.

For each patient, data were collected at baseline (e.g. day of ICU admission), daily throughout the ICU stay, and at ICU and hospital discharge. Data related to patient characteristics, outcomes, diagnostic investigations (i.e. microbiological and radiological), laboratory results and therapeutic interventions performed according to local protocols were collected.

The inclusion criteria were age ≥ 18 years, admission to the ICU, the presence of a CAP, occurred within 48 hours of hospital admission, and diagnosed by the clinician according to the criteria adopted at the participating center and the obtainment of an informed consent according to national regulation. Patients were excluded in case of refusal to participate in the study, infection occurred after more than 48 hours after hospital admission, hospitalization within the previous 30 days, residence in a healthcare facility (e.g., nursing home, intensive rehabilitation), terminal illness with poor short-term

prognosis according to the treating physician or patients included in the SIS-NET project during hospitalization in other wards (e.g. infectious disease wards).

The analyses aimed at describing the clinical patterns among ICU patients. The outcomes evaluated included the proportion of patients with CAP, ICU mortality, incidence of nosocomial infections, duration of ICU stay, total length of hospitalization, and duration of mechanical ventilation.

Procedures and Data Collection

Data collection was conducted prospectively using information extracted from patients' medical records and entered a pseudo-anonymized electronic database (OpenClinicaTM), fully compliant with GDPR regulations. Access to the platform was managed through tiered authorization levels, with differentiated permissions for data entry, data management, and monitoring, ensuring full traceability of changes and robust data protection. Each participating centre designated trained research personnel responsible for the accurate and timely recording of all required variables.

The dataset included a broad range of clinical and demographic information to comprehensively characterize the study population. Specifically, the following categories of data were collected: detailed anthropometric measurements, pre-existing comorbidities, key clinical parameters recorded throughout hospitalization, standardized organ dysfunction severity scores and indicators of systemic involvement, results from laboratory investigations, administered therapies, including timing and duration and a set of clinical outcome indicators such as complications, length of stay in the ICU and survival status. The aetiology of CAPs was categorized as polymicrobial when more than one microbiological pathogen was identified. The choice on the microbiological methods to be adopted and their timing were left at the discretion of the attending physicians as per their local protocols. The aetiology was further categorized based on the identification of only viral, only bacterial or mixed viral and bacterial isolates. Two researchers blindly evaluated

the modifications of antimicrobial therapy following fast microbiology results (MI, GC). Antimicrobial therapy was considered escalated in case of broadening of the antibiotic spectrum (including the change of molecules and the addition of further ones) or of addition of antiviral agents and de-escalation was defined as spectrum reduction or complete discontinuation. **Participating Centers and Representativeness**

Given the descriptive nature of the study, its observational design, and specific objectives, a convenience sample of consecutively treated patients at participating centers was included, without formal a priori sample size calculation.

Statistical Analysis

Descriptive statistics were used to describe the study population. Continuous variables were presented as mean and standard deviation when approximately normally distributed, and as median with interquartile range when their distribution departed from normality. Categorical variables were summarized as absolute and relative frequencies. For all estimates, 95% confidence intervals were reported to quantify the statistical uncertainty. The median time to ICU discharge alive and hospital discharge alive was estimated using Kaplan–Meier survival analysis. For each outcome, time zero was defined as the date of ICU admission (for ICU LOS) or hospital admission (for hospital LOS). The event was defined as live discharge from the ICU or hospital, respectively. Patients who died before discharge were censored at the earliest of death.

To explore the predictive value of variables potentially associated with mortality, both univariable and multivariable regression analyses were performed. Factors associated with ICU mortality were first examined using univariable logistic regression models (using the glm function with a binomial logit link). The explanatory variables included clinical parameters at admission, severity scores (APACHE II and SOFA), and immunocompromising conditions.

For continuous predictors, odds ratios were calculated per one standard deviation increase to enhance the comparability across measures. For categorical variables with more than two levels, a global likelihood ratio test was used. Because of the large number of explored associations, p-values were adjusted for multiple testing using the Benjamini–Hochberg procedure.

Given the limited number of outcome events and the risk of small-sample bias, the multivariable analysis of mortality was performed using logistic regression with Firth's penalization. Parameter estimates and 95% confidence intervals were obtained through profile penalized likelihood. Variables with p-values < 0.10 in the univariable analyses were entered into the multivariable models, and the final model was selected according to the lowest Akaike Information Criterion (AIC). All analyses were conducted by the study statisticians (MV, MC, MD) with clinical insights by MI and AC, using R Statistical Software (version 4.4.0), with statistical significance set at $p < 0.05$.

RESULTS

The cohort included 150 patients from 13 ICUs in Italy (Additional file 1, Supplementary Table 1), with a mean age of approximately 63 years (median 62.5), and a male predominance (61%). The occurrence rate of patients admitted with CAP among the overall cohort of patients admitted to the ICU in the participating centres was 2.5%. At the time of admission, the average APACHE II score was 17 and the average SOFA score was 7, with a median of 7 (IQR: 3.9). The comorbidity burden was substantial (Mean Charlson index 4.3). The most frequent comorbidities included COPD (25%), diabetes (30%), and a significant proportion of immunocompromised individuals (13%). Characteristics of the included patients are available at **Table 1**.

Baseline characteristics	N= 150
Age (≥ 18), mean $\pm$ SD	62.7 $\pm$ 14.1
Sex (Male), n(%)	92 (61.3%)
Height, mean $\pm$ SD	168.5 $\pm$ 9.7
Weight, median (Q1 - Q3)	75 (69-90)
APACHE II, mean $\pm$ SD	16.9 $\pm$ 7.9
CCI, mean $\pm$ SD	4.3 $\pm$ 2.4
SOFA, mean $\pm$ SD	6.8 $\pm$ 3.9
BMI, median (Q1 - Q3)	26.1 (23.7-32.3)
Onset Signs and Symptoms, n(%)	
Altered quantity/quality of sputum	27 (18%)
Dyspnea	120 (80%)
Fever	82 (55%)
Cough	62 (41%)
Source of Admission, n(%)	
Emergency Department – other hospital	29 (19.3%)
Emergency Department – same hospital	81 (54%)
Inpatient ward – other hospital	2 (1.3%)
Inpatient ward – same hospital	38 (25.3%)
NIV during hospitalization	67 (44.7%)
HFNO during hospitalization	31 (20.7%)
Comorbidities	
Diabetes mellitus, n(%)	45 (30%)
Chronic kidney disease, n(%)	14 (9.3%)
Renal replacement therapy, n(%)	4 (2.7%)
Active solid malignancy, n(%)	2 (1.3%)
Active hematologic malignancy, n(%)	7 (4.7%)
Chronic heart disease, n(%)	35 (23.3%)
Heart failure, n(%)	18 (12%)
Chronic liver disease, n(%)	15 (10%)
Cirrhosis, n(%)	7 (4.7%)
Chronic lung disease, n(%)	38 (25.3%)
COPD, n(%)	38 (25.3%)

Interstitial lung disease, n(%)	4 (2.7%)
Sleep apnea, n(%)	14 (9.3%)
Asthma, n(%)	10 (6.7%)
Alcohol and drug abuse, n(%)	18 (12%)
Current and former smoker, n(%)	65 (43%)
HIV, n(%)	6 (4%)
Chemotherapy in the past 30 days, n(%)	5 (3.3%)
Corticosteroid use, n(%)	14 (9.3%)
BMT, n(%)	4 (2.7%)
Neutropenia, n(%)	4 (2.7%)
AIDS, n(%)	2 (1.3%)
Chemotherapy, n(%)	9 (6%)
Immunosuppression status, n(%)	28 (19%)
Respiratory Support at ICU Admission	
CPAP	7 (4.7%)
No respiratory support	3 (2%)
NIV	35 (23.3%)
High-Flow Oxygen Therapy	13 (8.7%)
Low-Flow Oxygen Therapy	15 (10%)
Invasive Mechanical Ventilation	73 (48.7%)
NIV or CPAP Interface, n(%)	
Helmet	3 (7%)
Mask	38 (90%)
IMV respiratory settings	
Pplat, mean $\pm$ SD	20.9 $\pm$ 5.9
PEEP, mean $\pm$ SD	8.7 $\pm$ 3.1
Mandatory RR, mean $\pm$ SD	18.5 $\pm$ 4.8
Vt, mean $\pm$ SD	460.5 $\pm$ 78.9
Vt/kg (PBW), mean $\pm$ SD	7.6 $\pm$ 1.4
Arterial Blood Gas Analysis	
pH, mean $\pm$ SD	7.3 $\pm$ 0.1
PaO ₂ (mmHg), median (Q1 - Q3)	91 (70.8-114.3)
PaCO ₂ (mmHg), median (Q1 - Q3)	43.8 (34.7-57.6)

FiO ₂ (%), mean ± SD	65 ± 22.6
Lactate (mmol/L), median (Q1 - Q3)	1.4 (1-2.8)
Imaging	105 (70%)
Lung involvement: Unilateral/Bilateral, n(%)	
<i>Bilateral</i>	68 (45.3%)
<i>Unilateral</i>	37 (24.7%)
Laboratory	
WBC (10 ³ /μL), median (Q1 - Q3)	11.8 (8-16.5)
MDW, mean ± SD	22.2 ± 11.7
Procalcitonin (ng/mL), median (Q1 - Q3)	1.6 (0.4-14)
C-reactive protein (mg/dL), median (Q1 - Q3)	35.6 (17.2-172)

Data are reported as median (first quartile-third quartile), mean and standard deviation or counts and percentages, as appropriate.

AIDS, Acquired Immune Deficiency Syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, Body Mass Index; BMT, Bone Marrow Transplant; CCI, Charlson Comorbidity Index; CPAP, Continuous Positive Airway Pressure; COPD, Chronic Obstructive Pulmonary Disease; HFNO, High Flow Nasal Oxygen; HIV, Human Immunodeficiency Virus; MDW, Mean distribution width; NIV, Noninvasive ventilation; PEEP, Positive end expiratory pressure; Pplat, Plateau airway pressure; SOFA, Sequential Organ Failure Assessment; Vt, tidal volume; WBC, white blood cells.

Table 1. Characteristics of the included patients at baseline

The median PaO₂/FiO₂ ratio at admission was 144 [98-212], with a high FiO₂ requirement (median 65%). Radiological findings, when available, were often positive and bilateral. The clinical presentation consisted of dyspnea in 80%, fever in 55% and cough in 41%. Microbiological etiology was predominantly bacterial (≈67%), with a mixed virus+bacteria component in ≈24% of cases. The full list of microbiological isolates identified during the first 48h of ICU stay, regardless of the microbiological techniques adopted, is available in **Table 2**. Polymicrobial aetiology was identified in 41% of cases. **Table 2** also reports all the samples sent within the first 48h from ICU admission. The microbiological rapid testing methods locally available at the included centres are presented in the Additional file 1 (Supplementary Table 1). The baseline characteristics of patients grouped by bacterial,

viral or mixed aetiology of the infection are available in the Additional file 1 (Supplementary Table 2, Table 3).

Microbiological isolates from respiratory samples, (N = 133)*	
Viruses*	40 (30%)
Influenza A	14 (35%)
Respiratory Syncytial Virus (RSV)	8 (20%)
COVID-19 (SARS-CoV-2)	7 (18%)
Rhinovirus	4 (10%)
Human Metapneumovirus	2 (5%)
Epstein–Barr Virus (EBV)	2 (5%)
Human Coronavirus	2 (5%)
Influenza B	1 (3%)
Bacteria*	93 (70%)
Streptococcus pneumoniae	19 (20%)
Haemophilus influenzae	15 (16%)
Staphylococcus aureus	14 (15%)
Pseudomonas aeruginosa	8 (9%)
Escherichia coli	5 (5%)
Klebsiella pneumoniae	4 (4%)
Legionella species	3 (3%)
Moraxella catarrhalis	3 (3%)
Streptococcus pyogenes, Group A β -hemolytic	1 (1%)
Stenotrophomonas maltophilia	1 (1%)
Chlamydophila species	1 (1%)
Acinetobacter baumannii complex	1 (1%)
Serratia marcescens	1 (1%)
Other	17 (18%)
Etiology of CAP**	
Monomicrobial, n (%)	37 (59%)
Polymicrobial, n (%)	26 (41%)
Microbiological samples collected within the first 48h (N=170)***	
Bronchoalveolar Lavage (BAL) / mini – BAL / Protected Specimen Brush (PSB)	67 (39,4%)

Bronchoaspirate	27 (15,9%)
Sputum	20 (11,8%)
Pleural fluid	2 (0,7%)
Blood	54 (31,8%)

Table 2. Microbiological isolates from respiratory samples collected within 48h from ICU admission

Data are reported as median (first quartile-third quartile), mean and standard deviation or counts and percentages, as appropriate.

**The analysis on "Microbiological isolates from respiratory samples" has microbiological isolates as units, with n meaning number of isolates.*

*** The analysis on "Etiology of CAP" has patients as units, with n meaning number of patients.*

**** More than one sample could be collected per patient.*

Half of the patients received invasive mechanical ventilation at baseline. Among the documented ventilation modes, volume-controlled assist-control (VC-AC) was the most common and the mean tidal volume per kg of the predicted body weight was 7.6 ± 1.4 ml. The baseline characteristics of patients, grouped by aetiology (Additional file 1, Supplementary Table 1) and grouped by mortality status at ICU discharge (Additional file 1, Supplementary Table 2), are available in the Additional file 1.

Clinical outcomes

Mortality occurred in 21% of the included patients. The patients had a median duration of invasive mechanical ventilation of 8 days (Q1-Q3: 6-14). Median duration of empirical antimicrobial therapy was 3 days (1-6), while targeted therapy had a median duration of 6 days (3-10). Renal replacement therapy was needed in 16% of the patients and

vasopressors were administered in 51% of the patients for a median of 5 days. Prone positioning was adopted in 18% of patients and ECMO in 1%. The median time to ICU discharge alive was 11 days (95% CI 10–14), whereas the median hospital length of stay until discharge alive was 31 days (95% CI 22–38).

In 94 out of 150 patients (63%), rapid microbiological methods were applied within the first 48 hours. Eighty-six patients of these 94 patients had complete data on microbiology and antimicrobial therapies and were further evaluated. Rapid microbiological testing led to the modification of antimicrobial therapy in nearly 40% of these cases. The most common modification was the initiation of antimicrobial therapy in previously untreated patients (63% of escalation cases), followed by broadening of the antibiotic spectrum or by the addition of antiviral agents (18% and 16% of cases, respectively). Antimicrobial therapy was de-escalated in 13 patients, mostly through spectrum reduction, with complete discontinuation in 2 cases. No modifications in antimicrobial therapy after rapid microbiological testing results were observed in 45% of patients. Outcomes and organ support treatments are presented in **Table 3**. Additional file 1, Supplementary Table 4 shows the proportion of patients who developed ICU-acquired infections and their causative microbiological isolates. Additional file 1, Supplementary Table 5 shows data on respiratory support at ICU admission and outcomes grouped by geographical macroareas.

Outcomes	
Mortality, %	31 (21%)
Duration of invasive mechanical ventilation (d), median (Q1 - Q3)	8 (6-14)
ICU length of stay (d), median (Q1 - Q3)	11 (10-14)
Hospital length of stay (d), median (Q1 - Q3)	31 (22-38)
Tracheostomy, n(%)	25 (17%)
Extubation, n(%)	56 (37%)
ECMO, n(%)	2 (1%)
ECMO - days, mean $\pm$ SD	14.5 $\pm$ 0.7
Patients receiving at least one pronation session, n(%)	27 (18%)
Pronation - days, median (Q1 - Q3)	3 (2-4)
Steroids, n (%)	95 (63%)
Corticosteroid therapy - days, median (Q1 - Q3)	5 (3-8)
Renal replacement therapy, n(%)	24 (16%)
Renal replacement therapy – days, median (Q1 - Q3)	4.5 (2.8-9.2)
Vasopressors, n(%)	76 (51%)
Vasopressor therapy - days, median (Q1 - Q3)	5 (3-12)
Inotropes, n(%)	35 (23%)
Inotrope therapy - days, median (Q1 - Q3)	4 (2-10.5)

Data are reported as median (first quartile-third quartile), mean and standard deviation or counts and percentages, as appropriate.

Table 3. Outcomes and organ support treatments

After some exploratory univariate models with the aim of testing the association between mortality and all the baseline variables (OR estimation, CI and p-value in **Table 4**), a multivariable Firth logistic regression model with age, immunosuppressed status and polymicrobial infection was selected as the best model in terms of AIC.

Immunosuppressed status was associated with a more than threefold increase in the odd of death (adjusted OR 3.13, 95% CI 1.04–9.63; $p = 0.04$), while each 10-year increase in age was associated with a 54% increase in the odds of death (adjusted OR 1.54, 95% CI 1.06–2.35; $p = 0.02$). Polymicrobial infection showed a trend towards higher mortality

(adjusted OR 2.47, 95% CI 0.94–6.89; $p = 0.06$), although this association did not reach conventional statistical significance.

Table 4. Results of univariable and multivariable logistic regression for the outcome of mortality

Variable	Level	Univariate Model			Multivariable Model		
		OR	95% CI	p-value	OR	95% CI	p-value
APACHE II score	per 1-point increase	1.18	1.07-1.31	<0.001			
SOFA score	per 1-point increase	1.17	1.06-1.31	<0.001			
Any chemotherapy (Reference No)	Yes	7.76	1.91-38.80	0.01			
Age	per 10-year increase	1.05	1.01-1.09	0.01	1.54	1.06-2.35	0.02
SOFA cardiovascular component (Reference Score 0)*	Score 2	2.39	1.15-4.95	0.01			
	Score 3	0.73	0.28-1.99	0.50			
	Score 4	1.25	0.39-4.09	0.69			
Active haematological malignancy (Reference No)	Yes	9.42	1.91-68.50	0.01			
Immunosuppression status (composite variable) (Reference No)	Yes	3.12	1.23-7.82	0.02	3.13	1.04-9.63	0.04
Chronic heart disease (Reference No)	Yes	2.89	1.15-7.17	0.02			
Intermittent subglottic secretion drainage (Reference No)	Yes	2.47	1.06-5.75	0.04			
Prone positioning (Reference No)	Yes	2.5	0.97-6.27	0.05			
Charlson Comorbidity Index	per 1-point increase	1.13	0.99-1.29	0.06			
Use of inotropes (Reference No)	Yes	2.24	0.93-5.30	0.07			
Polymicrobial infection (Reference Monomicrobial)	Polymicrobial infection	1.91	0.78-4.81	0.09	2.47	0.94-6.89	0.06
Chemotherapy in the last 30 days (Reference No)	Yes	5.25	0.83-41.40	0.09			

* Odds ratios (ORs), 95% confidence intervals (CIs) and p-values were estimated using univariable logistic regression models and a multivariable Firth penalized logistic regression model. No patients had score 1 at SOFA cardiovascular component at baseline. APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; OR, Odds Ratio; SOFA, Sequential Organ Failure Assessment

Daily trends

Daily trends in patients' characteristics are presented in Additional file 1, Supplementary Table 6.

Across all repeated-measures mixed-effects analyses, strong differences emerged between the ICU survivors and non-survivors. $\text{PaO}_2/\text{FiO}_2$ ratio showed the clearest separation: non-survivors had substantially lower values throughout the ICU stay, and the trajectory over time diverged significantly (Interaction $p=0.002$). By day 14, the $\text{PaO}_2/\text{FiO}_2$ ratio was approximately 56% lower in patients who died. $\text{SpO}_2/\text{FiO}_2$ ratio demonstrated a similar pattern, with significantly worse values in non-survivors and distinct time trends ($p<0.001$ for both group and interaction). Lactate levels were consistently higher in non-survivors ($p<0.001$), and although they changed over time, the time course was similar between groups (non-significant interaction). The pH was lower in non-survivors and evolved over time, but again without evidence of differential temporal trajectories. PaCO_2 did not differ significantly between survivors and non-survivors. Overall, oxygenation markers ($\text{PaO}_2/\text{FiO}_2$ and $\text{SpO}_2/\text{FiO}_2$ ratios) were the variables that most clearly discriminated the dynamic evolution between survivors and non-survivors, whereas lactate and pH captured baseline differences but followed parallel trajectories. PaCO_2 did not appear a strong prognostic marker in this cohort. The results of the applied linear mixed-effects model and the graphical representation of daily trend are available in the Additional file 1 (Supplementary Table 6, Figure S1- S3). Respiratory support was assessed daily. Most changes were adopted in the first seven days and almost all the changes occurred in

the first 14 days. One of the most represented early transitions was endotracheal intubation and beginning of invasive mechanical ventilation from baseline (ICU admission) to the first ICU Day. **Figure 1** shows the daily trends of respiratory support, discharge and deaths over the first 14 days of ICU stay. Additional file 1, Supplementary table 7 shows missing value per variable.

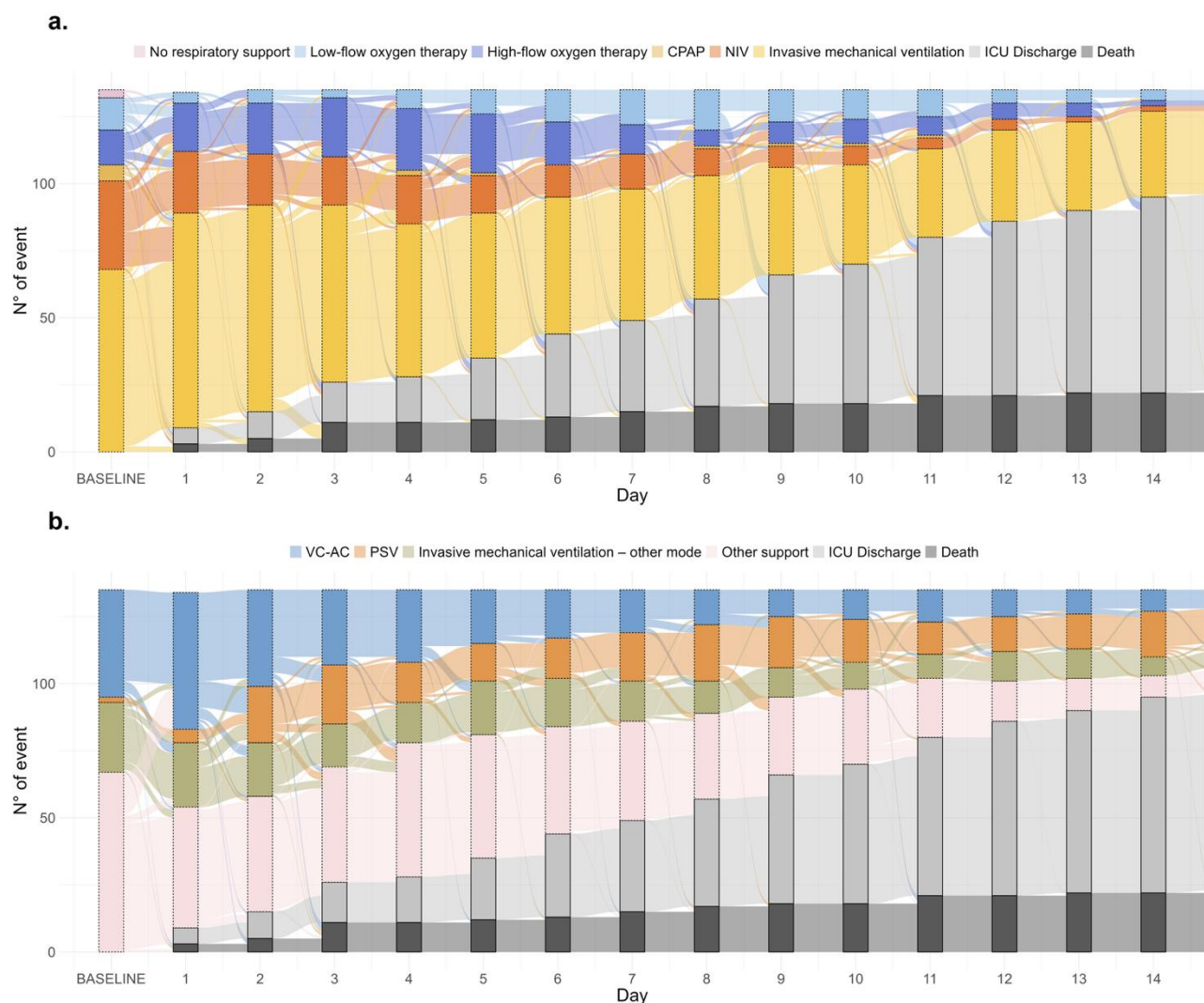


Figure 1. Daily trends of respiratory support (Panel A) and of respiratory support, discharge alive and deaths (Panel B) over the first 14 days

DISCUSSION

The present study is the most recent observational multicentre study providing data on the epidemiology, aetiology and clinical severity of patients with CAP admitted to Italian ICUs.

The main finding of the study is the independent association between age and immunosuppressed status and the outcome of mortality, regardless clinical severity at time of ICU admission. These factors may thus be predictors of an increased risk of unfavourable outcome in patients with severe CAP. Polymicrobial infections were also associated with higher odds of mortality, despite non significantly ($p=0.06$) possibly reflecting a more complex and disrupted interaction between the host and the pathogens causing the clinical syndrome.

Our study also confirms a classical predominance of bacterial microbiological isolates in CAP (i.e. *Streptococcus pneumoniae* and *Haemophilus influenzae*) and shows a high proportion of viral isolates, in line with the wide availability of molecular rapid microbiological methods and recent epidemiological findings (3,5). We also found a high percentage of patients with moderate or severe oxygenation impairment and a high prevalence of bilateral infiltrates on chest imaging.

The occurrence rate of CAP among the total number of patients admitted to ICU was 2.5%, in line with pre-pandemic era literature(6). We could argue that the occurrence rate of severe CAP among the total number of patients admitted to the ICU can be an early alert for future pandemics caused by novel pathogens, and the SIS NET ICU network would have been able to track this alert. On the clinical side, oxygenation markers were the variables that most clearly discriminated the dynamic evolution between survivors and non-survivors, whereas lactate and pH captured baseline differences but followed parallel trajectories.

Overall, our study was not intended to look for association between any treatment and clinical outcomes; however we collected data on intervention supported by current guidelines (1,2). We found a large use of corticosteroids (nearly in 60% of cases), used more at a higher proportion of patients compared to vasopressors (51% of patients), and

thus in line with recent guidelines (2), suggesting their use for severe CAP regardless of septic shock. In our cohort, corticosteroids were used for average 5 days and they were also used in patients with viral CAP. Fragmented evidence is currently available to support clinicians in the choice of corticosteroids duration (7) and specific indication based on etiology (2,8).

A proportion of patients were admitted to ICUs under non-invasive mechanical ventilation or other non-invasive support (e.g. high-flow nasal oxygen, HFNO) (9,10). A quote of such patients remained on non-invasive support throughout their ICU stay (see Supplementary Material), achieving the outcome without escalation to invasive ventilation (see **Figure 1**). The relatively small proportion of patients receiving non-invasive respiratory support at ICU admission may be attributable to the increasing availability of HFNO and NIV in non-ICU settings during the post-pandemic era (9,11). Notably, up to 21% and 45% of patients had already undergone HFNO and NIV, respectively, prior to ICU admission, suggesting that ICU admission may have occurred after failure of these strategies. The increasing proportion of patients receiving HFNO over time (Supplementary Table 6, daily trends), is also consistent with current evidence (12) supporting its role in post-extubation management of hypoxemic patients(13,14).

We also found a limited use of the helmet interface for providing NIV, despite Italy's extensive experience with this interface (15). Several factors could have contributed to this finding, including regional differences, center-specific protocols, and even generational or cultural influences on clinical practice(16). In addition, patient-related aspects (e.g. elevated median BMI, the proportion of patients with COPD) and potential patients' preferences might also have had a role (16). However, we acknowledge that our dataset does not provide data to support speculations on this point.

Looking at microbiological testing methods, the most relevant finding is that in almost the 63% of the included patients, a rapid testing method was adopted within the first 48h from ICU admission. This diagnostic pathway led to antimicrobial treatment modification in 40% of cases which results in line with current literature(17). Overall, these data underline important role of rapid diagnostic tests in the management of severe CAP in ICUs in Italy(17).

This study has some limitations. First, the observational nature and epidemiological and descriptive design preclude the evaluation of causative associations. The study period was limited to less than 12 months because of the scope of the allocated funding. Three centres joined the study later in the year, including a small number of patients; thus, the geographical representativity of the study may be limited. Moreover, the observational nature of the study implies a high heterogeneity of local protocols of diagnosis, management and treatments. For example, each centre was left free to adopt their preferred microbiological testing methods at their convenient timing and we did not collect data on the exact testing methods adopted per each patient. However, it is a strength of the study that we have included centres from all the Italian macroregions (Northern, Central and Southern), witnessing the ability of the network to collect data on infectious diseases and provide updated information on aetiology, clinical severity and diagnostic pathways.

CONCLUSION

Our study demonstrated the predominance of common pathogens as microbiological isolates in patients with severe CAP in the ICUs in Italy. Comorbidities, age and immunosuppressed status were independently associated with a higher odds of mortality. A high proportion of patients were managed with non-invasive respiratory support during their ICU stay. Rapid diagnostic tests were adopted for both diagnosis and therapy in 2/3 of CAP cases with substantial impact on the therapeutic management.

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List of abbreviations

CAP, community acquired pneumonia

HFNO, high flow nasal oxygen

ICU, intensive care unit

NIV, Noninvasive Ventilation

OR, Odds Ratio

PaCO₂, Partial Pressure of Arterial Carbon Dioxide

PaO₂, Partial Pressure of Arterial Oxygen

PaO₂/FiO₂, Ratio of Arterial Oxygen Partial Pressure to Fraction of Inspired Oxygen

DECLARATIONS

Human Ethics and Consent to Participate

Human Ethics approval was obtained and Consent to Participate was acquired by the included patients or their proxy as per national regulations.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

EP declared fees from general electric, AOP, Edwards lifescience, Hemonetics, BBraun and DOC generici, not related to the present project. All the other authors declared no competing interests for the present study. AC is an Associate Editor for Journal of Anesthesia Analgesia and Critical Care.

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Authors' contributions

Conception: MI, AC and AG. Study design and methodology: MI, AC, AG, MV, MC, MD.

Data collection: All the authors. Data analysis: MV, MC, MD with input by MI and AC. Data

visualisation: MV, MC, MD. Funding acquisition: AG. Project administration: AG. Writing of

the original draft: MI, GC, AC, MV, MC, MD. Reviewing, and editing of the final manuscript: All authors. All authors read and approved the final manuscript, are responsible for the contents and agreed to submit the manuscript.

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Figure Legends

Figure 1

Panel A

Daily trends of respiratory support over the first 14 days

Panel B

Daily trends of respiratory support, discharge alive and deaths over the first 14 days

ADDITIONAL INFORMATION

Filename: Additional file 1:

File format: .docx

Title of data: Supplementary Material

Contents:

1. Supplementary Table 1. Contribution of the centres and occurrence rate of CAP
2. Supplementary Table 2. Baseline patients' characteristics grouped by aetiology
3. Supplementary Table 3. Baseline patients' characteristics grouped by mortality status at ICU discharge
4. Supplementary Table 4. ICU-acquired infections and causative microbiological isolates
5. Supplementary Table 5. Respiratory support at ICU Admission and outcomes grouped by geographical macroarea
6. Supplementary Table 6. Daily trends of patients' characteristics
7. Supplementary Table 7. Missing values per variable
8. Supplementary Table 8. Linear mixed-effects model for daily trend and mortality
9. Supplementary Figure S1. Daily trend of serum lactate value grouped by outcome
10. Supplementary Figure S2. Daily trend of S/F ratio grouped by outcome
11. Supplementary Figure S3. Daily trend of P/F ratio grouped by outcome