

# Incidence, risk factors and prognostic impact of severe community-acquired pneumonia complications' in ICU: An observational cohort study

## Les complications liées aux pneumopathies aiguës communautaires graves en réanimation: Incidence, facteurs de risque et impact pronostique

Asma Mehdi, Meriem Cherif, Noussair Azzouz ; Eya Seghir ; Linda Messaoud, Asma Ouhibi, Ahlem Trifi, Sami Abdellatif.

University of Tunis El Manar , Faculty of Medicine of Tunis ,1007, University hospital of la Rabta, Medical Intensive Care Unit, Tunis, Tunisia.

### ABSTRACT

**Background:** Severe -Community-Acquired-Pneumonia (SCAP) is a public health concern. It is characterised by a dynamic profile leading to secondarily complicated forms. SCAP complications are under-studied in ICU while linked to mortality and healthcare costs. We hypothesize that SCAP complications are common in ICU and that they may be avoidable thru some clinical and paraclinical indicators. Thus, we aim to study the incidence, risk factors and prognostic impact of these complications in a Tunisian ICU.

**Methods:** It was an observational cohort study conducted over a period of two years in a Tunisian ICU. All patients admitted for a SCAP were included. The occurrence of complications was followed. Factors associated with these complications were analysed through a logistic regression analysis. Survival analysis was processed using the Kaplan-Meier curves linked with the Log-rank test.

**Results:** SCAP complications occurred in 78% of cases. The main local complications were ARDS (N=61) and pulmonary abscess (N=15). The main systemic ones were cardiovascular complications (N=151), acute kidney injury (N=131), septic shock (N=93) and sepsis-associated encephalopathy (N=98). *Klebsiella pneumoniae* was isolated in 54 cases. Multivariate analysis showed that a SOFA score  $\geq 2.5$  (OR=5.57 [2.86-10.83];  $p=0.000$ ), SMART-COP score  $\geq 4.5$  (OR=2.18 [1.09-4.35];  $p=0.027$ ), COPD history (OR=3.64 [1.73-7.66];  $p=0.001$ ) and age  $\geq 68$  years (OR=1.03 [1.01-1.05];  $p=0.001$ ) were significantly linked to CAP complications. These were independently linked to mortality (OR=8.59; 95% CI [3.21-22.9];  $p=0.003$ ). Survival analyses showed that the concomitant occurrence of both systemic and local complications decreased the survival delay time by an average of 15 days when compared to un-complicated patients.

**Conclusions:** Complications of SCAP are common in ICU with a dynamic and alarming microbiological profile. An early assessment of at-risk patients may tailor management and improve SCAP outcome.

**Keywords:** Severe- Community-Pneumonia- -Complications-Risk Factors-Mortality- ICU-Prognosis.

### RÉSUMÉ

**Contexte:** La pneumonie communautaire sévère (SCAP) est un problème de santé publique. Elle se caractérise par un profil dynamique menant à des formes secondairement complexes. Les complications du SCAP sont sous-étudiées en soins intensifs tout en étant liées à la mortalité et aux coûts de santé. Nous émettons l'hypothèse que les complications du SCAP sont fréquentes en réanimation et qu'elles pourraient être évitées grâce à certains indicateurs cliniques et paracliniques. Ainsi, nous visons à étudier l'incidence, les facteurs de risque et l'impact pronostique de ces complications dans une USI tunisienne.

**Méthodes:** Il s'agissait d'une étude observationnelle de cohorte menée sur une période de deux ans dans une unité de soins intensifs tunisienne. Tous les patients admis pour un SCAP étaient inclus. L'apparition de complications a été prise en compte. Les facteurs associés à ces complications ont été analysés par une analyse de régression logistique. L'analyse de survie a été traitée à l'aide des courbes de Kaplan-Meier liées au test de rang logarithmique.

**Résultats:** Les complications du SCAP sont survenues dans 78 % des cas. Les principales complications locales étaient le SDRA (N=61) et l'abcès pulmonaire (N=15). Les principales complications systémiques étaient les complications cardiovasculaires (N=151), l'insuffisance rénale aiguë (N=131), le choc septique (N=93) et l'encéphalopathie associée à la septicémie (N=98). *Klebsiella pneumoniae* a été isolée dans 54 cas. L'analyse multivariée a montré qu'un score SOFA  $\geq 2,5$  (OR=5,57), un score SMART-COP  $\geq 4,5$  (OR=2,18), un taux respiratoire  $\geq 27$  cycle/min (OR=3,64), un taux initial de créatinine sanguine  $\geq 82$   $\mu\text{mol/l}$  (OR=1,03) et une atteinte multilobe (OR=1,03) étaient significativement liés aux complications de la PAC. Ces derniers étaient indépendamment liés à la mortalité (OR = 8,59 ; IC à 95 % [3,21-22,9] ;  $p=0,003$ ). Les analyses de survie ont montré que la survenue concomitante de complications systémiques et locales réduisait en moyenne le délai de survie de 15 jours par rapport aux patients non compliqués.

**Conclusions:** Les complications du SCAP sont fréquentes en réanimation avec un profil microbiologique dynamique et alarmant. Une évaluation précoce des patients à risque peut adapter la prise en charge et améliorer les résultats du SCAP.

**Mots clés:** Pneumopathie infectieuse- Infection Communautaire-Sévérité-Complications-Facteur de risque-Mortalité-Réanimation.

### Correspondance

Asma Mehdi

Medical Intensive Care Unit, University Hospital Center of La Rabta and Faculty of Medicine, University Tunis, El Manar, Tunis, Tunisia.

Email: asmaelmehdi245@gmail.com

**What is known ?**

SCAP represents a major public health concern and requires both urgent diagnostic and therapeutic management. Several complications may arise during the evolutionary process of SCAP. That may impact patient prognosis.

**What this article adds ?**

Our study focused on a pathology that is still relevant in ICU with dynamic epidemiological data especially with the emergence of new pathogens and the increasing resistance to antibiotics, thus limiting therapeutic resources. This is even more pronounced with the secondarily complicated forms of CAP. Thus, thru our data, we could enrich national registries. In addition, our findings may help clinicians detect early SCAP at risk of complications to tailor patient management and reduce ICU cost.

## INTRODUCTION

Severe community-acquired pneumonia (SCAP) represents a major public health concern and requires both urgent diagnostic and therapeutic management. Several scoring systems have been developed to assess CAP severity, predict prognosis, and tailor patient management. These scores include: PSI (Pneumonia Severity Index), CURB-65 (Confusion, Uremia  $> 7 \text{ mmol/L}$ , Respiratory rate  $\geq 30$  cycles/min, systolic Blood pressure  $\leq 90 \text{ mmHg}$ , Age  $\geq 65$  years), SMART COP (Systolic blood pressure  $\leq 90 \text{ mmHg}$ , Multilobar infiltrates, Albumin  $< 3.5 \text{ g/dl}$ , Respiratory rate "age adjusted", Tachycardia  $\geq 125 \text{ bpm}$ , Confusion, Oxygen low "age adjusted" and  $\text{pH} < 7.35$ ), CAP-PIRO (Predisposition, Insult, Response, and Organ dysfunction), and the scores from the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS). [1]. According to various studies, 9 to 23% of CAP cases lead to intensive care and mortality ranges from 20% to 56%. [2,3] This rate varies from 25% to 30% in Tunisian series. [4–6]

Several complications may arise during the evolutionary process of SCAP. That may impact patient prognosis. Local complications may include mainly: pleural effusions, empyemas, cavitations and acute respiratory distress syndrome (ARDS). The systemic ones may include: septic shock, cardiovascular complications, hematological complications, diabetic ketoacidosis, etc.). [7] The incidence of these complications, the initial risk factors linked to their occurrence during ICU stay, and their prognostic impact (mortality, cost of care, length of stay) remain a subject of current interest. Few Tunisian studies have focused on these aspects of SCAP in the ICU.

Accordingly, the primary outcome of this study was to assess the occurrence of complications related to SCAP in a Tunisian ICU and to identify their associated risk factors. The secondary outcomes were to evaluate the overall incidence of SCAP, to describe its clinical, paraclinical, microbiological, and therapeutic characteristics, and to assess the prognostic impact of SCAP-related complications. That included complications present at inclusion or occurring during the ICU stay

## METHODS

### Study Design

It was a prospective and comparative cohort study conducted in the medical intensive care unit of La Rabta University Hospital Center over a period of two years (June 2023 - June 2025). Our department had a versatile activity with a capacity of fourteen beds.

### Study population

All patients aged 18 years or older admitted to the ICU for a SCAP were eligible for the study. When the diagnosis of a SCAP was established by the medical staff, the occurrence of local and/or systemic complications was monitored. The study population was thus subdivided into: complicated CAP versus uncomplicated CAP.

Exclusion criteria were: Hospital-acquired pneumonia, history of hospitalization in the previous 3 months, Active pulmonary tuberculosis / pulmonary fibrosis (Pulmonary involvement difficult to characterize), patients who did not consent to participate in the study.

### Definitions

**Severe community-acquired pneumonia (SCAP):** is a life-threatening condition defined by the presence of respiratory failure or symptoms of sepsis or septic shock. Objectively, we referred to the definition established by the IDSA/ ATS [8]. SCAP was defined by the presence of a single major criterion (Septic Shock requiring vasopressors, Respiratory failure requiring mechanical ventilation) or three minor criteria (Respiratory rate  $\geq 30$  cycles/min, arterial partial pressure of oxygen / the inspiratory concentration of oxygen ( $\text{PaO}_2/\text{FiO}_2$ )  $\leq 250$ , Multilobar infiltrates, Confusion, Blood Urea Nitrogen  $\geq 20 \text{ mg/dL}$ ; White blood cells count  $< 4000$  elements/ $\text{mm}^3$ , Thrombocytopenia  $< 100.000$  elements/ $\text{mm}^3$ , hypothermia and hypotension requiring intravenous fluids).

**Local complications:** those affecting exclusively the thoraco-pulmonary system. That includes pulmonary abscesses, necrosis, cavitation, pleural empyema or pyopneumothorax. Furthermore, ARDS was considered as a local complication. ARDS was defined by the acute onset (within 7 days) of respiratory failure, with hypoxemia ( $\text{PaO}_2/\text{FiO}_2 < 300$ ). The presence of radiological infiltrates not fully explained by nodules or pleural effusion was required for diagnosis. Furthermore, left ventricular filling pressures were evaluated in order to rule out a cardiogenic oedema. [9] Recently, ARDS definition has been extended to patients under high-flow nasal cannula with a minimum flow rate of 30L/min or non-invasive ventilation /CPAP with a minimum PEEP level of 5  $\text{cmH}_2\text{O}$  with a  $\text{PaO}_2/\text{FiO}_2$  ratio  $\leq 300$ . [10].

**Systemic Complications:** Sepsis or septic shock ; Cardiovascular complications (Acute coronary syndrome , arrhythmia , acute heart failure...); Metabolic

complications (Hyperglycaemic complications, acute renal injury, Critical Illness Related Corticosteroid Insufficiency.); haematological complications (Disseminated intravascular coagulation, Macrophage Activation Syndrome, isolated thrombocytopenia ..); Neurological complications related to septic encephalopathy. The diagnosis of sepsis-related-encephalopathy was made in the presence of altered consciousness ranging from stupor to coma, with normal brain imaging and a lumbar puncture ruling out infectious meningo-encephalitis.

**An unresolved sepsis** was defined by the persistence of infectious signs after 72 hours of an optimal antimicrobial therapy (i.e. posology and modality..)

All these complications were predefined and assessed prospectively.

### Collected data

For each patient, we recorded demographics, comorbidities, CAP severity scores, clinical features, initial laboratory findings, initial chest X-ray or computed tomography scan data, microbiological findings, treatment (respiratory supports, probabilistic antibiotic therapy prescribed and de-escalation options) and clinical outcomes.

Severity CAP scores recorded were: PSI, CURB-65, SMART COP, IDSA/ ATS score and CAP-PIRO.

In order to identify the causal pathogen, microbiological samples were routinely collected: respiratory samples (Cytobacteriological examination of sputum for non-intubated patients and deep Tracheal aspirate sampling for mechanically ventilated patients) and several blood cultures. A High respiratory panel (via nasopharyngeal and oropharyngeal swab) with Real-time PCR (Polymerase-Chain-Reaction) was systematically performed upon admission. That aimed to highlight viruses and atypical bacteria. The results were interpreted with caution, taking into account the epidemiological and clinical context.

### Management of SCAP

Patients with SCAP were managed according to a standardized protocol based on supportive care and early etiological treatment. Respiratory support was tailored to the severity of hypoxemia. Oxygen therapy was delivered using the most appropriate interface, ranging from standard nasal cannula and simple face mask to non-rebreather mask or high-flow nasal cannula (HFNC). Ventilation support was sometimes required with non-invasive ventilation (NIV), or invasive mechanical ventilation following endotracheal intubation. The choice of the optimal respiratory support was determined through discussion during daily medical rounds, taking into account the patient's clinical course and gas exchange parameters. In the event of hemodynamic instability, fluid resuscitation with crystalloids was initiated and guided by clinical examination and echocardiographic assessment of fluid responsiveness. Norepinephrine was introduced in cases of persistent signs of circulatory

failure despite adequate fluid resuscitation, or promptly in the presence of significant vasoplegia (defined as diastolic blood pressure < 35 mmHg). Hydrocortisone hemisuccinate was administered at a daily dose of 200 mg divided into 4 equal doses in all cases of presumed bacterial pneumonia, irrespective of the presence of septic shock. Empiric antibiotic therapy consisted of mono or dual bactericidal coverage, selected according to the suspected pathogens, disease severity, patient history, and clinical and laboratory findings. Antimicrobial therapy was subsequently reassessed and de-escalated based on microbiological documentation. The planned duration of treatment was 7 days on average, with early discontinuation considered in cases of favorable clinical evolution and a significant decrease in procalcitonin levels (>80%).

### Study outcomes

We focused mainly on the epidemiology of CAP complications, its risk factors and prognostic impact. That concerned mainly the cost of care, 28 mortality and length of stay in ICU.

### Statistical Analyses

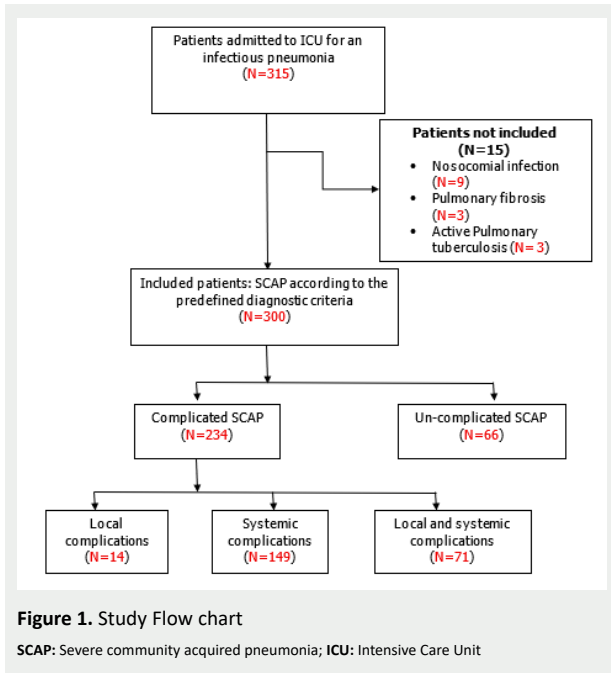
All statistical analyses were performed using IBM SPSS ver. 20 (IBM Corp., Armonk, NY, USA). Quantitative variables were expressed as mean  $\pm$  SD (for continuous and normally distributed ones) and as median [25%-75% percentile (Interquartile range: IQR)] for continuous non-normally distributed ones. Normality was assessed using the Kolmogorov-Smirnov test. Two groups were identified: Complicated versus uncomplicated SCAP. Quantitative variables were compared with a non-parametric Mann-Whitney test or T-student test as appropriate. Categorical variables were expressed as counts and percentages and compared using a chi-square test or Fisher's exact test as appropriate. The risk factors for SCAP complications were first screened with the univariate logistic regression model. The variables with a P-value of 0.05 or less were imported into a logistic regression analysis using the entered method. The quality of the regression model was assessed using the pseudo-coefficients R<sup>2</sup> of Cox Snell and Nagelkerke. Higher R<sup>2</sup> values indicated that the variation was explained by the model up to a maximum of one. Moreover, the thresholds for some quantitative variables were determined using ROC curves by selecting the best sensitivity-specificity pair. In order to analyse the prognostic impact of SCAP complications, survival analysis was processed using the Kaplan-Meier curves and compared by the Log-rank test (Local complications/ Systemic complications or both).

## RESULTS

### Study flow chart and baseline characteristics

During the study period, 300 patients were admitted for severe CAP according to predefined diagnostic criteria,

resulting in an incidence rate of 326 per 1000 admissions (32.6%). The majority of patients (85%) were admitted through the emergency department or were transferred from the pulmonology department of our institution. Fifteen patients were not included, especially when the community-acquired origin of pneumonia could not be definitively ascertained. This included cases involving hospitalization for more than 48 hours in another healthcare unit or the presence of established risk factors for multidrug-resistant pathogens, such as prior exposure to broad-spectrum antibiotic therapy. CAP complications (local/systemic) occurred in 78% of cases. The flow chart of the study is represented in the fig1.



As for baseline characteristics, male gender was predominant (Sex ratio: 2.03). Twenty-three patients were Immunocompromised: HIV-positive (N=5), immunosuppressive treatment (N=9), long-term corticosteroid treatment (N=7), neoplastic context (N=2). Table 1 shows the baseline parameters (Demographic, clinical, biological, and radiological) in all populations and, for each group, according to the presence of complications. Time to treatment initiation (TTI) was defined as the interval between hospital admission and the initiation of appropriate therapy.

### Supportive management

Respiratory support consisted of an alternating strategy between NIV and conventional oxygen therapy in 40.3% of cases, with a significantly higher proportion in uncomplicated pneumonia compared with complicated pneumonia (59.1% vs. 35%, respectively;  $p < 0.001$ ). An alternating NIV and HFNC strategy was implemented in 3% of secondarily complicated cases. Overall, invasive mechanical ventilation was required in 23.6% of patients, occurring more frequently in complicated pneumonia than in uncomplicated pneumonia (29.1% vs. 4.5%, respectively  $< 0.001$ ). Norepinephrine was required in

31% of cases complicated by septic shock, with a mean dose of 0.5  $\mu\text{g/kg/min}$ . Hydrocortisone hemisuccinate, administered according to the previously standardized dosage regimen, was prescribed in 90% of cases.

**Table 1.** Assessed baseline parameters in all patients according to the presence of complications

| Variable                                               | Total population (N=300) | Complicated CAP (N=234) | Un-complicated CAP (N= 66) | P          |
|--------------------------------------------------------|--------------------------|-------------------------|----------------------------|------------|
| <b>General data</b>                                    |                          |                         |                            |            |
| Age Med [IQR] (years)                                  | 65 [51-71]               | 66 [51.2-72]            | 63 [47.7-68]               | 0.023      |
| Male gender N (%)                                      | 201 (67)                 | 162 (69.2)              | 39 (59)                    | 0.08       |
| BMI Med [IQR] $\text{kg/m}^2$                          | 26.3 [23-29]             | 26 [22.8-29]            | 25.6 [23-28.5]             | 0.93       |
| <b>Habits and Comorbidities N (%)</b>                  |                          |                         |                            |            |
| Tobacco                                                | 180 (60)                 | 136 (58.1)              | 44 (67)                    | 0.25       |
| Drug Addiction                                         | 9 (3)                    | 8 (3.4)                 | 1 (2)                      | 0.68       |
| Hypertension                                           | 111 (37)                 | 96 (41)                 | 15 (23)                    | 0.006      |
| Diabetes                                               | 107 (35.6)               | 93 (39.7)               | 14 (21)                    | 0.004      |
| Chronic heart failure                                  | 46 (15.3)                | 41 (17.5)               | 5 (8)                      | 0.053      |
| AF                                                     | 26 (8.6)                 | 26 (11)                 | 0 (0)                      | 0.002      |
| CRF                                                    | 98 (29.7)                | 68 (29)                 | 21 (32)                    | 0.65       |
| COPD                                                   | 119 (39.6)               | 82 (35)                 | 37 (56)                    | 0.003      |
| Chronic Renal Failure                                  | 26 (8.6)                 | 23 (9.8)                | 3 (5)                      | 0.22       |
| Immuno-compromised                                     | 23 (7.7)                 | 18 (7.7)                | 5 (8)                      | 1          |
| Unfavorable SEC                                        | 160 (53.3)               | 127 (54.2)              | 33 (50)                    | 0.57       |
| <b>Clinical Findings</b>                               |                          |                         |                            |            |
| TTI (Days) Med [IQR]                                   | 3 [1-5]                  | 3 [1-5]                 | 2 [1-4]                    | 0.93       |
| Intercostal Drawing N (%)                              | 153 (51)                 | 128 (54.7)              | 25 (38)                    | 0.018      |
| Respiratory Rate Med [IQR] (cycles/min)                | 28 [25-32]               | 29 [26-35]              | 25 [18-30]                 | $<10^{-3}$ |
| Fever N (%)                                            | 33 (11)                  | 26 (11)                 | 7 (11)                     | 1          |
| MAP Med [IQR] (mmHg)                                   | 88 [80-100]              | 87 [79-99]              | 91 [84-102]                | 0.051      |
| Confusion/ Coma N (%)                                  | 81 (27)                  | 78 (33.3)               | 3 (5)                      | $<10^{-3}$ |
| <b>Laboratory Findings</b>                             |                          |                         |                            |            |
| P/F ratio Med [IQR]                                    | 225 [160-303]            | 213 [152-295]           | 246 [203-331]              | 0.004      |
| WBC Med [IQR] ( $\times 10^3/\text{mm}^3$ )            | 11.4 [7.8-16.5]          | 11.7 [8-16.7]           | 11 [7.6-14]                | 0.26       |
| Creatinine Med [IQR] ( $\mu\text{mol/L}$ )             | 85 [63-134]              | 93.5 [66-161]           | 65 [58-76]                 | $<10^{-3}$ |
| Thrombocytopenia N (%)                                 | 78 (26)                  | 75 (32.1)               | 3 (5)                      | $<10^{-3}$ |
| Lactate Mean $\pm$ SD (mmol/L)                         | $2.27 \pm 1.51$          | $2.3 \pm 1.58$          | $2.1 \pm 1.25$             | 0.28       |
| <b>Radiological Findings</b>                           |                          |                         |                            |            |
| Multilobar involvement on Chest X-ray and/ or CT N (%) | 188 (62.7)               | 157 (67.1)              | 31 (47)                    | 0.004      |

CAP: Community acquired pneumonia, MED: Median, IQR: Interquartile Range, AF: Atrial fibrillation, CRF: Chronic respiratory failure, COPD: Chronic obstructive pulmonary disease, SEC: Socio-economic conditions, BMI: Body mass index, TTI: Time to treatment initiation; MAP: Mean arterial pressure, WBC: White blood cells, SD: Standard deviation; CT: Computed tomography

### Anti-infective treatment strategies

Empirical antibiotic therapy was initiated in 90% (270/300) of patients with a presumed bacterial etiology. The prescribed regimens, in descending order of frequency, were amoxicillin–clavulanic acid (30.3%), cefotaxime combined with a quinolone (26.3%), cefotaxime combined with a macrolide (19.6%), cefotaxime alone (9.3%), and amoxicillin–clavulanic acid combined with a quinolone (1.8%). Amoxicilline-clavulanic acid and cefotaxime were used at a daily dose of respectively 3 and 6g. The most commonly used quinolone was fluoroquinolone at a daily dose of 500 mg twice daily. The macrolide used was erythromycin at a daily dose of 3 g. Antibiotic dosages was adjusted according to renal function. Oseltamivir (150 mg twice daily) was empirically added in three cases due to a suspicion of viral pneumonia. In four cases, a triple regimen consisting of cefotaxime, a quinolone, and linezolid was administered in the presence of risk factors for methicillin-resistant *Staphylococcus aureus*. Linezolid was administered at a daily dose of 600 mg twice daily. Among the 23 immunocompromised patients, treatment strategies included piperacillin–Tazobactam (16g/d adapted to renal function) combined with either a macrolide or a quinolone (6.6%), imipenem (3g/d adapted to renal function) combined with either aminoglycoside (1.5%), or a quinolone (0.4%)

### SCAP severity scores

The presence of high-risk comorbid conditions, signs

of respiratory distress (tachypnea, Intercoastal drawing, hypoxemia..), neurological impairment (confusion, coma..), and hemodynamic instability (sepsis, septic shock), as well as other organ dysfunctions (acute kidney injury , thrombocytopenia..), or an initially unfavorable clinical course, are considered markers of disease severity. However, to ensure a more objective and standardized assessment of severity, we systematically calculated validated severity scores for CAP in all patients. Most patients belonged to class IV and V of the PSI score (216/300) with a mean of  $113.4 \pm 39.7$ . The median CURB-65 was 2 [1-3]. The risk of 28-mortality related to SCAP was classified as moderate to high in 44.6% of cases when using the CAP-PIRO score. Moreover, among patients admitted for SCAP, 56% met the criteria for admission to the ICU according to the ATS/IDSA score. Furthermore, 46% had a high/very high risk of mechanical ventilation and vasopressors according to the SMART-COP score. The median score was 4 [3-6]. Table 2 shows the SCAP severity scores in all populations and for each group, according to the presence of complications. All the severity scores were significantly higher in complicated SCAP. The different thresholds and the area under the curve were also mentioned in table 2. The CAP-PIRO score had the best specificity for predicting complications ( $Sp=83\%$ ). In contrast, PSI score had the best sensitivity ( $Se=84\%$ ).

**Table 2.** SCAP severity scores according to the presence of complications

| Variable            | Total population<br>(N=300) | Complicated CAP<br>(N=234) | Un-complicated CAP<br>(N=66) | AUC  | 95% CI      | Cut-off | P                 |
|---------------------|-----------------------------|----------------------------|------------------------------|------|-------------|---------|-------------------|
| PSI $\pm$ SD        | 113.4 $\pm$ 39.7            | 121 $\pm$ 38               | 86 $\pm$ 32.2                | 0.75 | [0.69-0.81] | 80.5    | <10 <sup>-3</sup> |
| CURB-65 Med [IQR]   | 2 [1-3]                     | 2 [1-3]                    | 1 [0-2]                      | 0.76 | [0.69-0.82] | 1.5     | <10 <sup>-3</sup> |
| SMART-COP Med [IQR] | 4 [3-6]                     | 5 [3-6]                    | 3 [2-4.25]                   | 0.66 | [0.59-0.73] | 4.5     | <10 <sup>-3</sup> |
| CAP PIRO Med [IQR]  | 2 [1-3]                     | 3 [2-3.25]                 | 2 [1-2]                      | 0.70 | [0.64-0.77] | 2.5     | <10 <sup>-3</sup> |
| SOFA Med [IQR]      | 3 [2-6]                     | 4 [2-7]                    | 2 [1-2.25]                   | 0.77 | [0.71-0.82] | 2.5     | <10 <sup>-3</sup> |

CAP: Community Acquired Pneumonia, AUC: Area under curve, CI: Confidence interval, SOFA: Sequential Organ Failure Assessment

### Microbiological Findings

The infection was documented in 73 out of 300 patients. Based on multiplex PCR results, a viral pneumonia was diagnosed in 37 cases: severe acute respiratory syndrome coronavirus 2 (N=28), Influenza A (H1N1) (N=4), Influenza A (H3N2) (N=5) and an atypical pneumonia was diagnosed in 5 cases : *Legionella pneumophila* (N=2) and *Mycoplasma pneumoniae* (N=3). In addition, *Klebsiella pneumoniae* was isolated in 45 PCR performed with the expression of beta lactam resistance genes in 35 cases. Moreover, two cases of salmonella on high respiratory panel were reported among two patients under immunosuppressive treatment for Crohn's disease. *Pneumocystis jirovecii* pneumonia was diagnosed among 3 immunocompromised patients (PCR on a deep respiratory sampling).

For PCR-detected pathogens, cases of SCAP attributed

to atypical bacteria (N = 5) and influenza (N = 9) were systematically considered causative and managed with the addition of oseltamivir or a macrolide/quinolone when not already included in the empirical regimen. For other PCR-detected microorganisms, therapeutic decisions were guided by the patient's underlying condition (particularly immunocompromised status) and the overall clinical and biological severity. Targeted antibiotic therapy was initiated when the pathogen was deemed clinically relevant in the context of a fragile host and a severe clinico-biological presentation. Accordingly, *Klebsiella pneumoniae* was considered clinically significant and treated in 15 immunocompromised patients. Whereas the remaining 30 cases were interpreted as colonization.

Based on the conventional microbiological investigations (Cytobacteriological examination of sputum/deep Tracheal aspirate sampling), a bacterial pneumonia was documented in 28 cases: *Streptococcus pneumoniae* (N=6), *Haemophilus influenzae* (N=5), *Staphylococcus aureus* (N=4); *Klebsiella pneumoniae* (N=9), *Acinetobacter Baumannii* (N=2) and *Enterococcus* (N=1). All these pathogens, when detected above predefined significant thresholds ( $>10^7$  UFC/mL for Cytobacteriological examination of sputum and  $>10^6$  CFU/mL for tracheal aspirates), were considered causative and managed appropriately.

### SCAP local and systemic complications

Complications of SCAP occurred in 78% of cases with a median delay of one day since the diagnosis of SCAP. The main local complications were ARDS (N=61), pulmonary abscess (N=15), necrosis (N=2), pleural empyema (N=9), Pyo-pneumothorax (N=7) and pulmonary cavitation (N=1). The metabolic complications reported in our population of study were: Diabetic ketoacidosis (N=33), Acute kidney injury (N=132) Hyperosmolar state (N=4), Hypoglycemia (N=9) and Critical illness-related corticosteroid insufficiency (N=2). The hematological complications reported were Disseminated Intravascular Coagulation (N=6), Macrophage activation syndrome (N=3) and isolated thrombocytopenia (N=77). The cardiovascular complications were: Acute coronary syndrome (N=48), arrhythmia (N=44) and acute heart failure (N=59). Septic shock was reported in 93 cases and sepsis-related encephalopathy in 98 cases.

### Risk factors of SCAP complications

Multivariate analysis identified initial CAP severity scores, COPD history, and age as independent predictors of CAP-related complications (Table 3). In the multivariate analysis, the SOFA score was included as a validated severity and mortality prediction tool in ICU. Hypoxemia assessed by the  $\text{PaO}_2/\text{FiO}_2$  ratio, thrombocytopenia, Confusion/Coma, and serum creatinine were significantly associated with SCAP-related complications in univariate analysis; however, these variables were not included into the multivariate model because they constitute individual components of the SOFA score. The SMART-COP score was also incorporated into the multivariate analysis, as it is specifically designed to predict the need for intensive respiratory or vasopressor support. Accordingly, respiratory rate and multilobar involvement were not separately included, given that they are items within this score. The PSI, CURB-65 and CAP-PIRO scores were not included due to substantial overlap in their constituent variables. Regarding baseline characteristics, age and COPD, a condition associated with underlying lung damage that may predispose to secondary complications, were included in the model. Atrial fibrillation, hypertension, and diabetes were not retained because of the small number of non-complicated cases with these comorbidities, which could potentially bias the results.

**Table 3.** Factors associated with SCAP complications in multivariate analysis

|              | Cut-off    | OR [CI 95%]       | p     | AUC [CI 95%]; p                  |
|--------------|------------|-------------------|-------|----------------------------------|
| SOFA         | $\geq 2.5$ | 5.57 [2.86-10.83] | 0.000 | 0.729 [0.660-0.798] ; $<10^{-3}$ |
| SMART-COP    | $\geq 4.5$ | 2.18 [1.09-4.35]  | 0.027 | 0.635 [0.562-0.708] ; 0.001      |
| Age (Years)  | $\geq 68$  | 1.03 [1.01-1.05]  | 0.001 | 0.592 [0.520-0.663] ; 0.02       |
| COPD history | NA         | 3.64 [1.73-7.66]  | 0.001 | 0.605 [0.527-0.683] ; 0.009      |

OR: Odds ratio, AUC: Area under curve, CI: Confidence interval, NA: Not applicable,

### Outcome

In multivariate analysis, initial respiratory rate  $\geq 28$  cycles/min (OR 1.06; 95% CI [1.01-1.12];  $p=0.012$ ), an initial ratio of  $\text{PaO}_2/\text{FiO}_2 \leq 130$  (OR 1.25; 95% CI [1.12-1.40];  $p=0.001$ ) and the occurrence of complications (OR 8.59; 95% CI [3.21-22.9];  $p=0.03$ ) were linked to mortality.

On the other hand, ICU stay and costs were higher when SCAP was complicated (7 days [4–13] vs. 4 days [3–6],  $P=0.001$  for ICU stay) and (1817, 3 dinars [1084,2-2797,8] vs. 911,57 dinars [684,3-1355,2]  $p=0.001$  for ICU cost) in patients with SCAP complications and those without, respectively.

### Survival analyses

When both systemic and local complications occurred during the course of SCAP, it decreased the survival delay time by an average of 15 days when compared to uncomplicated patients (13.38 days  $\pm$  1.11 vs. 28,4 days  $\pm$  0.75;  $P<10^{-3}$ ). When systemic complications occurred alone, the survival delay time decreased by an average of 5 days (23,9 days  $\pm$  0,86 vs 28,4 days  $\pm$  0.75;  $P<10^{-3}$ ) Fig2.

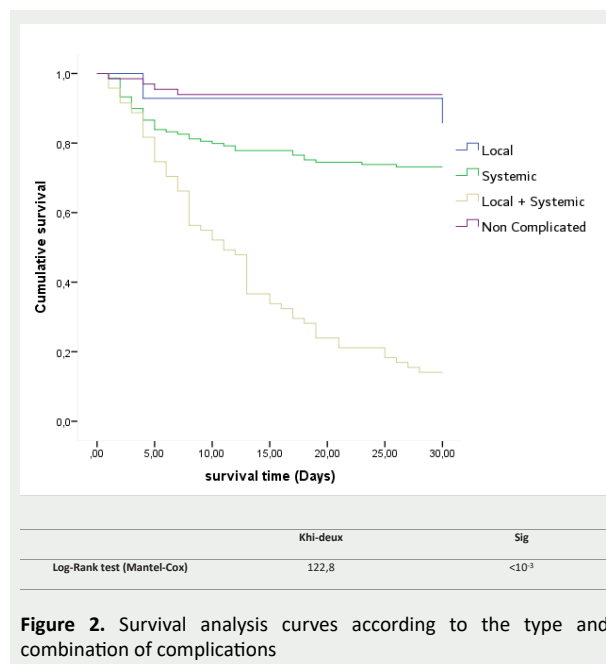


**Figure 2.** Survival analysis curves according to the type and combination of complications

## DISCUSSION

In our study, local complications occurred in 85 cases (28.3%) alone or associated with systemic complications. These complications, such as empyema, pulmonary abscesses and necrosis remain infrequent in patients with SCAP. [11–13] This elevated rate compared to the literature data may be explained by several factors. First, the severity of pneumonia from the outset. Second, the low rate of microbiological documentation that may be explained by several factors, including prior antibiotic exposure before admission (often related to self-medication), sub-optimal quality or interpretability of microbiological specimens, delayed sampling relative to symptom onset and inadequate transport conditions to the laboratory. That may have led to insufficient therapy since the causative agent is not targeted. Finally, the systemic use of CT scan in cases of unresolved sepsis or worsening dyspnoea may have increased the detection rate of local complications. Regarding systemic complications, we will discuss the most frequent ones reported in our population study, namely: cardiovascular complications, acute kidney injury (AKI), septic shock and sepsis-associated encephalopathy. The proportion of cardiovascular complications in the course of a SCAP was around 18%. From a pathophysiological standpoint, that could be linked to hypoxia resulting in a mismatch between needs and oxygen supply along with an increase in myocardial consumption of oxygen. Finally, the inflammatory storm and pro-thrombotic state associated with sepsis could increase the risk of cardiac infarction. [7,14] Regarding septic shock, our findings align with literature data with an incidence of around 33%. [15] On the other hand, AKI was reported in 18 to 34% of patients admitted in ICU for a severe viral or bacterial CAP which aligns with our data. [6,7] This renal-pulmonary interaction in the context of a SCAP was linked to hypoxia and low mean perfusion pressure of the kidney. [16] Some predisposing factors have been described: advanced age, chronic renal failure and coronary artery disease. [17] Sepsis-associated encephalopathy is a frequent complication of SCAP, ranging from delirium to coma, and is recognized as a marker of disease severity. It results from endothelial activation and a systemic inflammatory response, promoting persistence of infection [7, 18]

In our cohort, a SOFA score  $\geq 2.5$  and a SMART-COP score  $\geq 4.5$  were independently predictors of SCAP complications. It should be noted that these scores integrate various clinical (Coma, confusion...), biological (Creatinine level...), and radiological parameters (Multilobar involvement...). Looking at the literature data, there is a scarcity of studies addressing the impact of severity scores at initial presentation on the subsequent occurrence of complications. [19, 20] The majority of studies have addressed its impact on mortality which was a strong particularity of our series. Here, among 1343 patients hospitalized for SCAP for whom the occurrence of cardio-vascular complications was monitored, an initial respiratory rate  $\geq 30$  cycles/min was identified as independently associated with these complications

with an OR of 1.6; 95% CI [1.1–2.3]. [21] In our cohort, respiratory rate was not analyzed separately because it constitutes a component of the SMART-COP score. In another study, an initial creatinine level  $>132 \mu\text{mol/L}$  was linked with the occurrence of pneumococcal CAP complications with an OR of 2.01; 95% CI; [1.31–3.08];  $p=0.001$ . [22] In our cohort, creatinine level was not analyzed separately because it constitutes a component of the SOFA score. The presence of multilobar involvement increased the risk of complications as demonstrated in this meta-analysis. [23]. In our cohort, multilobar involvement was not analyzed separately because it constitutes a component of the SMART-COP score

From a microbiological standpoint, in our series, a pathogen was identified in 24.3% of cases. This documentation rate was low when compared to literature data. In fact, microbiological documentation rate ranged from 30 to 50%. [24–26] This variation could be explained by the compliance with sampling conditions, transport and storage. In a noteworthy deviation from expected findings. As for PCR detected micro-organisms, a striking observation was the isolation of *Klebsiella pneumoniae* in 45 over 77 high respiratory panels performed. Therapeutic decisions were guided by the patient's underlying condition—particularly immunocompromised status—and the overall clinical and biological severity. Targeted antibiotic therapy was initiated when the pathogen was deemed clinically relevant in the context of a fragile host and a severe clinico-biological presentation (15/45 cases). Otherwise, the microorganism was considered to represent colonization, and patients were managed with close clinical monitoring, including careful surveillance for signs of sepsis. *Klebsiella pneumoniae* ESBL was also found in 9 deep respiratory samples after standard bacterial culture. These unexpected results should serve as a call for increased vigilance in the context of a presumed community acquired pneumonia. Similarly, an incidence of 6% of PES pathogens (*Pseudomonas aeruginosa*, *Enterobacteriaceae* ESBL, and MRSA) was reported from a cohort of 1597 patients admitted for SCAP. [1] Given this significant concern, before any empirical antibiotic therapy, it would be wise to identify the risk factors for MDR in order to minimize the risk of therapeutic failure even in the context of CAP.

As for the prognostic impact of SCAP complications, in our cohort, their occurrence was independently associated with mortality. Moreover, the concomitant occurrence of local and systemic complications decreases survival by 15 days compared to uncomplicated forms. The analysis of survival according to the type of complications (Local, systemic or both) was a unique feature of our study. The impact of SCAP complications on ICU mortality has been well demonstrated in the literature. That involved mainly systemic complications. [19,27]

This study has several strengths. First, it included a relatively large sample size over a two-year period, encompassing both winter and summer seasons, thereby accounting for potential seasonal variability. No formal a priori sample size calculation was performed, as this was a prospective observational study including all consecutive patients admitted for SCAP during a

predefined two-year study period. Second, the systematic implementation of a respiratory panel at ICU admission enabled a more accurate characterization of the local epidemiology, particularly in the setting of severe CAP requiring ICU. In addition, the limited number of Tunisian studies specifically addressing severe CAP enhances the contribution of our findings to national data. Nevertheless, certain limitations must be considered. The low rate of bacteriological documentation, the underlying causes of which have been discussed above, may have affected the microbiological analysis. Furthermore, the absence of longitudinal assessment of biological parameters precluded evaluation of their dynamic evolution. Finally, the monocentric design may limit the external validity of our results. However, in the ICU setting, patients with severe pneumonia typically exhibit similar clinical severity despite individual variations. Moreover, the severity scores employed are validated, objective, and incorporate multiple clinical, biological, and radiological parameters, which likely minimizes the potential impact of case mix on our findings.

## CONCLUSION

This study showed that both local and systemic SCAP complications were common in ICU. CAP severity scores (SOFA score and SMART-COP score), initial respiratory rate, a sepsis-related encephalopathy, initial blood creatinine level, the extent of radiological involvement and finally an unresolved sepsis were the most concerning factors linked to the occurrence of SCAP complications. The concomitant occurrence of systemic and local complications reduced markedly the survival delay. Interestingly, which marked our microbiological data is the isolation of *Klebsiella pneumoniae* ESBL despite of the absence of multi-drug-resistance factors. These new epidemiological findings should serve as a warning to better manage empirical treatment in the context of a SCAP limiting its subsequent complication.

In conclusion, a few simple and practical parameters, if assessed early and proactively, could help us predict the risk of SCAP complications, particularly given the growing emergence of multidrug-resistant pathogens in community settings.

### Ethical approval of studies and informed consent:

The study followed the principles of the Declaration of Helsinki as revised in 2024. This study was approved by the local ethics Committee of la Rabta hospital (CERB 35/2025, 03/10/2025), and written informed consent was obtained from the patients or their legal representatives.

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