# Study Protocol

## ESCAPE 10 STUDY

## Epidemiology and determinants of outcomes of Severe Community Acquired Pneumonia in the Elderly


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**Protocol Version 2.**

1st April 2025

## 1. STUDY SYNOPSIS

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| Title: | Epidemiology and determinants of outcomes of Severe Community Acquired Pneumonia in the Elderly. |
| Acronym: | ESCAPE 10 STUDY. |
| Version and date of protocol: | Version 2, 1th April 2025. |
| Study Promotor: | Study Group Infections in the Elderly (ESGIE), European Society of Clinical Microbiology and Infectious Diseases ESCMID. |
| Principal Investigator: | Jordi Rello. |
| ClinicalTrials.Gov: | Pending. |
| Medical condition under investigation: | Severe Community-Acquired Pneumonia in the Elderly. |
| Study Type: | Multinational, observational, retrospective cohort study. |
| Inclusion criteria: | 1.Patients aged 65 years-old or older.<br>2.Patients with clinically and radiologically (Chest X-Ray (CXR), Computerized Tomography (CT) or lung ultrasound (LUS) confirmed pneumonia.<br>3.Patients fulfilling the protocol definition of sCAP |
| Exclusion criteria: | 1.Patients aged below the inclusion threshold (65 years old).<br>2.Recent hospitalization (above 48 h within the past 10 days) in acute healthcare settings.<br>3.Terminal events.<br>4.Patients receiving comfort care only or with documented decisions to forgo intensive medical interventions. |
| Sample Size and inclusion periods: | At least 500 patients will be enrolled over a period of 13 months (between January 1, 2024, and January 31, 2025). Each recruiting center will enroll 20 patients: 10 during the winter influenza epidemic period and 10 during the non-epidemic (summer) period. |
| Primary outcome: | 28-day mortality. |
| Secondary outcomes: | 1. Assessment of “Indicators and Standards of Quality in the Care and Medical Management of Patients with sCAP”<br>2.Case fatality rate. |

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| | 3.Overall (all-cause) mortality.<br>4.In-hospital (all cause) mortality.<br>5.Pneumonia-attributed in-hospital mortality.<br>6.Length of hospital stay (LOS).<br>7.Duration of ICU / High-dependency unit/ IMCU stay.<br>8.Duration of mechanical ventilation and ventilation-free days.<br>9.Rate of pneumonia-related complications: Ventilation Associated Pneumonia (VAP), Empyema, Acute Respiratory Distress Syndrome (ARDS), Bacteraemia, Septic Shock.<br>10.Frequency of delirium, Renal Replacement Therapy and quality indicators.<br>11.Identification of risk factors associated with adverse outcomes in sCAP.<br>12.Discharge status after stay in acute unit: Home, Nursing home, Rehabilitation.<br>13.Functional status at discharge.<br>14.Cognitive function at discharge. |
| Objectives: | 1. To obtain a comprehensive overview of the epidemiology of the sCAP pathogen and its relationship with geographic locations, countries, seasonality, coexistence with epidemic influenza periods, and patient outcomes in the post-COVID era.<br>2.To identify a set of quality indicators to be used as standard of care.<br>3.To assess gender differences in the epidemiology of sCAP in the elderly, to refine precision medicine management.<br>4.To identify clinical sub-phenotypes or endotypes associated with different outcomes.<br>5.To develop an educational tool to improve care and safety based on evidence identified by this study. |

## 2. BACKGROUND AND RATIONALE

Community-Acquired Pneumonia (CAP) is one of the most common infections, with an incidence ranging from 1 to 25 cases per 1,000 inhabitants per year [1]. Severe CAP (sCAP) represents its most lethal form and is associated with high mortality and morbidity rates [1].

Elderly patients constitute a highly heterogeneous group; yet they are significantly more predisposed to severe disease compared to younger individuals [2]. This increased vulnerability is attributed to the higher prevalence of comorbidities and the natural decline in immune function, known as immuno-senescence, that accompanies aging, reducing the differences between immunocompromised and immunocompetent in aging cohorts. Indeed, older age has been identified as an independent risk factor for severe disease [3], with mortality rates reported to range from 40% to 55.6% [4,5]. Gender differences in the incidence and pathogens of CAP have been reported [6] and a gender approach (SAGER guidelines) is required. However, no relevant data for sCAP in the post-COVID-19 era are known. There is a lack of quality indicators and identification of clinical sub-phenotypes.

While sCAP is a relatively common condition with a profound impact on the elderly population, there remains a disproportionately low number of observational studies examining outcomes and potential risk factors in this group. Identifying and characterizing risk factors associated with unfavorable outcomes in this heterogeneous population is crucial to optimizing treatment and improving care strategies.

Conducted across an international network of European countries, the 'Epidemiology and Determinants of Outcomes of Severe Community-Acquired Pneumonia in the Elderly (ESCAPE 10 study) is a quality improvement initiative aiming at identifying areas for improvement in patient care and management and ensuring better short-term clinical outcomes for elderly patients with sCAP, as well as improving efficiency, safety, and patient satisfaction.

This study takes into account seasonal variations in sCAP etiology and its association with the coexistence of epidemic influenza periods.

## 3. STUDY DESIGN

### Study Type

The ESCAPE 10 study is a multinational, observational, retrospective cohort study aimed at obtaining a comprehensive overview of the epidemiology of the sCAP pathogen and its relationship with geographic locations, countries, seasonality, coexistence with epidemic influenza periods, and patient outcomes in the post-COVID era. Additionally, the study focuses on improving the quality of patient care and short-term outcomes in elderly patients with sCAP. The primary emphasis will be on quality indicators and standards, as outlined in the Definitions section

The study will be conducted in countries with markedly different demographic and socioeconomic characteristics. **The co-ordinating site** will be the Critical Care Department, Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona, Spain. **The Steering Committee** is composed by Emine Alp Meşe (TK), Jordi Rello (SP),

Virginie Prendki (CH), Joan Sabater-Riera (SP), Despoina Koulenti (UK) & Paraskevi Fragkou (GR). JR & JSR are representing the Pneumonia ICP network from Centros de Investigación en Red de Enfermedades Respiratorias del Instituto de Salut Carlos III (CIBERES-SCIII). JR & VP are representing the ESGIE, DK Is representing Study Group for Infections in Critically Ill Patients (ESGCIP), PF is representing Study Group for Respiratory Viruses (ESGREV) and EA is representing European Committee on Infection Control (EUCIC), who is endorsing the study.

### Study Population

Elderly patients who fulfill the following inclusion and exclusion criteria and definitions could be enrolled in the study.

*Definitions*

1. **Elderly**: Patients aged 65 years and older.
2. **Severe CAP**: Community-acquired pneumonia (CAP) is considered as an acute infection of lung parenchyma which was acquired in the community in patients with no recent hospitalization in acute healthcare settings. **Severe CAP (sCAP)** is defined as the CAP patients admitted in an acute hospital as they might require organ support [adapted from 1]. For the purposes of this study, patients with immunosuppression, aspiration pneumonia or residing in nursing homes will be enrolled to have a picture of the real-world, and they will have a differential sub-analysis. Differentiation between patients requiring a) ward hospitalization, b) high-dependency unit and c) ICU will be done.

## 3. Indicators and Standards of Quality [7-10] in the Care and Medical Management of Patients with sCAP:

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| Diagnosis and Evaluation | The identification of CAP should be based on clinical and radiological criteria, using risk stratification scales such as CURB-65, SOFA and PIRO scores to determine the severity of the disease. |
| Antibiotic Treatment | Quality indicators include the initiation of empirical antibiotic treatment is recommended within 6 hours after the initial evaluation of the patient. The selection of antibiotics should be compliant with clinical guidelines that consider local antimicrobial resistance and patient characteristics. |
| Monitoring and Follow-up | It is essential to assess the clinical response to treatment within 48-72 hours. |
| Clinical Outcomes | Quality indicators include mortality rates and hospital readmissions, as well as improvement in patient quality of life after treatment. |
| Prevention | Promotion of vaccination, including pneumococcal vaccine and influenza vaccine, is essential for the prevention of CAP. |

*Inclusion criteria:*

Patients will be included if they fulfill all the following criteria:

1. Patients aged 65 years-old or older.
2. Patients with clinically and radiologically (Chest X-Ray (CXR), Computerized Tomography (CT) or lung ultrasound (LUS) confirmed pneumonia.
3. Patients fulfilling the protocol definition of sCAP.

*Exclusion criteria:*

Patients will be excluded if they fulfill at least one of the following criteria:

1. Patients aged below the inclusion threshold (65 years old).
2. Recent hospitalization (above 48 h within the past 10 days) in acute healthcare settings.
3. Terminal events.
4. Patients receiving comfort care only or with documented decisions to forgo intensive medical interventions.

**Sample Size and inclusion periods.**

We aim to include at least 500 patients. However, rather than targeting a specific sample size, we will follow a predefined 13-month (between January 1, 2024, and January 31, 2025) recruitment period to minimize bias associated with the seasonality of certain respiratory pathogens. Each recruiting center will include 20 patients: 10 during the winter influenza epidemic period and 10 during the non-epidemic (summer) period to obtain a balanced representation.

The study sample size has been determined arbitrarily. It is expected that each ESGIE member will include approximately 15–20 patients.

## 4. METHODS.

### Procedures & recruitment methods.

This retrospective international observational quality improvement study aims to collect and analyze data from elderly patients with severe community-acquired pneumonia (sCAP) To obtain a comprehensive overview of the epidemiology of the sCAP pathogen and its relationship with geographic locations, countries, seasonality, coexistence with epidemic influenza periods, and patient outcomes in the post-COVID era and identify opportunities for enhancing patient care, safety and satisfaction. Elderly patients admitted to the participating hospitals who meet the sCAP definition (outlined in the Definitions section), fulfill all inclusion criteria, and have no exclusion criteria could be enrolled. We will ensure adequate representation of male and female study participants. The recruitment period will span 8 months during the previously described periods.

Required data will be collected from electronic and/or paper medical records, and reviews of laboratory and radiology results. Follow-up will be conducted on Day 7 (±1), Day 28 (±2), since study enrollment if patients remain hospitalized. No interventions or sample collections are planned as part of this study as it is a retrospective study.

### Primary outcome.

The primary outcome of the ESCAPE 10 study will be 28-day mortality.

**Secondary outcomes:**

Additional outcomes will be:

1. assessment of “Indicators and Standards of Quality in the Care and Medical Management of Patients with sCAP” as shown in the Definitions.
2. Case fatality rate.
3. Overall (all-cause) mortality.
4. In-hospital (all cause) mortality.
5. Pneumonia-attributed in-hospital mortality.
6. Length of hospital stay (LOS).
7. Duration of ICU / High-dependency unit/ IMCU stay.
8. Duration of mechanical ventilation and ventilation-free days.
9. Rate of pneumonia-related complications: Ventilation Associated Pneumonia (VAP), Empyema, Acute Respiratory Distress Syndrome (ARDS), Bacteremia, Septic Shock.
10. Frequency of delirium, Renal Replacement Therapy and quality indicators.
11. Identification of risk factors associated with adverse outcomes in sCAP.
12. Discharge status after stay in acute unit: Home, Nursing home, Rehabilitation.
13. Functional status at discharge.
14. Cognitive function at discharge.

**Objectives:**

1.To obtain a comprehensive overview of the epidemiology of the sCAP pathogen and its relationship with geographic locations, countries, seasonality, coexistence with epidemic influenza periods, and patient outcomes in the post-COVID era.

2. To identify a set of quality indicators to be used as standard of care.

3.To assess gender differences in the epidemiology of sCAP in the elderly, to refine precision medicine management.

4.To identify clinical sub-phenotypes or endotypes associated with different outcomes.

5.To develop an educational tool to improve care and safety based on evidence identified by this study.

**Data collection.**

Data from this study will be collected in coded form, recorded and stored using REDCap (Research Electronic Data Capture). Each participant will be identified by a unique code automatically generated in REDCap, guaranteeing the dissociation of personal and clinical data. Each recruiting centre will have a protected equivalence table where each study patient will be collected and identified in REDCap with their identification data. Only one researcher from each centre with expertise in data management will have access. REDCap is a secure web application designed to support data capture in research studies. It includes HIPAA Security Rule compliance features such as real-time validation of data entry (e.g. for data types and range checks), a full audit trail, user-based privileges and a mechanism for exporting “de-identified” data to statistical packages (SPSS, SAS, Stata and R). Access to study data in REDCap will be restricted to study team members with authentication via personal user credentials and email.

Data of interest include (*but not limited to*): data related to the quality indicators, demographic information (age, self-reported sex, body mass index, ethnicity, recent travels abroad, working status, high risk or suspicious contacts), past medical history (details of previous respiratory tract infections and hospitalizations, dental status, close contact with the healthcare system, immunization status, current medications, baseline functional, nutritional and mental status (and relevant scores), chronic/background conditions, presence of catheters), previous exposure to antibiotics, known history of multi-drug resistant organisms, list of symptoms and symptoms and signs, findings of physical examination, disease severity scores (for current infection), routine laboratory biomarkers, microbiological and imaging data, treatment and supportive care received during current episode and list of possible complications (All variables collected in the study can be found in Annex 1).

**Statistical analysis plan.**

Data will be reviewed for inconsistencies, missing values, and outliers. Missing data will be handled using multiple imputation or sensitivity analysis if appropriate. Patient demographics, comorbidities, clinical presentation, and laboratory/radiology findings will be summarized. Group comparisons (e.g., survivors vs. non-survivors) using chi-square or Fisher's exact test for categorical variables and independent t-tests or Mann-Whitney U tests for continuous variables. For mortality, we will use Kaplan-Meier survival analysis for time-to-event data and cox proportional hazards regression to identify predictors of mortality. Logistic regression will be used to assess associations between baseline characteristics and adverse outcomes. Adjusted odds ratios (aOR) with 95% confidence

intervals (95% CI) will be reported. We will examine the relationships between laboratory/radiological parameters and clinical outcomes using Spearman or Pearson correlation. Sensitivity analysis will be performed if patient data are missing for certain variables and outcomes, to assess the robustness of the results and the impact of missing data on the study findings. A p-value <0.05 will be considered statistically significant and 95% CI will be reported for estimates.

## 5. ETHICAL CONSIDERATIONS.

This is a retrospective study using anonymized data, which will not require informed consent.-This study will be approved by the Research Ethics Committee of all participating institutions and will fully comply with the Declaration of Helsinki and the Sex and Gender Equity in Research (SAGER) Guidelines [11] as well as other locally relevant regulations. Participants' data will be collected, analyzed and handled under strict anonymity. No risks, harms, direct benefits, or incentives are expected for participants from this study, as it is an observational retrospective study. Substantial changes to the project set-up, the protocol and any relevant project documents will be submitted to relevant Ethics Committees for approval before implementation.

## 6. FUNDING.

This study will be initially funded by the research funds accessible to the principal investigator. Funding will be requested to cover the costs of study management and statistical analysis.

## 7. RESULTS DISSEMINATION.

Study findings will be submitted to high quality peer-reviewed journals and will be presented at national and international conferences and symposia, after approval by the Steering Committee. All authors should approve the final manuscript. The “ESCAPE 10 study group investigators” will be constituted by two representatives from centers with at least 15 valid cases. List of authors for global papers will be constituted by the Steering Committee members plus three additional authors for the top recruiters sites, plus the list of “ESCAPE 10 study group investigators” reported in alphabetical order in an Appendix (two designed members by investigator site). Other contributors will be reported in acknowledgments. List of authors for national data will be constituted by the principal investigators plus two contributors from top 5 recruiters sites, plus a list of “COUNTRY ESCAPE 10 study group investigators” reported in alphabetical order in an Appendix (two designed members by investigator site). Other contributors will be reported in acknowledgments. Findings will also be shared among research collaborators and institutional networks to foster discussion and future research opportunities.

## 8. REFERENCES.

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