Original Article

# SARS-CoV-2 *vs Streptococcus pneumoniae*: a comparison of clinical features, laboratory findings, and clinical outcomes in patients hospitalized at Alessandria's General Hospital

## SARS-CoV-2 *vs Streptococcus pneumoniae*: confronto di caratteristiche cliniche, risultati di laboratorio ed outcome clinici in pazienti ricoverati presso l'Ospedale di Alessandria

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**Key words:** diagnostic techniques and procedures, COVID-19, SARS-CoV-2, *Streptococcus pneumoniae*, pneumonia.



## ABSTRACT

**Aims:** the aim of the present study was to compare the clinical, anamnestic, and laboratory features and outcomes of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pneumonia and pneumonia caused by *Streptococcus pneumoniae* in hospitalized patients at the General Hospital of Alessandria, Italy.

**Materials and Methods:** radiological diagnosis of pneumonia by chest X-ray and/or chest Computed Tomography (CT); microbiological diagnosis of SARS-CoV-2 infection by nasopharyngeal swab Reverse Transcriptase - Polymerase Chain Reaction (RT-PCR), etiological diagnosis of *S. pneumoniae* pneumonia by positive urinary antigen detection and/or isolation of *S. pneumoniae* from respiratory and/or blood cultures.

**Results:** 222 patients were included, 171 with SARS-CoV-2 pneumonia and 51 with *S. pneumoniae*. SARS-CoV-2 group most frequently treated with antiviral drugs: 139/171 (81.3%) *vs* 1/51 (2.1%); p<0.001; they often needed oxygen therapy: 142/171 (83%) *vs* 27/51 (56.3%); p<0,001; and non-invasive mechanical ventilation: 59/171 (34.5%) *vs* 7/51 (14.6%); p=0.004. Mortality was higher in SARS-CoV-2 pneumonia patients: 46/171 (26.9%) than in pneumococcal pneumonia patients 5/51 (9.8%); p=0.011.

**Conclusions:** the study showed the increased prevalence of pneumonia caused by SARS-CoV-2 and *S. pneumoniae* in males than in females. Moreover, patients with SARS-CoV-2 pneumonia represent higher risk group for complications and death than *S. pneumoniae*.

**Obiettivi:** lo scopo del presente studio è stato quello di confrontare le caratteristiche cliniche, anamnestiche, di laboratorio e gli outcome della polmonite da SARS-CoV-2 e la polmonite causata da *Streptococcus pneumoniae* in pazienti ricoverati presso l'Ospedale di Alessandria.

**Metodi:** diagnosi radiologica di polmonite mediante radiografia del torace e/o Tomografia Computerizzata (TC) del torace; diagnosi microbiologica dell'infezione da SARS-CoV-2 mediante tampone rinofaringeo RT-2PCR, diagnosi eziologica della polmonite di *S. pneumoniae* mediante individuazione positiva dell'antigene urinario e/o isolamento di *S. pneumoniae* da colture respiratorie e/o ematiche.

**Risultati:** 222 pazienti inclusi, 171 con polmonite da SARS-CoV-2 e 51 con polmonite da *S. pneumoniae*. Gruppo SARS-CoV-2 più frequentemente trattato con farmaci antivirali: 139/171 (81,3%) *vs* 1/51 (2,1%); p<0,001; hanno spesso bisogno di ossigenoterapia: 142/171 (83%) *vs* 27/51 (56,3%); p<0,001; e ventilazione meccanica non invasiva: 59/171 (34,5%) *vs* 7/51 (14,6%); p=0.004. La mortalità è stata più alta nei pazienti con polmonite SARS-CoV-2: 46/171 (26,9%) rispetto ai pazienti con polmonite pneumococcica 5/51 (9,8%); p=0,011.

**Conclusioni:** lo studio ha mostrato una maggiore prevalenza di polmonite causata da SARS-CoV-2 e *S. pneumoniae* nei maschi piuttosto che nelle femmine. Inoltre, i pazienti con polmonite SARS-CoV-2 rappresentano un gruppo a rischio più elevato di complicanze e morte rispetto a *S. pneumoniae*.

## INTRODUCTION

In December 2019, a cluster of pneumonia of unknown etiology was reported in the area near the Huanan Fish Market in Wuhan, China.[1]

This causative agent was initially named Novel Coronavirus 2019 (2019-nCoV), but later, the International Committee for Taxonomy of Viruses renamed 2019-nCoV as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the disease it caused as Coronavirus Disease 2019 (COVID-19).[2]

On March 11, 2020, the World Health Organization declared COVID-19 a pandemic. On October 31, 2021, over 246 million confirmed cases and almost 5 million deaths were reported.

The clinical presentation of COVID-19 patients is quite variable, including asymptomatic cases and patients with flu-like symptoms (fever, dry cough, dyspnea, fatigue), up to ARDS patients caused by bilateral interstitial pneumonia.[3]

A recent systematic review including 30 studies with a total of 4,829 patients found that the main clinical symptoms of COVID-19 patients were fever (77.6%), cough (64.8%), fatigue (27.2%) and dyspnea (21.2%). Less commonly reported symptoms include headache or dizziness (15.2%), diarrhea (11.8%), nausea, and vomiting (5.9%). Some studies have reported disturbances of the sense of smell and taste that accounted respectively for 10.1% and 10%.

Finally, symptoms such as hemoptysis, chills, pain and chest tightness, anorexia, confusion, and rhinitis are rarely reported clinical features.[4] The most common laboratory alterations found in COVID-19 patients are an increase in transaminase, C-reactive protein, erythrocyte rate, interleukin-6, lactate dehydrogenase and a decrease in albumin, eosinophils, and lymphocytes.[5]

Overall, mortality associated with COVID-19 has been reported around 0.27% based on seroprevalence studies,[6] and 0.68% from a recent systematic review with meta-analysis.[7] In SARS-CoV-2 pneumonia patients, mortality reaches almost 12%,[8] a much higher value than mortality associated with other viral pneumonia such as influenza.[9] As the risk factors associated with mortality, a recent systematic review and meta-analysis of 186 observational studies evaluated 210,447 deaths between 1,304,587 COVID-19 patients[10] found that diabetes, hypertension, obesity and smoking were associated with increased mortality for COVID-19, contributing to almost 30% of deaths. Considering only Italian patients over 65 of age, another systematic review and meta-analysis showed cognitive impairment, diabetes, chronic kidney failure, and systemic arterial hypertension were the main diseases associated with increased mortality.[11]

### *Streptococcus pneumoniae* pneumonia

Pneumonia is an infection of the lung parenchyma. It is classically defined as Community-Acquired Pneumonia (CAP) if contracted outside the hospital, and Hospital-Acquired Pneumonia (and/or Ventilator) (HAP/VAP) if developed after hospitalization and/or after mechanical ventilation. Community-acquired pneumonia is a major global cause of morbidity and mortality in both immunocompetent and immunocompromised patients.[12] Clinical and lifestyle conditions associated with an increased risk of CAP include immunosuppression, history of pneumonia, chronic cardiovascular disease, cerebrovascular disease, stroke, cognitive impairment, neurological/psychiatric disorders, Chronic Obstructive Pulmonary Disease (COPD), bronchitis/asthma, dysphagia, diabetes, chronic neoplasms and hepatopathies, chronic kidney failure, alcohol abuse, smoking.[13] *Streptococcus pneumoniae* and respiratory viruses are among the most frequently identified pathogens in patients with CAP.[14] Other common bacteria that cause community-acquired pneumonia include *Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus*, and atypical microorganisms such as *Legionella pneumophila, Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*. The clinical presentation of CAP is variable, from mild pneumonia characterized by fever and cough to severe pneumonia with sepsis and respiratory failure and depends on the interaction between the patient's immune system, patient characteristics and the pathogen's virulence. From signs and symptoms indicative of CAP, such as cough, fever, sputum production, dyspnea and chest pain, the definitive diagnosis of CAP requires evidence of a new lung infiltrate on a chest X-ray, chest Computed Tomography (CT), or lung scan.[15] Overall, mortality during hospitalization for CAP has been described as around 6.5%, with a 30-day rate of 13%, a 6-month rate of 23.4%, and a 1-year rate of 30.6%.[16] A large part of CAP-related mortality could be attributed to a co-morbidity already present, especially in patients with very compromised general conditions and severe underlying diseases.[17] Among the most common blood tests required in the case of suspected CAP are white blood cells, C-reactive protein, and procalcitonin, which measure the systemic inflammatory state. Other tests, such as lactate measurement or renal and hepatic function and coagulative order, are useful for assessing associated organ damage, as observed in severe sepsis and multiorgan failure, and help the clinician assess the severity of the disease.[18] Several laboratory tests are available to assess pneumonia cause, including microscopy and culture of respiratory tract samples, blood cultures, antigen test in the urine, serum antibody, and nucleic acid amplification, like PCR.[18]

Since both SARS-CoV-2 and *S. pneumoniae* may cause severe pneumonia, which may indicate hospitalization, the purpose of this study was to compare clinical and laboratory data between two groups of patients, one diagnosed with SARS-CoV-2 pneumonia and the other one with *S. pneumoniae* to assess a possible significant difference in organ damage, inflammatory state and mortality caused by these two different causative agents.

## MATERIALS AND METHODS

### Design of the study

This was a retrospective, observational study on patients admitted to SS. Antonio e Biagio e Cesare Arrigo Hospital of Alessandria, Italy, with SARS-CoV-2 pneumonia from February 2020 to April 2020, and on patients admitted with *S. pneumonia* from January 2016 to May 2019.

The periods were chosen to avoid any possible overlap of the two pathologies. Patients with SARS-CoV-2 infection were included during the period which neither vaccine nor specific therapies were yet available, to minimize potential confounding effects.

### Study population

Inclusion criteria for this study included patients aged ≥18 years; radiologically diagnosis of pneumonia by chest X-ray and/or chest CT, microbiological diagnosis of SARS-CoV-2 infection by nasopharyngeal swab RT-PCR, etiological diagnosis of *S.*

*pneumoniae* pneumonia by positive urinary antigen detection and/or isolation of *S. pneumoniae* from respiratory and/or blood cultures; Availability of the following laboratory tests: oxygen saturation, total leukocyte counts, absolute counts of the elements of the leukocyte formula (neutrophils, lymphocytes, monocytes, eosinophils, basophils) platelet counts, C-reactive protein, erythrocyte rate, alanine aminotransferase, creatinine, lactic dehydrogenase.

Exclusion criteria for this study included febrile symptoms caused by pathologies other than pneumonia, and microbiological diagnosis of pneumonia caused by bacteria other than *S. pneumoniae* at admission.

### Clinical and laboratory data

All clinical data, including medical history, objective examination, therapy, and laboratory data, were obtained from the patient's medical chart and collected using the Research Electronic Data Capture (REDCap) platform.

### Diagnosis of SARS-CoV-2 infection

Nasopharyngeal swabs were collected by means of a Universal Transport Medium for Viruses, Chlamydia, Mycoplasma, and Ureaplasma (Copan UTM system; Copan, Brescia, Italy). SARS-CoV-2 detection was performed using the Alinity m SARS-CoV-2 AMP kit run on the Abbott Alinity m system (Abbott Molecular Inc.; Des Plaines, IL, USA). Both kit and instrumentation were employed according to the manufacturer's instructions for both the handling and interpretation of the results. The assay is a real-time RT-PCR test for the qualitative detection of nucleic acid from SARS-CoV-2 in nasal, nasopharyngeal, or oropharyngeal swabs and in bronchoalveolar lavage specimens. The system employs magnetic microparticle technology to capture, wash, and elute the nucleic acid. An internal control is introduced into each specimen at the beginning of sample preparation, and both a positive control and a negative control are processed concurrently. After the disruption of SARS-CoV-2 virions by guanidine isothiocyanate, nucleic acids are captured on the magnetic microparticles, and inhibitors and unbound sample components are removed by subsequent washing steps. The purified RNA is then combined with liquid unit-dose Alinity m SARS-CoV-2 activation reagent and liquid unit-dose Alinity m SARS-CoV-2. During the amplification step, the target RNA is converted to cDNA by the reverse transcriptase. The target sequences for the assay are in the SARS-CoV-2 RdRp and N genes of the SARS-CoV-2 genome, which are highly conserved and specific. Amplification of the three targets (SARS-CoV2 RdRp, SARS-CoV-2 N, and internal control) takes place simultaneously in the same reaction amplification/detection reagents. If the target sequences are present in the sample, the hybridization with complementary sequences separates the fluorophore and the quencher, allowing fluorescent emission and detection. The lowest concentration level with observed positive rates ≥95% is 100 virus copies/ml, and the maximum number of amplification cycles is 45.

### Etiological diagnosis of *Streptococcus pneumoniae* pneumonia

The etiological diagnosis of pneumonia was diagnosed by microscopic observation and culture of blood cultures, of specimens from the respiratory system (sputum, bronchoaspirate, bronchoalveolar lavage) and/or research of *S. pneumoniae* antigen by urine.

### Blood cultures

Blood cultures were collected during the febrile peak and incubated at 37°C in automatic assay BACTEC® FX (BD Diagnostics; Sparks, MD, USA). Blood samples taken from the patient with suspected *S. pneumoniae* pneumonia were inoculated into a pair of flasks (sets) containing culture broths for aerobic and anaerobic bacteria. If there are bacteria in the patient's blood, they consume nutrients from the broth, producing waste metabolites, including $CO_2$. $CO_2$ binds to a device at the bottom of each bottle and produces a fluorescence proportional to the $CO_2$ produced by the bacteria. The instrument reads the amount of fluorescence produced by the bottle every 20 minutes. If the fluorescence exceeds a determinate level over a determinate time, the instrument signals possible bacterial growth by acoustic and light signals. Then, the specialist extracts the suspected positive bottle from the incubator and takes an aliquot of blood/broth culture. One part of the aliquot is set up on a slide for microscopic investigation after Gram staining, and another portion is sown on agarized plate to allow the development of bacterial colonies to be identified and from which to set up the antibiogram. Agar used are Columbia agar enriched with 5% sheep's blood for the isolation of cocci and bacilli Gram-positive and Gram-negative; agar chocolate enriched with IsoVitale X (PVX Agar) for the isolation of demanding bacteria; Schaedler agar, which is an agar enriched with 5% sheep's blood with the addition of vitamin K1 and emina, for the isolation of obligate anaerobic bacteria. Columbia agar is incubated in aerobiosis, PVX agar in $CO_2$ enriched atmosphere and Schaedler agar in anaerobic.

### Respiratory specimens

Respiratory specimens were subjected to microscopic observation after Gram staining for leukocytes and bacteria identification to interpret the result of the cultural examination correctly. In the case of sputum, suitability was also assessed using the Q-score19, which applies positive values to the polymorphonuclear cells and negative values to squamous epithelia cells observed in a Gram-stained smear. It is used to evaluate specimen quality and determine the clinical utility of the cultural examination. All suitable specimens were included in the study and processed by sowing on agared soils: Columbia agar enriched with 5% sheep's blood with Colistin and Nalidixic Acid (CNA) for the isolation of cocci and Gram-positive bacilli; PVX Agar; Agar with lactose, neutral red, crystal violet and bile salts (Agar MacConkey) for selective-differential isolation of negative Gram bacteria. CNA and MacConkey soils were incubated in aerobiosis, PVX agar in a $CO_2$ enriched atmosphere. All soils were incubated for at least 72 hours at 37,000h C. Plate readings were performed every 24 hours.

### Statistical analysis

Descriptive statistics analysis was performed, stratified into three patient groups based on the type of respiratory infection. Statistical significance for group comparisons was assessed using the Mann Whitney test for continuous data, while the $\chi 2$ test or Fisher's exact test for categorical data. Qualitative data were presented as frequencies and absolute percentages, while quantitative data were reported as median and interquartile range. The significance level was set at $p \leq 0.05$. All statistical analyses were conducted using SPSS v.25 (IBM SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA).

## RESULTS

### Demographic data

Overall, 222 patients were included in the study, 171 with SARS-CoV-2 pneumonia and 51 with *S. pneumoniae*. Male patients were more frequent in both groups: 109/171 (63,7%) in SARS-CoV-2 group, and 29/51 (56,9%) in pneumococcal group. The comparison showed no significant differences (p=0,374). Similarly, the comparison of median age showed no significant differences: 73 years (IQR: 81-60) *vs* 77,1 years (IQR: 82,2-62,5) respectively; p=0,191.

### Comorbidity

Patients with pneumococcal pneumonia most frequently had COPD: 17/171 (9,9%) *vs* 12/51 (24,5%); p=0,011; a history of cancer: 15/171 (8,8%) *vs* 10/51 (20,4%); p=0,032 and oral anticoagulant therapy: 6/171 (4,5%) *vs* 6/51 (16.7%); p=0,022. The results of t are described in Table 1.

### Clinical data

Patients with SARS-CoV-2 pneumonia had significantly higher median body temperature values: 38°C (IQR:38.5-37.5) *vs* 37.5°C (IQR: 37.9-37.3); p=0.014 and more frequently reported fever as an initial symptom: 147/171 (87.5%) *vs* 27/51 (56.3%); p<0.001. Conversely, pneumococcal pneumonia patients had significantly higher median heart rate: 88 bpm (IQR:100-78) *vs* 93 bpm (IQR:115-80); p=0.025 and reported muscle pain: 4/171 (2.4%) *vs* 5/51 (10.4%); p=0.018 and dyspnea: 77/171 (45.8%) *vs* 31/51 (64.6%); p=0.048. The results are shown in Table 2.

### Laboratory data

Patients with pneumococcal pneumonia had significantly higher median values of total leukocytes: 6.730 cell/mm3 (IQR:9410-4.600) *vs* 10.390 cell/mm3 (IQR:15.470-6.888); p<0,001; absolute neutrophil count: 5.190 cell/mm3 (IQR: 7.770-3.530) *vs* 9.015 cell/mm3 (IQR:12.978-5.123); p<0.001 and C-reactive protein: 9.46 mg/dL (IQR:15.52-4.04) *vs* 18.16 mg/dL (29.25-13.81); p<0.001.

**Table 1. Comparison of comorbidity and home therapy values between SARS-CoV-2 pneumonia and *Streptococcus pneumoniae* pneumonia patients. Values are expressed as absolute numbers and percentages (%).**

| | COVID-19 pneumonia (n=171)* (%) | Pneumococcal pneumonia (n=51)** (%) | *p* |
|---|---|---|---|
| Comorbidities | | | |
| COPD | 17 (9.9) | 12 (24.5) | 0.037 |
| Diabetes mellitus | 26 (15.2) | 9 (18.4) | 0.912 |
| Arterial hypertension | 84 (49.1) | 18 (36.7) | 0.194 |
| Cardiovascular disease | 46 (26.9) | 17 (34.7) | 1.000 |
| Tumor | 15 (8.8) | 10 (20.4) | 0.000 |
| Chronic kidney disease | 14 (8.2) | 4 (8.2) | 0.882 |
| Drugs | | | |
| Antihypertensive | 49 (36.6) | 13 (36.1) | 1.000 |
| Corticosteroids | 10 (7.5) | 3 (8.3) | 1.000 |
| Oral anticoagulants | 6 (4.5) | 6 (16.7) | 1.000 |
| Antiplatelet agents | 40 (29.9) | 10 (27.8) | 1.000 |

*For these variables, data available for (n=) were: home therapy (n=134); **for these variables the data available for (n=) were: co-morbidity (n=49); home therapy (n=36); COPD, Chronic Obstructive Pulmonary Disease.

**Table 2. Comparison of clinical characteristics at the first admission to the hospital between SARS-CoV-2 pneumonia and *Streptococcus pneumoniae* pneumonia patients. Values are expressed as median and Interquartile Range (IQR) or absolute numbers and percentages (%).**

| | COVID-19 pneumonia (n=171)* | Pneumococcal pneumonia (n=51)** | *p* |
|---|---|---|---|
| **Clinical presentation** | | | |
| Body temperature (°C) | 38.0 (38.5-37.5) | 37.5 (37.9-37.3) | 0.018 |
| Systolic blood pressure (mmHg) | 130 (140-116) | 120 (150-105) | 0.130 |
| Diastolic blood pressure (mmHg) | 70 (80-60) | 70 (85-60) | 0.767 |
| Heart rate (bpm) | 88 (100-78) | 93 (115-80) | 0.061 |
| Respiratory rate (brpm) | 16 (20-14) | 16 (25-15) | 0.208 |
| Oxygen saturation (%) | 92 (96-86.8) | 91 (96-88) | 0.935 |
| Fever | 147 (87.5%) | 27(56.3%) | 0.000 |
| Cough | 78 (46.4%) | 20 (41.7%) | 1.000 |
| Headache | 5 (3%) | 1(2.1%) | 0.206 |
| Asthenia | 7 (4.2%) | 0 (0%) | 0.121 |

*For these variables, data available for (n=) were: fever, cough, headache, asthenia, diffuse muscle pain, dyspnea, diarrhea (n=168); **for these variables, data available for (n=) were: fever, cough, headache, asthenia, diffuse muscle pain, dyspnea, diarrhea (n=48).

On the contrary, SARS-CoV-2 pneumonia patients had more significant liver damage, as shown by their higher median alanine aminotransferase values: 25 IU/L (IQR:39-18) *vs* 20 IU/L (IQR:31-12); p=0.008. The results are described in Table 3.

### Therapy during hospitalization

SARS-CoV-2 pneumonia patients were most frequently treated with antiviral drugs: 139/171 (81.3%) *vs* 1/51 (2.1%); p<0.001; they often needed oxygen therapy: 142/171 (83%) *vs* 27/51 (56.3%); p<0,001; and non-invasive mechanical ventilation: 59/171 (34.5%) *vs* 7/51 (14.6%); p=0.004. The results are described in Table 4.

### Transfer to Intensive Care Unit and bacterial superinfection

No significant difference in the proportion of patients requiring transfer to intensive care units has been documented: 5/171 (2.9%) *vs* 4/51 (7.8%); p=0.118; Similarly, no significant difference in the number of subsequent bacterial infections: 7/171 (4.1%) *vs* 4/51 (8.2%); p=0.279.

### Outcome

Mortality was higher in SARS-CoV-2 pneumonia patients: 46/171 (26.9%) than in pneumococcal pneumonia patients 5/51 (9.8%); p=0.011.

## DISCUSSION

The first result was the increased prevalence of pneumonia caused by SARS-CoV-2 and *S. pneumoniae* in males than in females. This observation could be related to immune factors; in fact, women, compared to men, exhibit lower susceptibility to viral infections due to differences in innate immunity, hormonal factors, and sex chromosomes-related factors.

Immune regulatory genes encoded by the X chromosome in females are associated with lower viral load levels and reduced inflammatory states compared to males. Immune regulatory genes encoded by the X chromosome in females are associated with lower viral load levels and reduced inflammatory states compared to males, while CD4+ T lymphocyte levels are higher with better immune response. Women also produce higher levels of antibodies circulating longer in the bloodstream and produce lower



**Table 3. Comparison of laboratory characteristics at the first admitted to the hospital between patients suffering from SARS-CoV-2 pneumonia and *Streptococcus pneumoniae* pneumonia patients. Values are expressed as median and Interquartile Range (IQR).**

| | COVID-19 pneumonia (n=171) | Pneumococcal pneumonia (n=51) | *p* |
|---|---|---|---|
| **Lab parameters** | | | |
| White blood cells (cells/mm$^3$) | 6730 (9410-4600) | 10390 (15470-6888) | 0.000 |
| Neutrophils (cells/mm$^3$) | 5190 (7770-3530) | 9015 (12978-5123) | 0.000 |
| Lymphocytes (cells/mm$^3$) | 740 (1020-560) | 800 (1240-540) | 0.631 |
| Platelets (cells/µL) | 191000 (278000-147000) | 217000 (294000-139000) | 0.174 |
| Alanine aminotransferase (IU/L) | 25.00 (39.00-18.00) | 20.00 (31.00-12.00) | 0.011 |
| Creatinin (mg/dL) | 0.91 (1.25-0.74) | 0.97 (1.17-0.72) | 0.995 |
| Lactate dehydrogenase (IU/L) | 701.00 (908.00-535.00) | 538.50 (737.75-467.25) | 0.018 |
| C-reactive protein (mg/dL) | 9.46 (15.52-4.04) | 18.16 (29.25-13.81) | 0.000 |

**Table 4. Comparison of therapy administered during hospitalization between SARS-CoV-2 pneumonia and *Streptococcus pneumoniae* pneumonia patients. Data are expressed as absolute numbers and percentages (%).**

| | COVID-19 pneumonia (n=171) (%) | Pneumococcal pneumonia (n=51)* (%) | *p* |
|---|---|---|---|
| **Therapies administered** | | | |
| Antibiotics | 165 (96.5) | 46 (95.8) | 0.000 |
| Antivirals | 139 (81.3) | 1 (2.1) | 0.000 |
| Corticosteroids | 23 (13.5) | 11 (22.9) | 0.161 |
| Oxygen | 142 (83) | 27 (56.3) | 0.000 |
| Invasive mechanical ventilation | 19 (11.1) | 2 (4.2) | 0.100 |
| Non-invasive mechanical ventilation | 59 (34.5) | 7 (14.6) | 0.018 |
| Hydroxychloroquine | 144 (84.2) | - | - |
| Antithrombotic prophylaxis | 118 (69) | - | - |
| TocilizumabEV | 14 (8.2) | - | - |
| Baricitinib | 7 (4.1) | - | - |

*For this variable, data available for (n=) were: (n=48).

inflammatory IL-6 levels than males after viral infection: it is associated with better life expectancy. Moreover, there appears to be a greater expression of the angiotensin-converting enzyme 2 in males than in females. Additionally, lifestyle factors such as smoking and/or alcohol consumption, which are more prevalent among men, have been implicated in the discrepancy in the number of deaths. Moreover, females have demonstrated a more responsible attitude during the pandemic, adopting preventive measures such as frequent handwashing, the use of facial masks, and adherence to stay-at-home directives.[20-22]. This responsible behavior may contribute to the lower incidence and severity of respiratory infections in females compared to males. The increased prevalence of respiratory infections, including *S. pneumoniae* disease, among males has been consistently reported. The documented increased prevalence of COPD in *S. pneumoniae* patients has already been reported by several studies and systematic reviews. Patients with SARS-CoV-2 pneumonia were more likely to present with fever (≥37.5°C), which aligns with literature evidence. In fact, in a systematic review with meta-analysis that evaluated 54 clinical studies[23] fever was found in 81.2% of COVID-19 patients, followed by cough (58.5%), asthenia (38.5%) and dyspnea (26.1%). In the same way, another meta-analysis that included more than 50.000 COVID-19 patients showed that fever was the most frequent sign/symptom present in 89.1%.[24] Comparing laboratory data, ones in the two groups of patients with pneumococcal pneumonia were more likely to have elevated levels of total leukocytes, predominantly represented by neutrophil granulocytes, and C-reactive protein. This finding is in line with the pathogenesis of the inflammatory process during *S. pneumoniae* infection, where immune cells and epithelial cells secrete chemokines and cytokines that facilitate the migration of neutrophils into the lungs. When a bacterial infectious agent invades the respiratory tract, immune system cells and epithelial cells secrete chemokines and cytokines, promoting the migration of neutrophils into the lung through the walls of pulmonary capillaries.[25] Among the available biochemical data, elevated levels of alanine aminotransferase were observed in patients with SARS-CoV-2 pneumonia. This finding has already been described by other authors[26] and often represents liver damage induced by the virus, potentially exacerbated by pre-existing liver conditions. Conversely, the significant increase in C-reactive protein among patients with pneumococcal pneumonia is consistent with previous research associating C-reactive protein and procalcitonin as independent predictors of *S. pneumoniae pneumonia* this is in line with the results of a study performed on 75 patients that showed that C-reactive protein and procalcitonin were independent predictors of *S. pneumoniae* pneumonia.[27] The need for oxygen therapy and non-invasive mechanical ventilation was higher in patients with SARS-CoV-2 pneumonia. This is likely due to the more severe nature of this infection. This finding is supported by a recent meta-analysis conducted by Weerakkody *et al*.,[28] that assessed two randomized controlled trials comparing non-invasive ventilation and high-flow nasal oxygen therapy. The superiority of non-invasive ventilation in reducing the need for intubation was demonstrated. Although the inflammatory index values were higher in the *S. pneumoniae* population, the death rate was higher in the SARS-CoV-2 group. This outcome aligns with the specific period during which patients with SARS-CoV-2 pneumonia were evaluated in this study, and contracted the infection during the early stages of the first pandemic wave when it was most severe. Moreover, they were not able to access the currently available vaccinations or subsequently approved antiviral drugs. Therefore, this population represent the higher risk group for complications and death, which overlaps with the subgroup of patients who still refuse vaccination and subject themselves to a substantial risk of mortality similar to the patients in the study period. It is important to note that this study had some limitations including the small sample size of *S. pneumoniae* patients. A future study with a larger sample size and a multicenter design is needed to confirm these findings. The objective of a future study will be the comparison between the two populations through a multicentric study that includes a greater number of patients.

## CONCLUSIONS

In conclusion, this study showed that the mortality rate was higher in patients with SARS-CoV-2 pneumonia than in patients with pneumococcal pneumonia, even in the presence of substantial overlap of organ damage and lower inflammatory state than in the group suffering from *S. pneumoniae* pneumonia. This evidence underlines once again the need to undergo vaccination against SARS-CoV-2. Our findings suggest that there are important differences between the clinical presentations and outcomes of pneumonia caused by SARS-CoV-2 and *S. pneumoniae*. These differences may be due to the different pathogenic mechanisms of these two infections, as well as the different timing of this study, which was conducted at the onset of the COVID-19 pandemic.

Future studies are needed to investigate these differences further and to identify biomarkers that can be used to predict the severity of pneumonia caused by SARS-CoV-2 and *S. pneumoniae*.

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