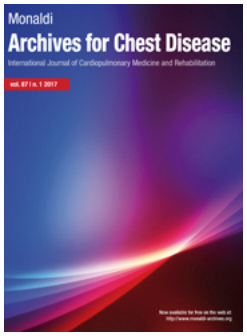

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Frequency of viral etiology in community-acquired pneumonia

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Conflict of interest: the authors declare that there is no conflict of interest.

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Abstract

The identification of etiology is very important when managing patients with community-acquired pneumonia (CAP). In Pakistan, studies regarding the viral etiology in CAP are scarce. The main objective of this study was to evaluate the frequency of viral etiology in CAP patients and analyze the clinical features and their impact on prognosis. Medical records of CAP patients admitted to Aga Khan University Hospital (Karachi, Pakistan) from March 2022 to February 2023 were retrospectively reviewed, patients who had microbiological tests performed within 48 hours of the hospital admission were included, and the frequency of viral and bacterial etiology was calculated. Patients who were immunocompromised were excluded. Epidemiological and clinical characteristics were examined, and the impact on prognosis was explored. A total of 166 patients were included; 115 (69.3%) patients were identified as having pneumonia with known causative microorganisms. A total of 83 (72.1%) patients had a viral etiology alone, 18 (15.6%) had only bacterial infection, and 14 (12.2%) had a viral and bacterial co-infection. Influenza A was most frequently detected (n=46/97; 47.4%), followed by Rhinovirus/Enterovirus (n=19/97; 19.6%). *Staphylococcus aureus* accounted for the majority (n=18; 56.3%) of cases among bacteria. Bacterial and viral-bacterial co-infection was significantly higher among non-survivors (38.1% *vs*. 16.6%, p=0.034). Confusion-Urea-Respiratory Rate-Blood Pressure-Age of 65 scores of 3-5 [odds ratio (OR) 4.234; 95% confidence interval 1.156-15.501], leukocytosis (OR 0.137; 0.030-0.636), high C-reactive protein (>10mg/L) (OR 1.008; 1.001-1.014), high serum procalcitonin level (≥0.5 ng/mL) (OR 10.731; 3.018-38.153), and mechanical ventilation required (OR 47.104; 13.644-162.625) were associated with mortality. Mechanical ventilation requirement was independently associated with increased odds of mortality (OR 43.407; 8.083-233.085). Of 166 patients, 21 (12.7%) had died, with the highest percentage (28.6%) seen in the viral-bacterial coinfection group (p=0.046). To conclude, respiratory viruses are increasingly being recognized as an important etiology in CAP, with higher mortality seen in bacterial infection, whether alone or with viral co-infection.

Key words: pneumonia, etiology, outcome, mortality, Pakistan.

Introduction

The term community-acquired pneumonia (CAP) is used to describe a lung infection that occurs in a non-hospitalized patient [1]. It is generally diagnosed after a new lung infiltrate is recognized on chest imaging (chest X-ray or computerized tomography). CAP is responsible globally for 3 million deaths annually [2]. Mortality rate can vary significantly, ranging from less than 1% to as high as 48%. This variation is associated with advanced age, the presence of co-morbid conditions, and the severity of CAP [3]. The identification of etiology is paramount when treating patients with CAP. In the past, *Streptococcus pneumoniae* was responsible for causing more than 90% cases of pneumonia in adults [4]. It has declined recently to only 10-15% of cases, partly due to widespread pneumococcal vaccination [4]. Recent studies investigating the etiology of CAP have revealed that respiratory viruses (RVs) are now more commonly responsible for CAP than bacteria. These prospective studies have also highlighted the challenge of identifying a specific pathogen in over 50% of adult cases [5]. Furthermore, several recent studies have also recognized that the involvement of respiratory viruses in CAP may have been underestimated, mostly due to a lack of appropriate diagnostic methods. The global COVID-19 outbreak has resulted in more than 6 million fatalities across the globe [6]. According to a recent systematic review, the prevalence of Influenza viruses in cases of CAP ranged from 6.2% to 13.7%. Similarly, Rhinoviruses were detected in 4.1% to 11.5% of the cases [1]. In Pakistan, there is limited data on CAP caused by respiratory viruses. A study from a tertiary care hospital of Karachi, demonstrated that the overall mortality rate associated with Influenza amounted to 15.9% [7]. However, there is paucity of data on other respiratory viruses that can cause CAP, including their frequency, clinical characteristics, and outcomes, owing to a lack of resources and appropriate diagnostic methods. Testing for specific pathogens in CAP is important since it can alter standard (empirical) management decisions, decreasing cost, drug adverse effects, and antibiotic resistance [8]. It is imperative to conduct studies within our population, employing PCR-based assays to evaluate the frequency of viral etiology in CAP that could influence patient management.

The objective of this study was to ascertain the prevalence of viral causes in cases of CAP within our population, as well as to delineate the clinical features and prognosis associated with these cases in a tertiary healthcare facility located in Karachi.

Materials and Methods

This was an observational study conducted in adult patients aged 18 years and above, that were admitted to Aga Khan University Hospital, Karachi-Pakistan from March 2022 to February 2023 and managed as CAP. We included patients who met the definition of CAP (described as a new infiltrate identified on a chest radiograph alongside clinical signs of a lower respiratory tract infection) and were tested with microbiological tests performed within 48 hours of the hospital admission, including BioFire FilmArray Respiratory 2.1 plus panel (RP2.1 plus panel) (BioMérieux, France). RP2.1 plus is a commercial automated multiplex PCR syndromic panel that uses nasopharyngeal specimens and provides identification of 23 pathogens associated with respiratory infections (19 viruses and 4 bacteria) in about an hour. Manufacturer's instructions were followed for testing by RP2.1. Along with this, patients also had culture of respiratory specimens (sputum, tracheal aspirates or bronchoalveolar lavage) and blood. Standard procedures were used for all microbiological cultures [9]. Briefly, respiratory specimens were cultured on blood chocolate, colistin nalidixic acid with sheep blood (CNA), MacConkey agars. Chocolate and CNA agar plates were incubated in 5% CO_2 at 37℃, whereas, MacConkey agar was incubated in air at 37℃ for 48 hours. Blood cultures were collected in BACT/ALERT® aerobic and anaerobic blood culture bottles (Biomerieux, France) and were incubated at 37℃ in BACT/ALERT® 3D automated microbial detection system for 5 days. Positive blood culture bottles were subcultured onto chocolate, sheep blood agar and MacConkey agars plates and incubated under appropriate conditions for 48 hours. Agar plates were read for microbial growth every 24 hours. Conventional biochemical tests (Gram stain, catalase, coagulase, DNase, sulphide-indole-motility (SIM), citrate, urease, triple sugar iron (TSI), Hugh & Leifson's oxidation/fermentation agar) were used for identification of pathogens. The conventional biochemical tests were supplemented with analytical profile index (API) (Biomerieux, France) where required. Susceptibility testing was performed according to Clinical and Laboratory Standards Institute's criteria [10]. Both Kirby Bauer and Vitek-2 (Biomerieux, France) were used for antimicrobial susceptibility testing as appropriate.

Patients were excluded from the study if they were immunocompromised (defined as HIV positive, those with active malignancy, those on continuous maintenance oral steroids, post-transplant patients, and those who are receiving chemotherapy), and those who developed symptoms of pneumonia 48 hours after admission.

A comprehensive evaluation of medical records and chest radiographs was conducted. Age, gender, smoking status, comorbid conditions, prior antibiotic use during last 30 days (broad-spectrum antibiotics frequently prescribed for CAP associated with bacterial organisms, like beta-lactams, macrolides, and fluoroquinolones), radiological findings and laboratory findings were recorded on a proforma. Blood test results that depict infection like white cell count, C-reactive protein, procalcitonin, and the results of viral PCR, cultures of sputum, and tracheal aspirates were also recorded. CURB 65 score was calculated for each patient to evaluate the initial severity of CAP. An analysis was conducted on outcomes which encompassed the duration of hospitalization, length of stay in the intensive care unit, mechanical ventilation required, discharge following recovery, and mortality during hospital admission.

This study obtained approval from the ethical review committee (ERC #2023-8526-24641) of Aga Khan University Hospital, Karachi.

Statistical analysis

Data entry and analysis were performed using the Statistical Package of Social Sciences (SPSS) for Windows (IBM Corp., Armonk, N.Y., USA) version 19.0. Data normality was examined. Quantitative variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) and qualitative variables were presented as frequency and percentages. For comparison of the non-numerical data, the Chi-square test was used. Independent samples t-test or Mann-Whitney U test was used to compare differences between the two groups. Depending on data distribution, one-way analysis of variance (ANOVA) or the Kruskal-Wallis H test was used for comparison of numerical data among groups. Regression analysis was performed to identify predictors of mortality and odds ratios (OR) with 95% confidence intervals (95% CI) were reported. *P* value <0.05 was considered as statistical significance.

Results

A total of 166 patients were included. The median age was 61.58 years (± 17.30) and 56% were female. A total of 115 (69.3%) patients were identified as having pneumonia with known causative microorganisms (Figure 1); the etiology remained unknown for 51 (30.7%) patients. The group with known etiology was divided into three groups: viral alone, bacterial alone, and

viral and bacterial coinfections. Eighty-three (72.1%) patients had a viral-only etiology, 18 (15.6%) patients had a bacterial infection, and 14 (12.2%) had a viral-bacterial coinfection. *Supplementary Table 1* summarizes the clinical characteristics of patients with CAP and all these subgroups.

Almost three-quarters (77.7%) of the patients were non-smokers. The most common comorbidities were hypertension (62.7%) diabetes mellitus (47%) and cardiovascular disease (28.3%). Most of the patients had a CURB score of 0-1 (47.6%) and no statistically significant difference was found among the groups (p=0.117).

On laboratory findings total leucocyte count (16.16 ± 9.32, p= 0.002) and C-reactive protein level (155.74 ± 87.98, P= 0.001) was significantly higher in the bacterial-only group.

On chest radiographs, 89% of patients had bilateral lung infiltrates. In contrast to the viral-only group, a larger proportion of patients in the bacterial-only group showed consolidation (66.7 vs. 30.1%, P <0.0001) on chest radiograph.

Etiology of community-acquired pneumonia

The frequency of respiratory viruses identified by multiplex PCR testing is presented in *Supplementary Table 2*. Influenza A was the most frequently detected accounting for (n= 46; 47.4%) of the total, followed by Rhino-Enterovirus (n= 19; 19.6%) and human Coronaviruses (n= 11; 11.3%).

In *Supplementary Table 3*, the distribution of bacteria isolated from culture positive patients is presented. The most commonly identified was *Staphylococcus aureus* that accounted for (n=18; 56.3%) cases, with Methicillin-Resistant *Staphylococcus Aureus (MRSA)* constituting (n=12; 37.5%) and Methicillin-Sensitive *Staphylococcus Aureus (MSSA)* (n=6; 18.8%). *Pseudomonas aeruginosa* was the next most common with a frequency of (n=9; 28.1%). *Klebsiella pneumoniae* was isolated in (n=3;9.4%) of the cultures whereas *Streptococcus pneumoniae* was isolated in (n=1; 3.1%) of the cultures. Mixed infection etiology was observed in 7 (21.9%) patients with positive bacterial cultures. Viral-bacterial coinfection accounted for (n=14; 12.2%) cases, with the most common co-infection being Influenza and *Staphylococcus aureus* (n= 8/14), out of which 6 were MRSA and 2 were MSSA.

Outcomes

A total of 32 patients (19.3%) were admitted to the intensive care unit (ICU). Notably, there were no significant distinctions observed among the groups in relation to the duration of ICU stay, and hospital stay (*Supplementary Table 1*). Shock as a complication was observed in a considerably larger proportion of patients (35.7%) in the viral-bacterial coinfection group, (p=0.006). However, no significant differences were observed among the groups in terms of pneumothorax, NSTEMI, and parapneumonic effusion. Of the 166 patients, 21 (12.7%) died, with the highest proportion of death (28.6%) seen in the viral-bacterial coinfection group (p=0.046). *Supplementary Table 4* shows a comparison of clinical characteristics between survivors and non-survivors. There was no significant difference identified in age, gender, smoking status, comorbidities, and prior antibiotic use. Most survivors (51.7%) had a CURB-65 score of 0-1 whereas a significantly higher frequency of non-survivors had a CURB-65 score of 2 (47.6%) and 3-5 (33.3%) respectively (p-value = 0.019). As far as blood tests were concerned, non-survivors had a significantly higher value of serum creatinine [1.40 (1.05 – 2.65) vs 1.15 (0.80 – 1.60), p=0.017] as compared to survivors. C-reactive protein (140.13 ± 97.05 vs 90.79 ± 70.74, p =0.012) and serum procalcitonin levels [4.39 (1.50 – 20.50) vs 0.18 (0.09 – 0.92), p<0.001] were found to be substantially higher in the non-survivor group when contrasted with the survivor group. Consolidation on chest radiograph was seen in a higher frequency of non-survivors as compared to survivors (81% vs 42.1%, p=0.001). Frequency of mechanical ventilation (81% vs 8.3%, p <0.0001) was also higher in the non-survivor group. Non-survivors had a higher frequency of shock (81% vs 4.1%, p <0.0001), pneumothorax (14.3% vs 0%, p =0.02), and NSTEMI (52.4% vs 11%, p<0.0001). Non-survivors had higher rates of bacterial and bacterial-viral co-infection (38.1% vs 16.6%, p=0.034).

Mortality predictors

An evaluation of the factors associated with mortality in patients with CAP was carried out using univariate and multivariable analyses (*Supplementary Table 5*). On univariate analysis, CURB-65 score of 3-5 (OR 4.234; 95% CI, 1.156 – 15.501; p = 0.029), leukocytosis, high C-reactive protein, high serum procalcitonin level, consolidation on the chest radiograph, and mechanical ventilation required were associated with mortality. On multivariable analysis,

only mechanical ventilation requirement was identified as an independent predictor of mortality (OR 47.104; 13.644 – 162.625; p<0.0001).

Discussion and Conclusions

The main aim of our study was to evaluate the frequency of viral and bacterial etiology in CAP patients, examine their clinical characteristics, and identify the factors contributing to mortality, in a tertiary care hospital of Karachi, Pakistan. Among the organisms that were identified, the majority were respiratory viruses, with Influenza A being the most common followed by Rhino-Enterovirus, Coronaviruses, and Influenza B, with a viral bacterial co-infection rate of 12.2%. No organism could be identified in a significant number of patients (30.7%). This is in accordance with recent literature that shows respiratory viruses to be a more common etiology of CAP than previously thought. The EPIC study, which focused on the etiology of pneumonia in the community, was a comprehensive and extensive research endeavor conducted across multiple centers in the United States. This study employed active surveillance techniques and involved a large population sample. The findings of the study revealed that among the cases analyzed, viruses were detected in 23% of individuals, bacteria in 11% of individuals, and a combination of both bacteria and viruses in 3% of individuals [5]. Moreover, a recent systematic review highlighted that in studies where viral PCR was consistently conducted, a respiratory virus was detected in approximately 30 to 40% of patients [1]. In Pakistan, literature regarding the etiology of community-acquired pneumonia is scarce, with little data on viral etiology of CAP in adults, other than influenza. In a large multi-center study conducted in Pakistan among patients with influenza-like illness, 1489 patients (24%) were found positive for influenza viruses [11]. In addition, a recent study conducted in major hospitals of Islamabad on patients with severe acute respiratory illness, showed that 1617 (24%) of hospitalized patients were positive for influenza [12]. However, an analysis of 2,488 adults in the United States indicated differences in virus prevalence, with Rhinovirus (9%), Influenza A and B (6%), Metapneumovirus (4%), and RSV (3%) showing diverse national frequencies [13]. This demonstrates regional differences in the frequency of each respiratory virus causing CAP globally. Given the high prevalence of the influenza virus and suboptimal vaccine coverage in our population, healthcare professionals should promote yearly influenza vaccination, particularly in high-risk populations, as recommended by the World Health Organization [14].

Among the organisms that were identified, bacteria were isolated in 32 (27.8%) patients. The most frequent among them was Methicillin-Resistant *Staphylococcus aureus* (MRSA), found in 37.5% of cases, followed by *Pseudomonas aeruginosa* (28.1%). The prevalence of *Streptococcus pneumoniae* in culture positive patients was observed to be merely 3.1%, which stands in stark contrast to international studies where this bacterium has been identified as the predominant pathogen in 20%–60% of individuals [15]. Possible reasons for low *Streptococcus pneumoniae* and *Haemophilus influenzae* frequency in our cohort could be prior antibiotic therapy before hospitalization and poor-quality sputum samples. Furthermore, the introduction of Haemophilus influenzae type b (Hib) vaccine in children as part of Expanded Programme on Immunization (EPI) in 2008 could have reduced the reservoir in our population. The increasing prevalence of community-acquired MRSA in Pakistan is a big concern, with a study in Peshawar showing frequency of community-acquired MRSA to be as high as 42% [16]. Another study found frequency of MRSA in Pakistan to be high as compared to northern Europe [17]. Several factors could account for the difference in prevalence rates, including the unique clinical characteristics of the patients being studied, the presence of risk factors specific to our community, and microbial ecology unique to our region. Considering that the patients in our cohort were suspected of having viral etiology based on their medical history, it is possible that this could contribute to the higher frequency of *Staphylococcus aureus*. Our study identified Influenza viruses as the most prevalent, and it is well-documented that *Staphylococcus aureus* often leads to secondary bacterial pneumonia following Influenza [18]. CAP, in patients who have already taken antibiotics, is likely to be with organisms usually not covered with the empiric recommendations, e.g. MRSA. Underlying structural lung disease also predisposes airways to become colonized with gram negative organisms, like *Pseudomonas aeruginosa*.

In the evaluation of clinical characteristics between survivors and non-survivors, we found that non-survivors had a significantly higher CURB 65 score compared to survivors and a higher CURB65 score was a strong predictor of mortality. Even though there have been conflicting results on the superiority of one scoring system over the other, a recent meta-analysis demonstrated that CURB65 exhibited a slight advantage in predicting early mortality and displayed higher sensitivity (96.7%) and specificity (89.3%) in forecasting the need for intensive care support, as compared to the pneumonia severity index (PSI) [19]. This highlights the importance of early risk stratification of CAP patients using CURB65 score when they are

triaged on arrival to the emergency department, or outpatient clinics. The comparison between non-survivors and survivors revealed elevated creatinine levels in the former group, a finding consistent with multiple studies highlighting the detrimental effects of acute kidney injury (AKI) on outcomes in community-acquired pneumonia (CAP) [20-22].

Concerning the factors associated with mortality in our study, CURB 65 score two or more, raised serum C-reactive protein and procalcitonin, consolidation on chest x-ray and mechanical ventilation required are associated with mortality in univariate analysis. The raised C-reactive protein is also identified an independent marker of severity of CAP in other studies [23]. This is also consistent with several other studies that have linked procalcitonin with disease severity and prognosis in CAP [24-26]. Compared to these studies, in our analysis, raised procalcitonin and CRP did not demonstrate statistical significance in the multivariate analysis, even though they are recognized as important indicators of disease severity in community-acquired pneumonia (CAP). The limited sample size may have contributed to this outcome. Using procalcitonin not only as a marker of bacterial infection but as a prognostic marker will help early assessment of pneumonia severity and can also form a good alternative to CURB 65 to help early clinical decision-making, especially in patients with co-existent illness that has an impact on CURB 65 score.

The importance of early risk stratification lies in the fact that of patients hospitalized for CAP, 10-30% may need an intensive care unit (ICU) [27-29]. Overall, 32 patients (19.3%) were admitted to the ICU in our study, and requirement of mechanical ventilation turned out to be the strongest independent factor associated with mortality. This could be partially attributed to the gravity of the illness necessitating mechanical ventilation, or it could be a result of its associated complications such as ventilator-induced lung injury (biotrauma, atelectrauma, volutrauma, barotrauma) and ventilator-associated pneumonia (VAP) [30]. The mortality rates for ventilator-associated pneumonia (VAP) are typically between 25% and 50%, but there are instances where this figure can increase to 70% [31].

The present study revealed a co-infection rate of 12.2% between viral and bacterial pathogens. Notably, a significantly higher proportion of patients in this cohort developed shock as a complication, when compared to individuals with isolated viral or bacterial infections. Both bacterial and viral bacterial co-infection groups were associated with mortality in the univariate analysis, however, did not show significance in multivariate analysis. As mentioned above,

limited sample size could have contributed to this outcome. In this regard, a meta-analysis of thirty-one studies showed an increase in mortality among patients with pneumonia due to viral-bacterial co-infection [32], however, other studies have failed to demonstrate this [33]. This can be explained by numerous pernicious interactions between bacteria and viruses, that could produce impaired mucociliary clearance, upregulation of receptors that can be used by bacteria for adherence and infection, and a dysregulated immune response [34-36]. More efforts should be made to understand the complex interactions between bacteria and viruses causing co-infection in CAP, ensuring necessary measures are taken to improve outcomes.

The study's limitations include the small sample size, which prevents the generalization of results to the broader population. Consequently, several well-established prognostic factors in pneumonia did not show significance in the multivariate analysis. Therefore, a larger, multicenter study is necessary to confirm these findings. Secondly, since most bacterial cultures were taken from sputum samples, and viruses from PCR of nasopharyngeal swabs, there would have been lower sensitivity and accuracy to detect lower respiratory tract infections. Perhaps, samples from bronchoalveolar lavage could be tested for both bacteria and viruses for more accuracy in diagnosing lower respiratory tract infections. Finally, we captured length of ICU stay in whole days and therefore patients with <24 hours stays were noted as 0 days (especially patients with relatively less severe disease). This may have led to high number of 0-day entries for survivors, resulting in a median IQR of 0 for this particular group.

Notwithstanding these constraints, the present study sheds light on the origins of viral pneumonia in adult individuals residing in a prominent urban center in lower middle-income country. It also explains the clinical features and outcomes associated with this condition, particularly in a region where epidemiological information is scarce concerning community-acquired pneumonia.

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Online supplementary material:
Supplementary Table 1. Clinical characteristics of patients with community-acquired pneumonia (n=166).
Supplementary Table 2. Frequency of viral etiology in biofire filmarray positive community-acquired pneumonia patients (n=97).
Supplementary Table 3. Frequency of specific bacterial organisms in culture-positive community-acquired pneumonia Patients (n=32).
Supplementary Table 4. Comparison of clinical characteristics between survivors and non-survivors (n=166).
Supplementary Table 5. Factors associated with Mortality in patients with community-acquired pneumonia (n=166).

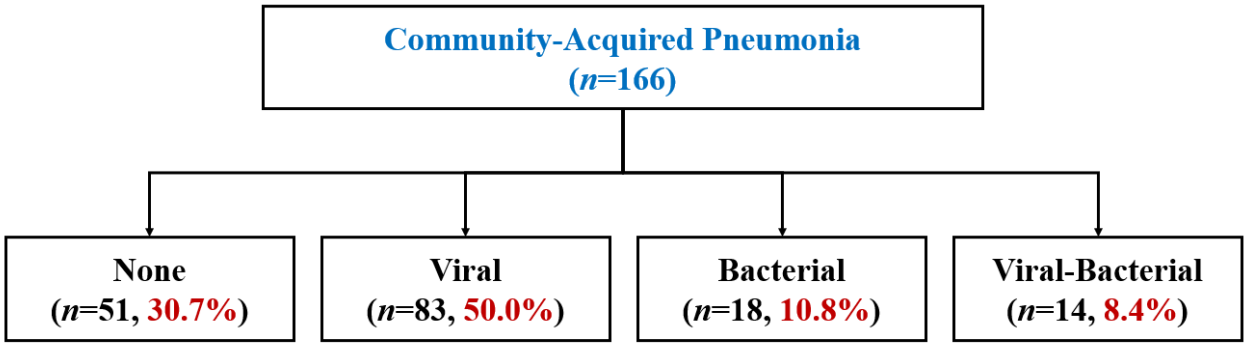

Figure 1. Distribution of viral-bacterial infection in patients with community-acquired pneumonia.