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Prevalence of Bacterial Lower Respiratory Tract Infections at a Tertiary Hospital in Jordan

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Abstract

Background: Lower respiratory tract infections (LRTIs) are a major cause of morbidity and mortality globally. The World Health Organization (WHO) estimates that LRTIs are the most common global cause of death from infectious diseases. However, the specific etiologic agent associated with LRTI is often unknown. We determined the bacterial infections and seasonal patterns associated with LRTIs among hospitalized cases at Jordan University Hospital (JUH) for a period of five years.

Methods: We conducted a retrospective multi-year study among hospitalized patients in Jordan on LRTI-associated bacterial etiology.

Results: We found bacterial infections among 105 (21.1%) out of 495 LRTI patients. The most frequently identified bacteria in the LRTI patients were *Staphylococcus aureus* (7.7%) followed by *Pseudomonas aeruginosa* (5.1%). Most of the LRTI patients (95.2%) had at least one chronic disease and many were admitted to the Intensive Care Unit (16.8%). Of the 18(3.64%) patients with LRTIs who died at the hospital, 2 had a bacterial infection. We noticed a seasonal pattern of bacterial infections, with the highest prevalence during the winter months.

Conclusions: Our findings suggest that early identification of bacterial agents and control of chronic disease may improve clinical management and reduce morbidity and mortality from LRTIs.

Keywords
Bacterial; Lower Respiratory Tract Infections; Pneumonia; Jordan.

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Introduction

Lower respiratory tract infections (LRTIs) continue to be a major cause of morbidity and mortality worldwide. The World Health Organization (WHO) estimates that LRTIs, including pneumonia and acute bronchitis,cause about 3.5 million deaths globally per year [1]. Community-acquired pneumonia (CAP) is a severe form of LRTI that can progress to a critical condition requiring hospitalization. It can be life-threatening, especially for the elderly with chronic diseases and can quickly turn fatal [2]. Adult CAP can be caused by abroad spectrum of etiological agents including bacteria. However, by far, *Streptococcus pneumoniae* has been found to be the most common bacteria in CAP cases. For example, a review of 41 European studies found *S. pneumoniae* to be the most prevalent bacteria among CAP cases [3-6], followed by *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila,* and *Haemophilus influenzae,* while *Staphylococcus aureus* was the least common among studied bacteria as a causative agent of CAP [6]. A meta-analysis involving 38 studies from Asia also showed a similar pattern with *S. pneumoniae* being the most common pathogen identified in LRTI (13.3%), followed by *M. pneumoniae*, and *H. influenzae*. On the other hand, *Staphylococcus aureus* was isolated only in 4.0% of patients [7]. Relatively little is known about bacterial infection among CAP patients in Jordan. Consistent with findings from other parts of the world, a single study in Jordan among only 35 adult CAP patients reported *S. pneumoniae* to be the most common bacteria (26%), followed by *C. pneumoniae* (23%) and *H. influenzae* (17%) more than a decade ago [8]. Since then, no study has been conducted on the recent trends of bacterial infection among LRTI cases in Jordan.

Therefore, it is critical to have information on the etiological agents associated with LRTI in Jordan and the surrounding region for a number of reasons. First, in many countries of the region, antibiotic resistance is increasing [9], particularly against *S. pneumoniae* [10]. Second, there is increased variation of causative bacteria in infections, contributed to by extensive and unregulated antibiotic use, and the introduction of vaccines against pneumococcal antigens [7]. Third, the pattern of causative agents may differ by geographic area due to seasonal variations [11]. To address the above issues, we have conducted for the first time a large multi-year study among hospitalized patients in Jordan on LRTI-associated bacterial etiology. The findings of the study will provide information on the trends of bacterial agents causing LRTI in Jordan, help clinical management with the appropriate use ofantibiotics, and ultimately reduce the burden of morbidity and mortality from LRTI in the region.

Method

Data collection and study design

Jordan University Hospital (JUH) is a teaching hospital in the north of Amman, the capital of the Hashemite Kingdom of Jordan. Study subjects were patients admitted by the pulmonary medicine and critical care primary team from January 2011 to January 2016. The LRTI cases were defined as having cough, purulent sputum, dyspnoea, thoracic pain, fever, chills, myalgia, and confusion [12].The LRTI cases were sub-typed into acute bronchitis and pneumonia. Acute bronchitis was defined as the presence of fever (>38°C), cough, increased sputum production, rhonchi, and wheezing, with no radiographic evidence of pneumonia. Pneumonia was defined by new or progressive lung infiltrate (i.e., increased density on chest X-ray due to the presence of pus, protein, or air within the parenchyma of the lung), consolidation, pleural effusion, or cavitations on chest X-ray along with the symptoms of acute bronchitis [13]. We documented vital signs, such as temperature, heart rate, blood pressure, respiratory rate, and their level of consciousness. We

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also reviewed the study participants'current and past medical histories, including chronic diseases. Data on demographics and smoking were collected from their medical records. We also recorded the patients' date of admission, to identify possible seasonal patterns.

As a part of this analysis, we examined the patients' chest X-rays, to identify any radiologic changes. Blood culture and sputum culture were done for all patients and were the primary method for identifying the bacterial agents. In addition, urinary antigens were tested for *S. pneumoniae* and *Legionella* spp [14, 15].

Collection and isolation of bacteria

First, laboratory personnel performed Gram staining on all specimens, then bacterial cultures were prepared for two different growth conditions, one for aerobic and the other for anaerobic bacteria, in the BacT/Alert system (OrganonTeknika Corp., Durham, N.C.) [16]. If the culture was positive for anaerobic bacteria, blood agar plates were used as differential media. CLED agar was used for selected Gram-negative bacteria and chocolate agar for fastidious bacteria, such as *Haemophilus influenzae* and *Neisseria meningitidis*. As of 2015, we used a multiplex polymerase chain reaction (PCR) respiratory panel for the detection of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Legionella pneumophila*, *Legionella longbeachae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*, since the detection rate by PCR is significantly higher than culture methods [17].

The severity of pneumonia

We classified the severity of LRTI in our study population using the Confusion, Blood Urea Nitrogen, and Blood pressure (CURB-65) score [18]. CURB-65 is a clinical quantification scale that has been validated for predicting mortality in community-acquired pneumonia [19] and infection of any site [19]. CURB-65 has been recommended by the British Thoracic Society for assessing the severity of pneumonia [20]. A severity score for CURB-65 is estimated by adding 1 point for the following risk factors:confusion, blood urea nitrogen >7 mmol/L, respiratory rate ≥30 breaths/min, systolic blood pressure ≤90, diastolic blood pressure ≤60 mmHg and for individual's age 65 years or older. We reviewed the endpoints of the outcome including improvement and hospital discharge, death and recurrent admission and whether they had developed complications, including intubation for acute respiratory distress syndrome (ARDS), respiratory failure, and other complications like pleural effusion, septic shock, disseminated intravascular coagulation (DIC), myocardial infarction (MI), or renal complications.

Statistical analysis

We used SPSS software for analyzing the collected data (SPSS Inc., Chicago, Illinois, USA). We applied the Pearson Chi-squared test (X^2 test) and t-test to compare groups with categorical and continuous variables respectively. The analysis compared between pneumonia and acute bronchitis in their etiology, outcomes, and mortality rates. Statistical significance for the results in all these two-tailed statistical tests was $p<0.05$.

Results

Patients' characteristics

This study included 495 patients. The average age of the study participants was 58 years (range 13-92). Males (57.9 ± 19.3) were slightly older than females (57.7 ± 17.3). There were 55 % males and 45% females. Out of the 495 patients, 115 were current smokers (23%), 242 were non-smokers (49%), 60 were ex-smokers (12%), and 78 patients (16%) did not specify their smoking habits. In this study, 411 (83%) of the patients had at least one chronic illness, with 57% having multiple comorbidities. Pulmonary diseases were present in 216 (44%) patients

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and diabetes mellitus (DM) was among 191 patients (39%) **(Table 1)**.

Clinical diagnosis of LRTIs

Table 1. Patients demographics.

Patient Characteristics	No. of Patients	Percent
Age (years)		
Mean Age + SD (yr)	57.79 ± 18.43 range (16-92)	
Median Age	62 years	
Gender		
Male	274	55.4
Female	221	44.6
Smoking		
Current Smoker	115	23.2
Ex-Smoker	60	12.1
Non-Smoker	242	48.9
Unknown	78	15.8
Co-morbidities	411	83.0
Cardiovascular Diseases	272	55.0
Pulmonary diseases	216	43.6
Diabetes Mellitus	191	38.6
Renal Diseases	57	11.5
Other co morbidities	142	28.7

More than half of the patients were diagnosed with pneumonia (59%) and the rest (41%) with acute bronchitis. The mean CURB-65 score was 1.3 ± 0.9. Of the 495 patients, 49 patients (10%) developed complications during hospitalization, with some patients developing more than one complication concurrently. The complications were as follows: 26 (5.3%) patients developed pleural effusion, 4 (0.8%) myocardial infarction (MI), 6 (1.2%) septic shock, 5 (1%) renal complications, and 2 (0.4%) developed disseminated intravascular coagulation (DIC). We found more patients with pneumonia (73.5%) had developed a complication as compared to those with acute bronchitis (p=0.02) during hospitalization. A total of 83/495 (17%) patients were admitted to the intensive care unit (ICU), and 18 (3.64%) of these patients died during hospitalization.

Bacterial isolates analysis

A total of 105 (21.1%) bacteria isolates were detected in investigated LRTI patients **(Table 2)**. The most frequently identified bacteria species was *S. aureus* (7.7%), followed by *P. aeruginosa* (5.1%), *Klebsiella* spp. (3.2%) and *Acinetobacter*spp (2.2%). *S. Pneumoniae* was identified in 0.8% of cases. Other Gram-negative bacteria were identified in 4.2% of the cases. *P. aeruginosa* was significantly associated with acute bronchitis cases (p = 0.01) **(Table 3)**. The pattern of antibiotic resistance among predominant bacteria isolated from patients admit-

Table 2. Causative agents identified among LRTI cases.

Clinical Characteristics	No. of Patients	Percent
Pathogen identified	157	31.7
Bacteria	105	21.2
Staphylococcus aureus	35	7.7
Pseudomonas aeruginosa	25	5.1
Klebsiellas pp.	16	3.2
Acinetobacter spp.	11	2.2
Streptococcus pneumoniae	4	0.8
Viral agents*	69	13.9

*: Reported in reference 37.

Table 3. Comparison between bacterial causative agents of pneumonia and acute bronchitis.

Causitive Agent	Pneumonia		Acute Bronchitis		Total	P Value
	Positive		Positive			
	n	%	n	%	n	
S. aureus	20	57.1	15	42.9	35	0.69
P. aeruginosa	9	36	16	64	25	0.01
Klebsiella spp.	7	43.8	9	56.2	16	0.16
Acinetobacter spp.	5	45.5	6	54.5	11	0.37
S. pneumoniae	1	25	3	75	4	-

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ted for LRTI is presented in **Table 4**. We classified the patients based on their month of admission in order to investigate seasonal variation **(Figure 1)**. Interestingly, *S. aureus* was found to have a peak incidence in January and November, following the same trend as viral LRTI **Figure 2**.

Table 4. Antibiotic resistance pattern of predominant bacteria isolated from patients admitted for LRTI.

Antibiotic	Bacteria		
	P. aeruginosa	*Klebsiela spp.*	*Acinetobacter Spp*
	%	%	%
Tigecycline	33.3	16.7	15.4
Gentamicin	33.3	33.3	30.8
Cefotaxime	16.7	50.0	84.6
Cefoxitin	16.7	41.7	92.3
Ceftriaxone	16.7	58.3	84.6
Ertapenem	16.7	41.7	76.9
Amikacin	16.7	33.3	61.5
Cefepime	33.3	58.3	76.9
Ceftazidime	41.7	58.3	69.2
Ciprofloxacin	50.0	50.0	76.9
Imipenem	16.7	16.7	84.6
Aztreonam	25.0	50.0	84.6
Meropenem	25.0	50.0	76.9
Piperacillin/ Tazobactam	25.0	50.0	76.9
Colistin Sulphate	8.3	33.3	7.7
	S. pneumoniae	*S. aureus*	
	%	%	
Ampicillin	100	92	
Chlormphenicol	0	4	
Clindamycine	100	28	
Erythromycine	100	64	
Levofloxacin	0	48	
Linexolide	0	8	
Oxacillin	100	52	
Tigacycline	0	8	
Vancomycin	0	0	
Gentamycin	100	24	

Figure 1: Monthly distribution of the most prevalent bacterial causative agents of LRTI: This figure shows the monthly distribution of *S. aureus*, *P. aeruginosa*, and *Klebsiella* spp.

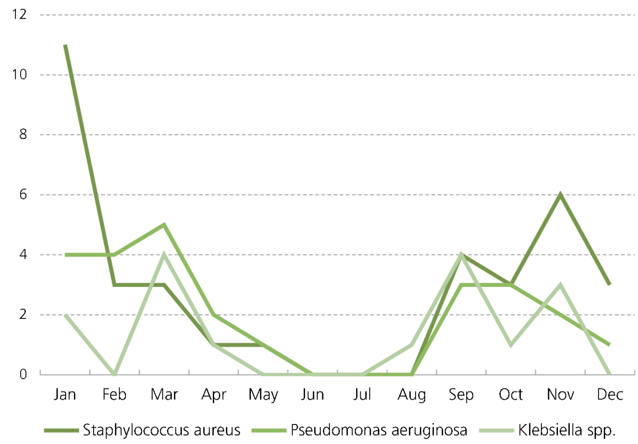
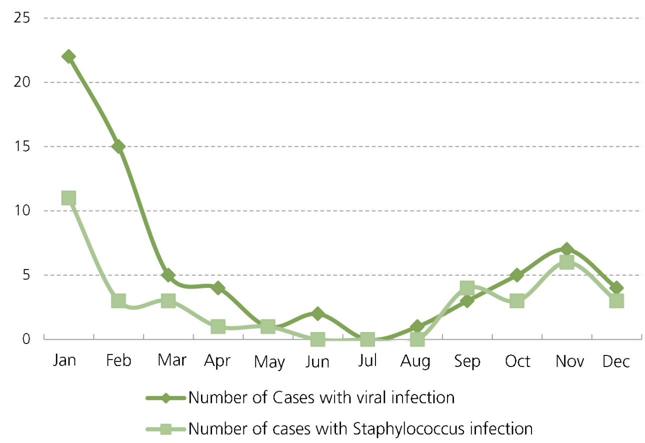


Figure 2: The monthly variation of Staphylococcus LRTI and its relationship with the monthly variation of viral LRTI. Both *S. aureus* and viral LRTI peaked in January and followed the same seasonal variation.



ICU case analysis

A majority of the patients (57; 69%) admitted to the ICU had pneumonia, while the rest (26; 31%)

had acute bronchitis. The average age of the patients admitted to ICU was higher (68 ± 16.7 years) than the rest of the study participants (56.5 ± 18.5 years) and the majority of them were males (61%). As expected, the average CURB-65 score for the ICU patients were significantly higher than those at inpatient wards (2.11 and 1.16, respectively (p< 0.0001). A causative agent of LRTIs was identified in 37.3% of patients admitted to the ICU, with 26.5% of patients testing positive for bacterial agents. The most frequently identified causative agents were *Klebsiella* spp., *P. aeruginosa*, and *S. aureus*. Each of these bacterial species was identified in 6 cases (7.23%), followed by other Gram-negative bacteria, which were identified in 5 cases (6%). *Acinetobacter* spp. was identified in 3 cases (3.61%), while *S. pneumoniae* and *Burkholderia* spp. were each isolated from only one ICU patient (1.2%).

When comparing the causative agents between pneumonia and acute bronchitis in ICU patients, 5 (8.8%) of the pneumonia patients were infected with *Klebsiella* spp., 5 (8.8%) were infected with *S. aureus*, 4 (7%) patients had *P. aeruginosa* and 3(5.3%) patients had other Gram-negative bacteria infections. On the other hand, only one of those diagnosed with acute bronchitis was infected with *Klebsiella* spp., additionally, one patient had *S. aureus*, 2 (7.7%) patients had *P. aeruginosa* and 2 (7.7%) patients had Gram-negative bacteria as the causative agent. Most of the patients in the ICU (95%) had at least one chronic comorbidity including cardiovascular diseases in 59 (71.1 %), 41 (49.4%) had DM, 31 (37.3%) **(Table 1)**. Pulmonary and renal diseases were presented in 16 (19.3%) of the patients. Complications were developed in 22/83 (26.5%) of the patients admitted to ICU, and of these, 14 patients (16.9%) died and which represented 78% of all deaths in our study.

Analysis of fatal cases

The total number of patient deaths associated with LRTI in our study was 18 (3.64%) patients out of 495 patients with LRTI over five years. Of the fatalities, 14 (77.8%) patients died from pneumonia and the other 4 (22.2%) from acute bronchitis. The median age at death was 70 years; 10 (55.56%) of them were males. Of the 18 patients who died, 17 (94.4%) had comorbidities; 10 (55.6%) had DM, and 9 (50%) had cardiac disease.

The mean CURB-65 score of death cases was 2.11 ± 0.83, which is significantly higher than the CURB-65 score of living cases, which was 1.29± 0.89 (p = 0.001).The identified bacterial causative agents of the death cases have shown that the two patients had a bacterial infection (11.1%).

Discussion

To our knowledge, this is the first large multi-year study in Jordan to determine bacterial agents associated with LRTI. Identification of the pathogens causing LRTI constitutes the basis for the selection of empirical antimicrobial treatment, which improves the outcome of LRTI patients [21]. The most commonly isolated bacterial agent for LRTI at our hospital was *S. aureus* (7.7%), followed by *P. aeruginosa* (5.1%) and *Klebsiella* spp (3.2%). In comparison, the most commonly identified bacterial causative agent for LRTI was *S. pneumoniae* in Asia and Europe [6,7]. Our findings show a different pattern of causative agents than an earlier study in Jordan, where *S. pneumoniae* was the most commonly isolated bacteria (26%), followed by *C. pneumoniae* (23%), *H. influenzae* (17%), *M. pneumoniae* (9%), *Legionella pneumophila* (6%) and *Klebsiella* spp. (6%). In addition, most of the Gram-negative isolates were from patients who had comorbid conditions [8]. The previous study in Jordan was conducted only among 35 cases in 2006. The differences in findings could be due to a change of prevalence of the causative agents of LRTI [8], the wide use of antibiotics in Jordan without prescription in recent years [22]. Since then, the pneumococcal vaccines has also be introduced in Jordan. The administration of pneumococcal vaccines was found to reduce antimicrobial resistance and the burden of pneumonia-associated hospitalizations on the healthcare system [23, 24].

The incidence of *S. pneumoniae* as a causative agent for LRTI was 0.8% in our study, which is approximately equal to the rates found in Srinagar/India, in 2010 (1%) [23]. The difference in

the causative agents of infection in different countries was proposed to be a result of the frequent use of antibiotics, changes in environmental pollution [25]. Upon comparison between the causative agents of pneumonia and acute bronchitis, *P. aeruginosa* was significantly associated with acute bronchitis cases in our study. This finding is contradictory to the results of previous studies that classified them as common causative agents of pneumonia [26].

Antimicrobial resistance is an issue of significant concern worldwide. About two-thirds of all antibiotics prescriptions are for respiratory tract infections, and the lack of knowledge regarding microbiological aetiology may increase the influence of patient demand in addition to other non-clinical factors, leading to an increase of inappropriate antibiotic prescription [27]. A recent study conducted in Jordanian patients with otitis external infection emphasizing on the pathogenic characteristics of *P. aeruginosa* isolates showed that each of ceftazidime, ciprofloxacin, imipenem and azetreonam had high to moderate susceptibility to *P. aeruginosa* in the range of (82-68%), respectively. Gentamicin and amikacin had high rates of resistance in the range of (72-57%) respectively. Only one isolate was resistant to colistin (3%) [28]. Our results demonstrated 50% resistance for ciprofloxacin, while 2 isolates of *P. aeruginosa* were colistin- resistant (8.3%). These results are alarming, especially with the presence of previous evidence of multi-drug resistant *P. aeruginosa* [29].

S. aureus and *S. pneumoniae* showed high rates of resistance to ampicillin (92%, 100% respectively). On the other hand, all isolates of *S. aureus* and *S. pneumoniae* were susceptible

for vancomycin. Recent studies showed high rates of methicillin-resistant *S. aureus* (MRSA) among Jordanian patients, necessitating careful evaluation of antimicrobial susceptibility results of isolates in vitro prior to prescribing antimicrobial agents [30].

Upon observing theseasonal variation, we found that bacterial LRTI peaked in January. In comparison, a study carried out in Iraq has shown that February was the peak month and August had the fewest admissions due to LRTI [31]. In our study, *S. aureus* infection, in particular, peaked in January, while *P. aeruginosa* peaked in March and *Klebsiella* spp. peaked in both March and September. In general, pneumonia incidence varies throughout the year, and it occurs more commonly in the seasons of winter and autumn [32, 33], with the highest number of deaths taking place during winter months [34]. This can be explained by the strong wind and relative humidity that aid in spreading airborne microorganisms. Additionally, in low temperatures, inhibition or competition between different types of microorganisms is weak, allowing more species to coexist in the atmosphere [35]. However, even though the impact of seasonality on the dynamics of bacterial agents causing LRTIs is gaining interest, LRTI should not be considered as a seasonal disease since it occurs throughout all seasons [36].

In a previous study conducted at Jordan University Hospital during the same timeframe, investigating the etiology of viral respiratory tract infections in Jordanian patients between 2011 and 2016, Fast-track Diagnostics (FTD)® Respiratory21 Kit (Fast-track Diagnostics, Junglinster, Luxembourg) real-time PCR was used for 170 patients, and they were positive for seasonal Influenza A virus in 7.1% of patients, influenza B in 4.1%, Parainfluenza virus in 7.6%, RSV in 4.7%, adenovirus in 4.1%, metapneumovirus in 4.1%, coronavirus 229E/NL63 in 4.1%, and rhinovirus in 3.5%. Rapid test PCR (RT-PCR; Cepheid GeneXpert®, Sunnyvale,California, USA) was done for 495 patients, and the percent of cases who were positive for H1N1pdm009 virus was 4.2% [37].

Furthermore, we found that viral infections and *S. aureus* infections follow the same trend of seasonal variation. Pneumonia caused by *S. pneumoniae* and *S. aureus* are a known life-threatening complication of seasonal influenza [38-42], suggesting that *S. pneumoniae* and *S. aureus* infections may represent complicated influenza LRTI that requires special attention in order to decrease the risk of further morbidity and mortality.

One of the primary aims of the healthcare system is to reduce the morbidity and mortality of the patients. In our study, 16.8% of patients were admitted to the ICU, and overall 9.9% of the 495 developed complications related to their LRTI. The mortality rate of LRTI in our study was 3.64%, which is very similar to the mortality rate found in Japan (3.1%) in a study published in 2013 [43], while it reached approximately 10% in a study published 2006 in Germany [44], and which is around the average in-hospital mortality of CAP [45]. The low mortality rate in Jordan may be due to the death of critical patients before presentation to hospitals, or death soon after the presentation of symptoms, before specimens can be collected [46]. The higher rate reported in Germany can be attributed to the high incidence of *S. pneumoniae* [47], as well as due to the presence of pneumococci, *Legionella* or *Enterobacteriaceae* infections, which were associated with increased risk of mortality [44]. DM was the most common comorbidity in the patients who died in our study since it was present in 10/18 patients (55%) who died. This supports the rationale that the management approach of LRTIshould be based on the associations between age, comorbidity, etiology, and severity [48].

Since the mean age of our patients was (57.79 ± 18.43 years), and most of them had comorbid conditions (83%), we suggest that prophylactic measures should be taken to prevent the development of LRTI in those patients. Several vaccines, including influenza and pneumococcal vaccines, are recommended for the elderly. Pneumococcal vaccinesare highly recommended for chronic obstructive pulmonary disease patients in order to prevent pneumonia [49, 50]. In addition, the admitted patients must be continuously monitored, and CURB65 score must be calculated regularly, to predict any deterioration in the clinical course of LRTI, since the CURB-65 score has been validated for predicting morbidity and mortality in community-acquired pneumonia [19].

Limitations

Our study showed a positive bacterial test result only in 21.1% of patients. The pathogen-detection rate is towards the lower end of etiologic studies of pneumonia in adults. Isolation of etiological agents ranged between 20% and 76% in other studies conducted around the world [21, 43, 51-57]. Potential explanations for low detection yields in our study include low sensitivity of blood cultures [21], inability to obtain lower respiratory tract specimens, non-infectious causes (aspiration pneumonia), late presentation, partial treatment and antibiotic use before sample collection [51, 58].

Another limitation of our study was the lack of 1-year follow-up to determine the one-year mortality rates of pneumonia. Most of our patients had multiple chronic illnesses, for which the one-year mortality rate after developing LRTI may approach 40% [45, 59]. Further studies with one-year follow-up period are encouraged, to study the long-term morbidity and mortality of LRTI in Jordanian population.

In conclusion, this current study demonstrated that the most prevalent organism identified to be associated with LRTI was *S. aureus* in Jordanian hospitalized patients. We have found that the mortality rate of hospitalized patients with LRTI in JUH was 3.64%, which can be decreased by early identification and proper treatment of high-risk patients. The causative agents for lower respiratory tract infections vary throughout the year. It was found to be more common in the winter season, especially in

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January. The findings need to be replicated in similar settings in Jordan and possibly other countries in the region.

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Authors Contributions

NO: planned, conceptualized, supervised the study, participated in manuscript writing, and approved the final manuscript.

IB: planned and conceptualized the study, collected the data, conducted literature review, participated in manuscript writing and approved the final manuscript.

FP, ZI: participated in manuscript writing, revised the manuscript, and approved the final manuscript.

ZO, MA, MO: Collected the data, conducted literature review, and participated in manuscript writing, and approved the final manuscript.

RF, AW: participated in manuscript writing and approved the final manuscript.

NA: performed statistical analysis. He participated in manuscript writing, and approved the final manuscript.

Conflict of Interest

The authors have no conflict of interest to declare.

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