Bader et al. Int J Respir Pulm Med 2015, 2:3
ISSN: 2378-3516

International Journal of
Respiratory and Pulmonary Medicine

Research Article: Open Access

Outcomes of Moderate-Severe Community-Acquired Pneumonia in Patients with Diabetes Mellitus: Impact of Systemic Steroids and Time to First Dose of Appropriate Antibiotic Therapy

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Abstract

Purpose: In patients with diabetes mellitus (DM), community-acquired pneumonia (CAP) is associated with significant morbidity and mortality. The primary objective of the study was to describe the clinical outcomes and risk factors for moderate-severe CAP in hospitalized patients with DM.

Methods: We conducted a retrospective cohort study of 156 hospitalized patients with DM and moderate-severe CAP at two tertiary medical centers. Multivariate logistic and Cox regression analysis were applied to assess factors associated with complications, length of hospital stay (LOS) and mortality.

Results: Thirty one (19.9%) patients died and 81(51.9%) experienced complications during the study period. Common complications included respiratory failure (25.6%) followed by intensive care admission (16%). In the multivariate analysis, time from triage to first dose of appropriate antibiotic therapy > 4 hours (OR 6.5, 95% CI 2.2 - 18.8, p = 0.001) and development of complications (OR 5.7, 95% CI 2.1 – 15.4, p = 0.001) were associated with increased CAP related in-hospital mortality. The mean LOS was 11 days and patients developing CAP related complications 24 hours post admission had prolonged LOS (p = 0.001). Independent risk factors for prolonged LOS included presence of complications (HR 0.19, 95% CI: 0.09 – 0.41, P = 0.003), duration of antibiotics (HR 0.9, 95% CI 0.85 – 0.95, p = 0.0002), and administration of systemic steroids (HR 0.51, 95% CI 0.31 – 0.84, p = 0.01).

Conclusions: Delayed administration of antibiotics, administration of systemic steroids and CAP related complications were associated with negative outcomes in diabetic patients with moderate-severe CAP.

Keywords

Community-acquired pneumonia, Diabetes mellitus, Mortality, Complications, Length of hospital stay

Introduction

Community-acquired pneumonia (CAP) is the leading cause of infection related hospitalization and a major cause of morbidity and mortality in developing countries [1].

CAP associated mortality in hospitalized patient's ranges from 8 to14% and up to 37% in patients admitted to the intensive care unit (ICU) [2-4]. Several factors including age, septic shock, confusion and multilobar pneumonia have been associated with increased mortality [5-7]. Validated scores, such as CURB-65 and Pneumonia Severity Index (PSI), are commonly used to predict mortality [8,9].

In addition, patients with diabetes mellitus (DM) are at an increased risk of developing infections and complications with CAP being the most common [10]. Studies have shown that pre-existing diabetes was associated with a higher risk of death following CAP. Factors associated with increased mortality in these patients included multilobar infiltrates, comorbidities, age, bacteremia, septic shock, infection with Gram-negative organisms and hyperglycemia [11-13]. However, previous studies did not assess the impact of time from triage to administration of first dose of appropriate antibiotics in CAP complication rates LOS or mortality. Finally, clinical characteristics and outcomes of hospitalized diabetics with moderate-severe CAP are unknown. In previous work, we found that a delay in administration of first dose antibiotics in this patient population was associated with increased in-hospital mortality. ; However, we did not include all degrees of severity nor evaluate other outcomes [14].

The primary objective of this study was to describe the clinical characteristics and risk factors for moderate-severe CAP in hospitalized patients with DM including outcomes such as development of complications, LOS and in-hospital mortality.

Materials and Methods

The current study was conducted at two tertiary teaching hospitals.

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Citation: Bader MS, Abouchehade K, Brooks AA, Yi Y (2015) Outcomes of Moderate-Severe Community-Acquired Pneumonia in Patients with Diabetes Mellitus: Impact of Systemic Steroids and Time to First Dose of Appropriate Antibiotic Therapy. Int J Respir Pulm Med 2:027

Received: March 26, 2015: **Accepted:** September 07, 2015: **Published:** September 10, 2015

The Human Investigation Committee and the Institutional Review Board of Memorial University of Newfoundland and Eastern Health granted full ethics approval for the study. Given the retrospective nature, informed consent from study patients was waived.

For this current study, we drew from original data published in our previous study [14]. The medical records, including electronic copies, of all diabetic patients admitted for CAP from January 2002 to December 2007 were examined. Patients were identified through the medical record department by discharge diagnosis codes for both CAP and DM.

For the study period, we included adult patients aged 18 years or older with a diagnosis of any type of DM hospitalized for confirmed CAP, PSI classes IV and V. We excluded patients with hospital-acquired pneumonia (HAP), cystic fibrosis, immunocompromised condition, less than18 years of age and those who received antibiotic therapy as an outpatient prior to presentation to the emergency department (ED), or required insulin during hospital stay without a prior history of DM.

CAP was defined as the presence of a new infiltrate on chest x-ray and 2 or more of the following: fever, new or increasing cough or sputum production, dyspnea, chest pain, and new focal signs on chest examination. The diagnosis of DM was based on past medical history documented on the current or previous admissions. Antibiotic therapy was considered appropriate if consistent with the Infectious Diseases of America (IDSA) and American Thoracic Society (ATS) guidelines [15]. Complications of CAP were defined as the development of one of the following during the current hospitalization: respiratory failure, septic shock, empyema, death, and requirement for ICU admission, cardiac ischemia, arrhythmias, and other conditions (e.g. clostridium difficile associated infection, acute kidney injury, acute pulmonary edema, diabetes ketoacidosis, hyperosmolar hyperglycemic state, and hypoglycemia). Respiratory failure was defined as a requirement of intubation or ≥ 50% oxygen requirement and septic shock was defined as a systemic inflammatory response syndrome with hypotension not responsive to adequate fluid resuscitation in the context of proven CAP and absence of other causes. Empyema was defined utilizing chest computed tomography and thoracentesis results. Cardiac ischemia was defined as the presence of typical chest pain or equivalent requiring treatment and either new positive serum troponin or ECG changes. Arrhythmias were defined as the presence of new onset or exacerbation of a preexisting abnormal rhythm on ECG (e.g. symptomatic bradycardia, atrial fibrillation, atrial flutter, multifocal atrial tachycardia, supraventricular tachycardia, torsades de pointes, ventricular fibrillation or tachycardia, and cardiac arrest). In-hospital mortality was defined as death by any cause from onset of current admission.

Based on the distribution of the data, categorical variables were analyzed using chi-square test or Fisher's exact test, whereas continuous variables were analyzed by Wilcoxon rank-sum test. We divided the study patients into two groups: patients who received their first dose of antibiotic therapy ≤ 4 or > 4 hours post triage. We constructed two multivariate logistic regression analyses to determine risk factors associated with in-hospital mortality and development of complications 24 hours post admission. In addition, we also constructed a multivariate cox regression analysis to determine risk factors associated with prolonged LOS using LOS in days and time to event variable as the dependent variables. We selected the independent variables in the three models based on the clinical and statistical significance from the unvariate analysis. We considered possible interaction, assessed the goodness-of-fit of logistic regression and examined the proportional assumption of Cox regression. Statistical analysis was performed using SAS, version 9.2 (SAS Institute, Inc., Carey, NC, USA), and p values ≤ 0.05 were considered significant.

Results

A total of 209 patients with CAP and DM were identified from the original study. We included 156 patients with pneumonia PSI classes IV (97 patients) and V (59 patients) in the analysis. The demographic and clinical characteristics of the study cohorts are shown in Table 1. The majority of the patients had underlying chronic medical conditions with chronic heart diseases being the most common (84.6%) followed by chronic lung diseases (39.7%).

During the follow up period from admission until discharge, 31 patients died with an in hospital mortality of 19.9%. Twenty three (74.2%) patients who died received their first dose of appropriate antibiotic > 4 hours from triage while 50 (40%) of those who survived received their first dose > 4 hours from triage at ED (p = 0.001). Those who died had relatively longer duration of CAP symptoms prior to presentation to the ED compared to surviving patients (p = 0.04).

Clinical characteristics of diabetic patients with mild (PSI classes II and III) and moderate-severe CAP comparison are summarized in Table 2.

A greater number of patients with moderate-severe CAP had comorbid conditions, hospitalization in the previous 3 months and resided in long-term care facility (LTCF) compared to patients with mild CAP. Causes for increased more delay in time to first dose of appropriate antibiotic therapy observed in patients with moderate-severe CAP compared to patients with mild CAP was unclear (p = 0.02).

Clinical characteristics of diabetic patients with moderate-severe CAP, stratified by the time to first dose of antibiotic therapy are shown in Table 3. Twenty three (31.3%) patients who received their first dose of appropriate antibiotic therapy > 4 hours from triage died versus 8 (9.6%) patients who received antibiotics ≤ 4 hours (p = 0.001).

In the multivariate analysis, the following factors were associated with increased in-hospital mortality of diabetic patients with moderate-severe CAP: time to first dose of appropriate antibiotic therapy > 4 hours from triage (OR 5.4, 95% CI 1.9 - 15.7, p = 0.002) and development of complications (OR 5.7, 95% CI 2.1 – 15.4, p = 0.001). Duration of symptoms prior to presentation to the ED was not associated with increased mortality (p = 0.1).

CAP related complications were observed in 81 (51.9%) patients and the majority, 59 (78.2%) developed 24 hours post admission (Table 1). The most common complications were respiratory failure (25.6%) followed by admission to ICU (16%) (Table 2).

In the multivariate analysis, we found prolonged LOS to be independently associated with complications of CAP that developed after 24 hours of admission (p = 0.001). Time to first dose of appropriate antibiotic therapy was not a significant predictor in the model (p = 0.2).

There were 15 patients who developed cardiac complications and 6 (40%) of them died. Including cardiac complications were significant predictors of in-hospital mortality in diabetic patients with moderate-severe CAP when included into the model (OR 5.6, 95% CI 1.3 – 24.3, p = 0.02). In addition, time to first dose of appropriate antibiotic therapy > 4 hours from triage also proved to be a significant predictor of in-hospital mortality in this patient population (OR 6.5, 95% CI 2.2 - 18.8, p = 0.001).

The mean LOS of the study cohorts was 10.5 days. We assessed predictors of LOS in multivariate Cox regression model where low hazard ratios (HRs) of discharge correspond to an association of the factors with prolonged LOS. In the model, presence of complications (p = 0.003), duration of antibiotics (HR 0.9, 95% CI 0.85 – 0.95, p = 0.0002), and use of systemic steroids (HR 0.51, 95% CI 0.31 – 0.84, p = 0.01) were independently associated with prolonged LOS (Table 4). Delayed antibiotic administration was not associated with prolonged LOS (P = 0.7)

The impact of complications on LOS may be confounded by time to first dose of appropriate antibiotic (p = 0.05). Following consideration of the interaction and adjusting for the effects of other variables in the model, complications were found to be associated with prolonged LOS (p = 0.003). The HR of discharge for complications

Table 1: Characteristics of patients with moderate-severe community-acquired pneumonia

Characteristic	All Patients (n = 156)	Deceased Patients (n = 31)	Survived Patients (n = 125)	*p*-value	Patients with Complications (n = 81)	Patients without complications (n = 75)	*p*-value
Age (years)	74.36 ± 10.78	77.07 ± 7.78	73.69 ± 11.32	0.06	72.33 ± 11.71	76.55 ± 9.26	0.01
Gender				0.55			0.26
Male	83 (53.21%)	18 (58.06%)	65 (52%)		47 (58.02%)	36 (48%)	
Female	73 (46.79%)	13 (41.94%)	60 (48%)		34 (41.98%)	39 (52%)	
Co-morbid Conditions							
Chronic heart disease	132 (84.62%)	26 (83.87%)	106 (84.80%)	1.000	67 (82.72%)	65 (86.67%)	0.52
Chronic lung disease	62 (39.74%)	14 (45.16%)	48 (38.40%)	0.54	35 (43.21%)	27 (36%)	0.41
Cancer	42 (26.92%)	11 (35.48%)	31 (24.80%)	0.26	16 (19.75%)	26 (34.67%)	0.05
Neurologic disease	46 (29.49%)	14 (45.16%)	32 (25.60%)	0.05	27 (33.33%)	19 (25.33%)	0.30
Chronic renal disease	44 (28.21%)	11 (35.48%)	33 (26.40%)	0.37	29 (35.8%)	15 (20%)	0.03
Patients from LTCF	31 (19.87%)	8 (25.80%)	23 (18.40%)	0.45	19 (23.46%)	12 (16%)	0.32
Systemic steroids use	41 (26.28%)	7 (22.58%)	34 (27.20%)	0.66	21 (25.93%)	20 (26.67%)	1.000
Duration of symptoms before presentation (days)	4.95 ± 5.44	7.68 ± 7.97	4.24 ± 4.34	0.04	5.14 ± 4.75	4.74 ± 6.14	0.67
Hospitalization in last 90 days	35 (22.58%)	8 (25.81%)	27 (21.77%)	0.64	17 (20.99%)	18 (24.32%)	0.70
Weekend admission	49 (31.41%)	11 (35.48%)	38 (30.40%)	0.67	25 (30.86%)	24 (32%)	1.000
Time to first appropriate antibiotic since time of triage (hours)	6.62 ± 9.01	9.35 ± 5.76	5.95 ± 9.54	0.01	7.39 ± 11.46	5.79 ± 5.16	0.26
First appropriate antibiotic >4hours since time of triage	73 (46.79%)	23 (74.19%)	50 (40%)	0.001	37 (45.68%)	36 (48%)	0.87
Time to first appropriate antibiotic since time of physician assessment (hours)	4.80 ± 5.08	8.13 ± 5.86	3.84 ± 4.42	0.001	4.77 ± 5.32	4.84 ± 4.87	0.93
Time seen by physician since time of triage (hours)	0.95 ± 1.20	1.04 ± 0.90	0.93 ± 1.28	0.60	1.08 ± 1.33	0.82 ± 1.04	0.24
Duration of antibiotics (days)	11.05 ± 4.61	11.07 ± 5.93	11.04 ± 4.25	0.98	11.49 ± 5.09	10.54 ± 3.99	0.20
Length of hospital stay (days)	10.48 ± 1.53	11.29 ± 15.17	9.54 ± 8.85	0.10	13.53 ± 12.37	7.19 ± 6.75	0.0001
Patients on macrolide	80 (51.28%)	13 (41.94%)	67 (53.60%)	0.32	41 (50.62%)	39 (52%)	0.87
Patients on fluoroquinlones	43 (27.56%)	8 (25.81%)	35 (28%)	1.000	23 (28.40%)	20 (26.67%)	0.59
Positive culture (respiratory or blood)	13 (8.33%)	2 (6.45%)	11 (8.80%)	0.16	6 (7.41%)	7 (9.33%)	0.11
Complications	81 (51.92%)	27 (87.10%)	54 (43.20%)	<0.0001			
Complications within 24 hours of admission	54 (34.62%)	21 (67.74%)	33 (26.40%)	<0.0001			
Complications after 24 hours of admission	59 (37.82%)	23 (74.19%)	36 (28.80%)	<0.0001			
Cardiac complications	13 (8.33%)	6 (19.35%)	7 (5.60%)	0.02			
Death					27 (33.33%)	4 (5.33%)	<0.0001

LTCF: long term care facility

Data expressed as mean ± SD or frequency and percentage as indicated.

Table 2: Comparison of clinical characteristics of patients with mild and moderate-severe community-acquired pneumonia (CAP)

Characteristic	All patients With CAP (n = 209)	Patients with mild CAP (n = 53)	Patients with moderate-severe CAP (n = 156)	*p*-value
Age (years)	71.36 ± 12.93	62.08 ± 14.81	74.36 ± 10.78	<0.0001
Gender				0.34
Male	107 (51.20%)	24 (45.28%)	83 (53.21%)	
Female	102 (78.80%)	29 (54.72%)	73 (46.79%)	
Co-morbid Conditions				
Chronic heart disease	164 (78.47%)	32 (60.38%)	132 (84.62%)	<0.0001
Chronic lung disease	80 (38.28%)	18 (33.95%)	62 (39.74%)	0.52
Cancer	47 (22.49%)	5 (9.43%)	42 (26.92%)	0.01
Neurologic disease	50 (23.92%)	4 (7.55%)	46 (29.49%)	0.001
Chronic renal disease	48 (22.97%)	4 (7.55%)	44 (28.21%)	0.001
Patients from LTCF	33 (15.79%)	2 (3.77%)	31 (19.87%)	0.004
Systemic steroids use	57 (27.27%)	16 (30.19%)	41 (26.28%)	0.60
Duration of symptoms before presentation (days)	4.94 ± 5.26	5.10 ± 5.04	4.95 ± 5.44	0.86
Hospitalization in last 90 days	39 (18.75%)	4 (7.55%)	35 (22.58%)	0.02
Weekend admission	67 (32.06%)	18 (33.96%)	49 (31.41%)	0.74
Time to first appropriate antibiotic since time of triage (hours)	6.16 ± 7.94	4.60 ± 3.43	6.62 ± 9.01	0.02
First appropriate antibiotic >4hours since time of triage	96 (45.93%)	23 (43.04%)	73 (46.79%)	0.75
Time to first appropriate antibiotic since time of physician assessment (hours)	4.50 ± 4.73	3.21 ± 3.13	4.80 ± 5.08	0.02
Time seen by physician since time of triage (hours)	1.0 ± 1.20	1.19 ± 1.24	0.95 ± 1.20	0.25
Duration of antibiotics(days)	10.79 ± 4.20	9.91 ± 2.63	11.05 ± 4.61	0.03
Length of hospital stay (days)	9.47 ± 9.70	6.42 ± 5.79	10.48 ± 10.53	0.001
Patients on macrolide	115 (55.02%)	35 (66.04%)	80 (51.28%)	0.08
Patients on fluoroquinlones	56 (26.79%)	13 (24.53%)	43 (27.56%)	0.72
Positive culture (respiratory or blood)	22 (10.53%)	9 (16.98%)	13 (8.33%)	0.13
Complications	91 (43.54%)	10 (18.87%)	81 (51.92%)	<0.0001
Complications within 24 hours of admission	60 (28.71%)	6 (11.32%)	54 (34.62%)	0.001
Complications after24 hours of admission	65 (31.10%)	6 (11.32%)	59 (37.82%)	0.0002
Cardiac complications	17 (8.13%)	4 (7.55%)	13 (8.33%)	1.00
Respiratory failure	41 (19.61%)	1 (1.89%)	40 (25.64%)	<0.0001
Septic Shock	4 (1.91%)	0	4 (2.56%)	0.57
Empyema	1 (0.48%)	0	1 (0.46%)	1.000
Cardiac ischemia	7 (3.35%)	1 (1.89%)	6 (3.85%)	0.68
Arrhythmias	12 (5.74%)	3 (5.66%)	9 (5.77%)	1.000
Intensive care admission	25 (11.96%)	0	25 (16.03%)	0.001
Others complications	28 (13.40%)	4 (14.29%)	24 (15.48%)	0.17
Death	32 (15.31%)	1 (1.89%)	31 (19.87%)	0.001

LTCF: long term care facility

Data expressed as mean ± SD or frequency and percentage as indicated.

was estimated to be 0.19 (95% CI: 0.09 – 0.41) and 0.47 (95% CI: 0.29 – 0.77), for patients with time to first dose of appropriate antibiotic > 4 hours and ≤ 4 hours of triage (Table 4), respectively.

Discussion

To our knowledge, this is the first study to review the outcomes and associated risk factors for moderate-severe CAP in patients with DM.

Firstly, we found time to first dose of appropriate antibiotic therapy > 4 hours from triage was associated with increased in-hospital mortality of diabetic patients with moderate-severe CAP. These patients were 5.4 times more likely to die compared to patients who received their first dose within 4 hours of triage in ED. In our original study we found diabetic patients with CAP receiving their first dose of appropriate antibiotic therapy > 8 hours from triage were 4 times more likely to die compared to those who received the first dose within 8 hours of triage in ED. Our original study included diabetic patients with varying severity of CAP where 72.3% (149/206) had moderate-severe CAP [14]. In our current study, we identified a narrower 4-hour window for time to first dose to be an important prognostic factor for moderate-severe CAP. Ideal time to first dose of appropriate antibiotic for patients with CAP continues to be debated in the literature. The major concern for initiating antibiotic as early as possible is the risk of inappropriate antibiotic use, antibiotic resistance, and antibiotic-related side effects in patients with unconfirmed diagnosis [16-18]. However, the European guidelines recommend initiating antibiotic therapy within the first four hours for hospitalized CAP patients and within one hour of hospitalization for patients with severe CAP and septic shock [19,20]. The latest IDSA/ATS consensus guidelines recommend administering first dose of antibiotic therapy in the ED after the diagnosis of CAP [15]. A recent matched case-control study showed that administration of appropriate antibiotic therapy within 3 hours was associated with decreased mortality of severe pneumococcal pneumonia [21].

Almost half of patients in this study received their first dose of antibiotic > 4 hours from triage. There was greater delay in administration of first dose of antibiotic therapy in patients with moderate-severe than in patients with mild CAP (P = 0.02) (Table 2); however, cause for delay is physicians' initial assessment of patients in the moderate-severe is group is unclear (p = 0.003) (Table 3). Since we did not assess the clinical manifestations of CAP in our cohort patients or the timing of chest x-rays in the ED, these may have contributed to the delay of physicians' assessment and antibiotic therapy. Efforts for a more rapid and reliable diagnosis of CAP could facilitate assessment and timely administration of appropriate antibiotics [15,19,20].

Secondly, the study showed a high rate of complication (52%) where half occurred day 1 post admission (Table 1). The study showed that complications were associated with increased in-hospital mortality, and prolonged LOS. Cardiac complications,

Table 3: Comparison between patients with early versus delayed therapy for moderate-severe community-acquired pneumonia (CAP)

Characteristic	Patients with time to first dose of appropriate antibiotic therapy ≤ 4 hours since triage (n = 83)	Patients with time to first dose of appropriate antibiotic therapy > 4 hours since triage (n = 73)	*p*-value
Age (years)	73.30 ± 11.60	75.56 ± 9.70	0.19
Gender			0.26
Male	48 (57.83%)	35 (47.95%)	
Female	35 (42.17%)	38 (52.05%)	
Co-morbid Conditions			
Chronic heart disease	69 (83.13%)	63 (86.30%)	0.66
Chronic lung disease	31 (37.35%)	31 (42.47%)	0.62
Cancer	16 (19.28%)	26 (35.62%)	0.03
Neurologic disease	22 (26.51%)	24 (32.88%)	0.48
Chronic renal disease	24 (28.92%)	20(27.40%)	0.86
Patients from LTCF	15 (18.07%)	16 (21.92%)	0.56
Systemic steroids use	18 (21.69%)	23 (31.15%)	0.20
Duration of symptoms before presentation (days)	4.27 ± 3.85	5.90 ± 7.02	0.12
Hospitalization in last 90 days	15 (18.29%)	20 (27.40%)	0.19
Weekend admission	28 (33.73%)	21 (28.77%)	0.61
Time seen by physician since time of triage (hours)	0.64 ± 0.55	1.37 ± 1.64	0.003
Duration of antibiotics(days)	10.93 ± 4.32	11.18 ± 4.95	0.74
Length of hospital stay (days)	9.92 ± 9.71	11.12 ± 11.42	0.48
Patients on macrolide	45 (54.22%)	35 (47.95%)	0.52
Patients on fluoroquinlones	24 (28.92%)	19 (26.03%)	0.72
Positive culture (respiratory or blood)	9 (10.84%)	4 (5.48%)	0.14
Complications	44 (53.01%)	37 (50.65%)	0.87
Complications within 24 hours of admission	28 (33.73%)	26 (35.62%)	0.87
Complications after 24 of admission(hours)	26 (31.33%)	33 (45.21%)	0.10
Cardiac complications	7 (8.43%)	6 (8.22%)	1.000
Death	8 (9.64%)	23 (31.31%)	0.001

Data expressed as mean ± SD or frequency and percentage as indicated.

Table 4: Predictors of length of hospital stay in patients with moderate-severe Community-acquired pneumonia (CAP)

Parameter	HR	95% CI	*p*-value
Duration of antibiotic therapy	0.9	0.85 – 0.95	0.0002
Duration of symptoms prior presentation	0.97	0.93 – 1.01	0.13
Systemic steroids use	0.51	0.31 – 0.84	0.01
Time to first dose of appropriate antibiotic since time of triage*complications			0.05
Complications			0.003
Time to first dose of appropriate antibiotic since time of triage > 4 hours	0.19	0.09 – 0.41	
Time to first dose of appropriate antibiotic since time of triage ≤ 4 hours	0.47	0.29 – 0.77	

particularly arrhythmias, were the third most common complications and were associated with high mortality (40%) (Table 2). Cardiac complications have been commonly reported in recent studies and they are associated with increased short term and long term CAP related mortality [22,23]. The high rate of arrhythmias in our study may be related to DM, high prevalence of heart and pulmonary diseases, or systemic inflammatory response and hypoxemia, leading to myocardial cell dysfunction [24].

Thirdly, our study showed that systemic steroids did not have an impact on mortality or complications but were associated with prolonged LOS. The use of systemic steroids as adjuvant therapy for CAP continues to be controversial. The current guidelines do not recommend the use of systemic steroids without considering comorbidities and severity of infection [15,19,20]. A recent randomized controlled trial showed that systemic corticosteroids were associated with decreased treatment failure due to complications but no improvement in mortality in hospitalized patients with a significant inflammatory response and severe CAP. The decrease in treatment failure is mainly due to less radiographic progression demonstrated in patients who received systemic steroid therapy [25]. Contrary to our findings, recent studies and a meta-analysis showed that systemic steroid therapy was associated with shorter time to clinical stability and shorter LOS in hospitalized patients with CAP [26,27]. However, another study showed systemic steroid therapy was associated with prolonged LOS in patients with CAP, which is consistent with our findings in a similar population (patients with comorbid conditions and high PSI) [28]. Systemic steroid therapy was associated with hyperglycemia in CAP clinical trials. [25,29] In our study, prolonged LOS may be due to uncontrolled hyperglycemia; however, we did not study the impact of systemic steroid use on blood glucose control. Although we did not identify the indications of systemic steroids use in our study, approximately 40% of patients had chronic lung diseases (Table 1). Moreover, none of the patients received chronic outpatient systemic steroid therapy on presentation to the ED. The impact of systemic steroid therapy on outcomes of CAP in diabetic patients requires further investigation with randomized clinical trials considering glycemic control.

Lastly, the mean LOS was 11 days, which is longer than reported in previous studies [7,15,19,20]. This might be due to the fact that our cohort included elderly patients with an average age of 74 years, moderate-severe CAP and high rate of comorbid conditions.

Our study identified several factors (duration of antibiotic therapy, complications, systemic steroid use) that were independently associated with prolonged LOS in diabetic patients with moderate-severe CAP. It is unclear if the duration of antibiotic therapy is a cause or result of prolonged LOS. We assessed the impact of acute illness and comorbid conditions but we did not account for the impact of psychosocial factors on LOS. Current guidelines recommend discharging patients as soon as they are clinically stable, have no other active medical problems, and have a safe environment for continued care [15,19,20]. With the aging population, social, functional and nursing-related factors will play a significant role in affecting LOS [30].

The strengths of our study include verifying the diagnosis of CAP in all included patients through thorough review of medical records and chest x-ray findings.

In addition, we used the PSI score, which has been validated as a severity measure of CAP [8,9]. We excluded patients who received antibiotic therapy prior to their presentation to the ED. Finally, we defined appropriate antibiotic therapy for CAP based on the latest recommendations from IDSA/ATS guidelines [15].

One of the limitations is the observational nature of our study where the significant predictor of certain outcome might represent a surrogate marker for other aspects of clinical care rather than being directly responsible for that outcome (e.g. duration of antibiotic and LOS). Furthermore, many determinants may be unknown or measured with error, resulting in residual confounders where the impact and direction of influence cannot be predicted. We did not assess the impact of several factors on the outcomes of moderate-severe CAP such pneumococcal and influenza vaccination status, time to clinical stability, and degree of hyperglycemia. Furthermore, we did not assess long-term outcomes of CAP such as 30 day or 1 year mortality and quality of life status. Finally, we did not have clear explanation for delayed antibiotic therapy in our patients.

In conclusion, moderate- severe CAP in patients with DM is associated with high risk of in-hospital mortality, complications and prolonged LOS. Since delayed antibiotic therapy might be associated with increased in-hospital mortality of moderate-severe CAP, rapid assessment and diagnosis followed by administration of empirical antibiotic therapy is recommended. Systemic steroid therapy should be avoided in this patient population unless it is required for indications other than CAP (e.g. asthma exacerbation).

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

We certify that the manuscript has not been published and is not being considered for publication elsewhere.

The study was approved by the human subjects committee and the institutional review board of the respective institutions. The institution review board has waived informed consent.

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