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ORIGINAL RESEARCH

Clinical Outcomes of Community-Acquired Pneumonia in Patients with Diabetes Mellitus

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Abstract

Background: Studies have found admission hyperglycemia as a predictor of poor outcomes in Community acquired Pneumonia (CAP), whereas others have not. The objective of this study was to evaluate the impact of diabetes mellitus (DM) on mortality as well as Length of stay (LOS) and Time to clinical stability (TCS) of hospitalized patients with CAP.

Materials and Methods: Adult patients hospitalized with CAP enrolled at Community-Acquired Pneumonia Organization (CAPO) database with DM were categorized as admission blood glucose $\geq$ 250 mg/dL (diabetes mellitus blood sugar (BG) > 250) and admission blood glucose $\leq$ 250 mg/dL (DM BG $\leq$ 250). CAP outcomes included: all-cause in-hospital mortality, all-cause 28-day mortality, length of stay (LOS) and time to clinical stability (TCS).

Results: From a total of 7,303 patients with CAP, 294 (17.7%) had DM; out of whom 960 (13.1%) patients had BG $\leq$ 250 mg/dL, and 334 (4.6%) patients had BG > 250 mg/dL. The in-hospital mortality was 9.3% for controls, 9.9% for the DM BG $\leq$ 250 mg/dL group and 13.4% for DM BG > 250 mg/dL group (p=0.04). Patients with DM BG > 250 mg/dL compared to the control group had a higher risk of in-hospital mortality (Hazard ratio (RR) = 1.32, 95% CI: 1.02-1.72, p = 0.034) and 28-day mortality (RR = 1.31, 95% CI: 1.01-1.71, p = 0.048). Patients in the DM BG $\leq$ 250 mg/dL group compared to the control group did not have a greater risk for in-hospital mortality (RR = 1.23, 95% CI: 0.16-8.09, p = 0.237), 28-day mortality (RR = 1.09, 95% CI: 0.90-1.32, p = 0.398), LOS (HR = 0.93, 95% CI: 0.85-1.02, p = 0.130), or TCS (HR = 0.95, 95% CI: 0.87-1.05, p = 0.320).

Conclusions: DM patients with BG > 250 mg/dL were associated with increased in-hospital mortality and 28-day mortality. Further studies are needed to link the role of hyperglycemia to CAP outcome.

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1 Background

Diabetes mellitus (DM) is among the most common chronic diseases worldwide, accounting for an enormous strain on healthcare resources, increased morbidity and mortality, and decreased quality of life[1]. High rates of infectious complications and poor response to infections such as community acquired pneumonia (CAP) are often reported among patients with DM[2,3]. Establishing clear relationships between DM and mortality in CAP are also confounded by comorbidities in this population including cerebrovascular events, cardiovascular disease, and kidney disease, all of which negatively impact clinical outcomes in CAP[4].

Studies have reported inconsistent results regarding the impact of DM on clinical outcomes of patients with CAP. Several investigations have shown increased CAP mortality among patients with DM compared to patients without DM[5–7], whereas others found no association[1]. Similarly, some studies have found admission hyperglycemia as a predictor of poor outcomes in CAP[8,9], whereas others have not[10]. There are also other important outcomes measures in CAP patients like length of hospital stay (LOS) and Time to Clinical Stability (TCS) that have been shown to predict inpatient as well as post-discharge adverse outcomes in CAP[11]. Very few studies examined these outcomes in patients with DM and CAP[11].

The objective of this study was to evaluate the impact of DM on mortality as well as LOS and TCS of hospitalized patients with

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CAP from the data obtained from the Community-Acquired Pneumonia Organization (CAPO) database.

The objective of the study is to compare outcome of community acquired pneumonia in diabetic population in comparison with non-diabetic population. In addition, we will compare the outcomes between the non-diabetic population (Control group) with diabetic group with Blood glucose of more than or equal to 250 and also look at the association between the control group with diabetic group with Blood glucose less than 250.

2 Materials and Methods

2.1 Study Design

This was a retrospective observational study of adult patients hospitalized with CAP from 40 hospitals in 13 countries. Data were collected from patients admitted from June 2001 to June 2006 by members of the Community-Acquired Pneumonia Organization (CAPO). The local institutional review boards at each hospital approved the study. Non-consecutive medical records of hospitalized patients with a clinical diagnosis of CAP were randomly selected for review at each of the participating hospitals. Data collected included information on comorbidities, laboratory data, radiographic findings, clinical findings upon admission, and clinical outcomes as indicated in the study definition. For each case, a clinical investigator completed and submitted a case report form electronically to the database at the CAPO study center at the University of Louisville (Kentucky, U.S.A.). Validation of data quality was performed by a group of investigators before cases were entered into the database. Details and objectives of CAPO have been published [12].

2.2 Study Definitions

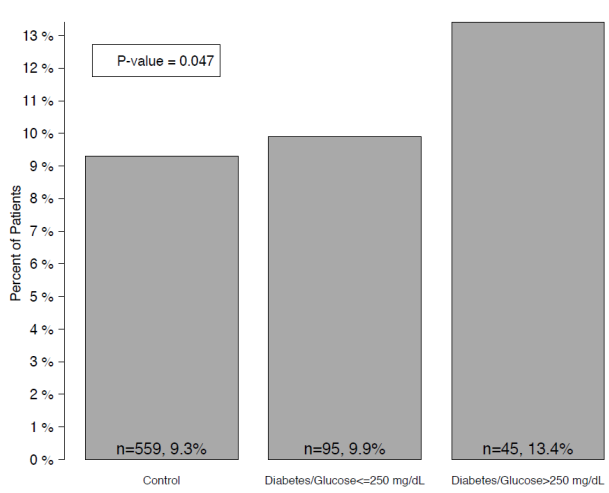
CAP was defined as the presence of a new pulmonary infiltrate on a chest radiograph at the time of hospitalization that was associated with at least one of the following: 1) new or increased cough; 2) an abnormal temperature ($< 35.6^{\circ}$C or $> 37.8^{\circ}$C); 3) an abnormal blood cell count (WBC), which is considered to be present if the patient had WBC $>$ 10.500 cells/μL, leukopenia (WBC) $<$ 4.500 cells/μL, or left shift ($>$ 5% immature neutrophils). Additionally, pneumonia was considered community acquired if a patient had no previous history of hospitalization within the 90 days prior to admission. DM was defined as a previously diagnosed by a physician; a prescription of insulin or oral anti-hyperglycemic drug, or random plasma glucose of $>$ 250 mg/dL on admission. Although the cutoff for undiagnosed DM is 200 mg/dL, the 250 mg/dL cut-off in this study was chosen only because the data for blood glucose values were collected according to the CAPO protocol following the Pneumonia Severity Index (PSI). In our study, patients with DM were categorized into two groups: one group with blood glucose $>$ 250 mg/dL (DM BG $>$ 250) and other group with blood glucose $\leq$ 250 mg/dL (DM BG $\leq$ 250). The control group includes population with no prior DM diagnosis in medical records and no prescription of insulin/oral anti-hyperglycemic drugs and with the plasma glucose of $\leq$ 250 mg/dL at the time of admission. Four outcome measures were examined for this study: all-cause in-hospital mortality, all-cause 28-day mortality, LOS from admission to discharge or expiration, and Time to Clinical stability. The time to clinical stability was calculated as the number of days from the date of hospital admission to the date that patient met clinical stability criteria. Clinical stability was defined as follows: improved clinical signs (improved cough and shortness of breath), lack of fever for at least 24 hours, improving leukocytosis (decreased at least 10% from the previous day), and tolerating oral intake [13].

2.2.1 Statistical Analysis

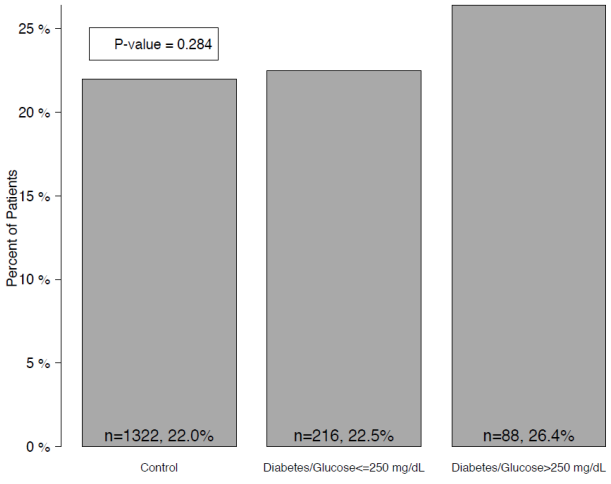
Baseline patient characteristics between the control group, DM $\leq$ 250 mg/dL and DM $>$ 250 mg/dL were compared using chi-squared tests for categorical variables and the Mann-Whitney U-test for continuous variables. To examine the effects of DM $\leq$ 250 mg/dL and DM $>$ 250 mg/dL on in-hospital mortality, 28-day mortality, LOS and TCS, a backward selection logistic regression model was constructed, including each group as dummy variables with the control group as the reference group. To control for confounding in the evaluation of the effect of diabetes status on each of the four outcomes (in-hospital mortality, 28-day mortality, TCS and LOS), multivariable regression models were used: Poisson regression with robust error variance estimates for dichotomous outcomes and Cox proportional hazards for time to event outcomes. Variable selections for the models were chosen via a two-step process. First, generalized linear models were constructed for each outcome, separately. Each model included all potential candidate confounders listed in **Table 1**. Variables with a p-value of $\leq$ 0.10 were included in a second regression model that selected the most parsimonious best fitting model using a genetic algorithm based on sample-size corrected Akaike information criteria. This allowed a different set of candidate confounding variables to be selected for each outcome. The variables remaining in this best fit model were included in a final regression model.

3 Results

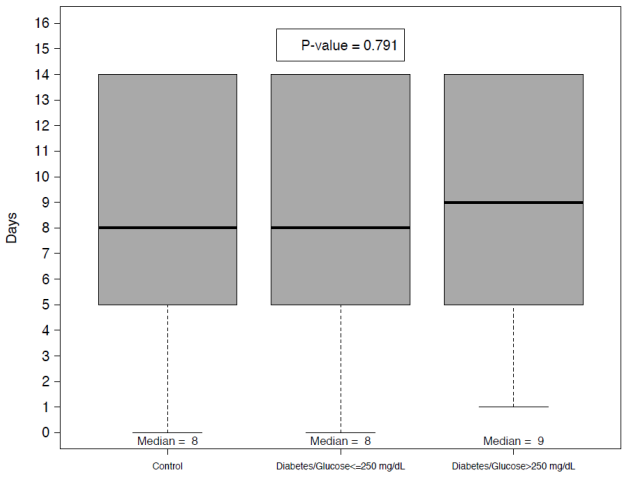
A total of 7,303 patients with CAP were examined in this study. DM was identified in 1,294 (17.7%) patients, out of whom 960 (13.1%) patients had BG $\leq$ 250 mg/dL, and 334 (4.6%) patients had BG $>$ 250 mg/dL. Patient demographics, comorbidities, clinical characteristics, and laboratory results are shown in **Table 1**. Study participants with DM were more commonly male, older, had greater comorbidities, and had a higher PSI score. The Primary outcomes used in this study are in-hospital mortality, 28 days mortality, Length of stay (LOS) and time to clinical stability. The unadjusted rate of the measured outcomes in different groups is presented in **Figure 1**. The only significant finding was found for in-hospital mortality which showed a significant increasing trend from 9.3% in the control group to 9.9% and 13.4% respectively in the DM BG $\leq$ 250 mg/dL and DM BG $>$ 250 mg/dL (p=0.04) The univariate and multivariate logistic regression results of the impact of DM on the clinical outcomes of hospitalized patients with CAP are shown in **Table 2**. Patients with DM BG $>$ 250 mg/dL compared to the control group had a statistically significant higher risk of in-hospital mortality (Relative Ratio (RR) = 1.32, 95% CI: 1.02-1.72, p = 0.034) and 28-day mortality (Relative Ratio (RR) = 1.31, 95% CI: 1.01-1.71, p = 0.048). However,



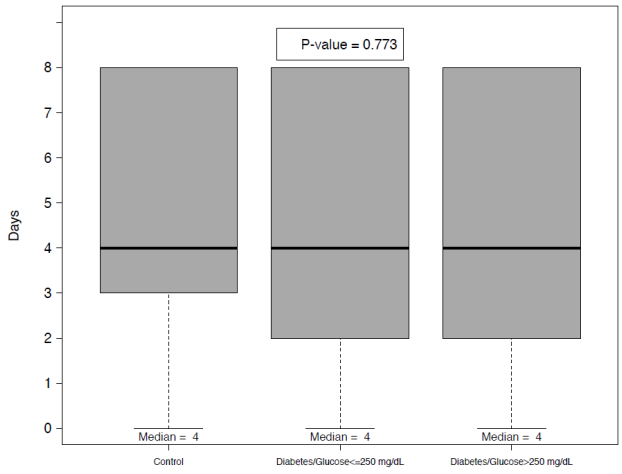
(a) In hospital mortality



(b) 28-day mortality



(c) Length of stay



(d) Time to clinical stability

Fig. 1 Unadjusted crude rate of the measured outcomes in the control and diabetes groups

Table 1 Characteristics of control group (no DM), patients with DM blood glucose > 250 mg/dL

Variable	Control group n=6009 n (%)	DM BG≤250 n=960 n (%)	DM BG>250 n=334 n (%)	*P*-Value
Demographics				
Age, Median (IQR)	68 (32)	71 (19)	70 (21)	<.0001
Male Gender	3562 (59.3)	642 (66.9)	205 (61.4)	<0.001
Comorbid Conditions				
COPD	1491 (24.8)	289 (30.1)	70 (21.0)	<0.001
Liver Disease	331 (5.5)	53 (5.5)	18 (5.4)	0.955
Renal Disease	518 (8.6)	179 (18.6)	42 (12.6)	<0.001
Neoplastic Disease	604 (10.1)	109 (11.4)	29 (8.7)	0.305
Congestive Heart Failure	951 (15.8)	251 (26.1)	90 (26.9)	<0.001
Cerebrovascular Accident	806 (13.4)	162 (16.9)	68 (20.4)	<0.001
Laboratory and Physical Findings				
PaO_2 <60mm Hg	1917 (31.9)	307 (32.0)	126 (37.7)	0.085
Hematocrit <30%	437 (7.3)	92 (9.6)	25 (7.5)	0.043
Blood Urea Nitrogen ≥30 mg/dl	1647 (27.4)	316 (32.9)	119 (35.6)	<0.001
pH 7.35	328 (5.5)	60 (6.2)	30 (9.0)	0.02
Sodium <130 mmol/liter	394 (6.6)	63 (6.6)	49 (14.7)	<0.001
Temperature <35°C or ≥40°C	419 (7.0)	62 (6.5)	29 (8.7)	0.388
Systolic Blood Pressure <90mm Hg	349 (5.8)	39 (4.1)	14 (4.2)	0.05
Heart Rate ≥125 beats /min	771 (12.8)	88 (9.2)	55 (16.5)	0.001
Respiratory Rate >30 breaths/min	1163 (19.4)	139 (14.5)	71 (21.3)	0.001
Severity of Disease				
Need for Intensive Care	840 (14.0)	125 (13.0)	61 (18.3)	0.056
Multilobar Infiltrates	1646 (27.4)	281 (29.3)	83 (24.9)	0.257
Pleural Effusion	1274 (21.2)	210 (21.9)	81 (24.3)	0.391
Altered Mental Status	863 (14.4)	146 (15.2)	59 (17.7)	0.216
Pneumonia Severity Index, Median (IQR)	92 (54)	101.5 (45.25)	115 (54)	<0.001
Quality of Care and Prevention				
Blood Cultures Obtained	4181 (69.6)	707 (73.6)	234 (70.1)	0.038
History of Pneumococcal Vaccine	842 (15.7)	189 (19.7)	71 (21.3)	<0.001
History of Influenza Vaccine	850 (17.0)	170 (21.7)	68 (23.0)	<0.001

Note: Reference group is non-DM patients with blood glucose level ≤ 250 mg/dL (control group)

Table 2 Adjusted results by multivariate logistic regression model

Outcome	Blood Glucose (mg/dL)	Risk Ratio (95% CI)		*p*-value	
		Univariate	Multivariate	Univariate	Multivariate
In-hospital Mortality	≤250	1.07(0.87-1.32)	1.23(0.16-8.09)	0.551	0.237
	>250	1.45(1.09-1.92)	1.32(1.02-1.72)	0.015	0.034
28-day Mortality	≤250	1.02(0.89-1.18)	1.09(0.90-1.32)	0.79	0.398
	>250	1.2(0.96-1.5)	1.31(1.01-1.71)	0.13	0.048
Length of Hospital Stay	≤250	1.03(0.97-1.06)	0.93(0.85-1.02)	0.19	0.130
	>250	0.89(0.78-1.02)	0.97(0.84-1.11)	0.19	0.630
Time to Clinical Stability	≤250	0.99(0.91-1.07)	0.95(0.87-1.05)	0.83	0.320
	>250	1.03(0.91-1.18)	1.13(0.98-1.31)	0.83	0.086

Notes: (a) The confounders in this study includes variables like in-hospital mortality: PaO_2<60 mmHg, ICU admission or transfer, Hematocrit <30%, BUN ≥30mg/dl, Systolic BP<90mmHg, pH<7.35, respiratory rate >30 breaths/min, Multilobar infiltrates on chest xray. Prior influenza vaccination

(b) Reference group is non-DM patients with blood glucose level ≤ 250 mg/dl (control group)

no significant increase in TCS (HR = 1.13, 95% CI: 0.98-1.13, p = 0.086) and LOS was found (HR = 0.97, 95% CI: 0.84-1.11, p = 0.630). Patients in the DM BG ≤ 250 mg/dL group compared to the control group did not have a statistically significant greater risk for in-hospital mortality (RR = 1.23, 95%: 0.16-8.09, p = 0.237), 28-day mortality (RR = 1.09, 95% CI: 0.90-1.32, p = 0.398), LOS (HR = 0.93, 95% CI: 0.85-1.02, p = 0.130), or TCS (HR = 0.95, 95% CI: 0.87-1.05, p = 0.320).

4 Discussion

Our study reveals that patients with DM and BG > 250 mg/dL had a higher in-hospital mortality and 28-day mortality compared to those in the control group, whereas those with DM and BG < 250 mg/dL did not appear to adversely affect any clinical outcomes compared to the control group. There was no significant difference among the three groups when comparing TCS and LOS. These four outcomes were measured after adjusting for confounders in the multiple Cox regression and multiple logistic regression analysis. The higher mortality of CAP found in patients with DM and BG > 250mg in the present study is consistent with prior investigations. Previous studies generally showed the association between hyperglycemia and higher mortality[8,9], but the effects of well-controlled or pre-existing diabetes on clinical outcomes in patients with CAP have not been well studied. One contributing factor to the aforementioned inconsistencies is the lack of a clear definition of uncontrolled and controlled DM; which have been based on plasma glucose measures upon hospital admission. A recent multicenter prospective cohort examined DM patients admitted with CAP from 2003 to 2009[8]. This study showed mild hyperglycemia (108-198 mg/dL) at hospital admission to be associated with risk of death at 90 days (RR=1.56, 95% CI: 1.22-2.01, P<0.001) and higher risk of death in those with severe hyperglycemia (blood glucose > 252 mg/dL) (HR=2.37, 95% CI: 1.62 to 3.46, P > 0.001)[8].

Our study association of BG > 250 mg/dL with high mortality of patients with CAP could be analyzed in two ways. One way is whether BG < 250 mg/dL is a predictor of poor outcome or

whether it is an effect of severity of CAP, leading to poor clinical outcomes. Robinson et al. have demonstrated that any acute illness can cause hyperglycemia due to combination of multiple metabolic effects including raised glucocorticoid hormone concentrations, elevated plasma catecholamine levels and increased peripheral insulin resistance[14]. Multiple hypotheses have been proposed to evaluate how hyperglycemia can cause adverse effect in acute illness. Van de Berghe et al have proposed that hyperglycemia causes cellular glucose overload and oxidative stress increasing the superoxide and peroxynitrate production; which may cause mitochondrial toxicity. This may eventually lead to organ and tissue dysfunction contributing to death[15]. Glucose in airway secretions could predispose to respiratory infection by promoting bacterial growth or interfering with local innate immunity[16].

However, unlike the present study, patients with pre-existing DM had a higher risk of mortality (RR = 2.47 95% CI: 2.05 to 2.98, $p = < 0.001$) regardless of blood glucose levels upon admission. A retrospective analysis of two multicenter cohorts showed an increase in 1-year mortality in the Gen IMS cohort for pre-existing DM (unadjusted RR = 1.41, 95% CI: 1.12-1.76, $p = 0.002$), this increase in mortality persisted after adjustment for cardiovascular and renal disease (HR= 1.3, CI: 1.03-1.65)[7]. However, in the Health ABC cohort, the association between pre-existing diabetes and 1-year mortality was not found to be significant (1.87, 95% CI: 0.76-4.6, $p = 0.16$)[7]. A Danish population based cohort study found increased 30-day (MRR = 1.16, 95% CI: 1.07-1.27) and 90-day (MRR = 1.10, 95% CI: 1.02-1.18) mortality among those with DM compared to those without DM however both mortality risk diminished after adjustment for hyperglycemia upon admission[6]. Conversely, a Canadian population based prospective cohort study found no significant association between blood glucose levels on admission and 90-day mortality after adjusting for functional status and PSI score (RR = 1.30, 95% CI: 0.88-1.93) for those in the 11.1-20 mmol/l group)[10]. Our study has strengths and limitations. The main limitation is that this study was not specifically designed to evaluate outcomes of CAP in diabetic patients. The CAPO database is designed to track multiple factors associated with CAP outcomes with the limitation of assessing BG > 250 mg/dL as the only BG level. Despite this shortcoming, this series of 1294 diabetic patients is adequately powered to evaluate the association between these 2 conditions. There was no documentation how aggressive the blood glucose was controlled during patient hospital course and this could have impacted the outcomes. Lack of hemoglobin A1C documentation is a weakness of our study to evaluate the retrospect control of DM among our patients. Also this is a retrospective, non-consecutive study and there was no stratification for treatments. One of the strengths of the study is the large patient population included in the study. We conclude that it is the presence of DM with BG > 250 mg/dL that contributes to increased in-hospital mortality and 28-day mortality. This implies that the mere presence of Diabetes mellitus does not contribute to the increase in In-hospital mortality, 28 days mortality, length of stay and time to clinical stability. It is the presence of hyperglycemia in Diabetic population that contributes to the poor outcome. This emphasizes on the fact that more efforts are needed to increase awareness of impact of hyperglycemia in DM on the clinical outcomes of CAP. These results indicate the importance of keeping the blood glucose of CAP patients under control. In addition, further studies are needed to link the role of hyperglycemia to CAP outcome to better understand this association.

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