Admission hypoglycaemia is associated with adverse outcome in community-acquired pneumonia

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Abstract

Background

The aim of this study was to investigate if hypoglycaemia is associated with outcome in community-acquired pneumonia.

Methods

A prospective observational study of patients presenting with community-acquired pneumonia in NHS Lothian, UK. Admission plasma glucose was measured with division into hypoglycaemic (<4.4 mmol/L or <79.0 mg/dL) and non-hypoglycaemic (≥4.4 mmol/L or ≥79.0 mg/dL) groups. Outcomes of interest were 30-day mortality, need for mechanical ventilation and inotropic support. Multivariable logistic regression was used to compare these outcomes in hypoglycaemic patients compared to non-hypoglycaemic, adjusting for diabetes mellitus, prior statin use and pneumonia severity index.

Results

There were 1050 patients included in the study with 5.4% classified as hypoglycaemic. Increased rates of 30-day mortality (28.1% vs 7.5%, p<0.0001), need for mechanical ventilation (29.8% vs 6.5%, p<0.0001) and inotropic support (21.1% vs 4.8%, p<0.0001) were observed in hypoglycaemic patients compared to non-hypoglycaemic. On multivariable analysis, hypoglycaemia was independently associated with increased 30-day mortality [OR 2.25 (95% CI 1.1-4.7), p=0.03], need for mechanical ventilation [OR 3.8 (95% CI 1.9-7.5), p=0.0002] and inotropic support [OR 2.9 (95% CI 1.4-6.3), p=0.0006].

Conclusion

Admission hypoglycaemia is associated with increased risk of 30-day mortality, need for mechanical ventilation and inotropic support in patients presenting with community-acquired pneumonia.
Introduction

There has been increasing interest in the influence of glycaemia on outcome in acutely unwell patients. Hypoglycaemia has previously been shown to be a predictor of adverse outcome in patients with gram positive and gram negative sepsis [1-3].

Although hyperglycaemia has been shown to be a factor associated with poor outcome in community-acquired pneumonia (CAP) [4-6] and is one of 20 variables used to calculate the pneumonia severity index (PSI) [4], no study to date has investigated the association of hypoglycaemia and outcome in CAP. The aim of this study was to investigate if admission hypoglycaemia is associated with increased risk of mortality, need for mechanical ventilation and need for inotropic support, in patients presenting with CAP.
Methods

The Edinburgh Pneumonia Study is a prospective observational study of adult patients presenting with a diagnosis of CAP between January 2005 and January 2008 to NHS Lothian, UK. This manuscript reports a sub-analysis of this study investigating the effect of hypoglycaemia on outcome. The study was approved by the Lothian Research Ethics Committee.

Patients were included in the study if they presented with a new infiltrate on chest radiograph and had 3 or more of the following symptoms or signs (cough, sputum production, breathlessness, pleuritic chest pain or signs consistent with pneumonia on auscultation).

Exclusion criteria were: hospital-acquired pneumonia (development of symptoms >48 hours following admission or discharge from an acute care facility <2 weeks prior to admission); active thoracic malignancy; immunosuppression (defined as current (>28 day) use of oral prednisolone at any dose or other immunosuppressive drugs (methotrexate, azathioprine, cyclosporin and anti-tumour necrosis factor alpha agents) or patients with solid organ transplantation); known adrenal insufficiency; intravenous or subcutaneous insulin therapy on admission prior to measurement of plasma glucose; pulmonary embolism and patients in whom active treatment was not considered appropriate (palliative care).

Site of Care and Data Collection

At the study sites in NHS Lothian, patients present either as self referral to Accident and Emergency or via General Practitioner referral to a medical assessment unit.
Patients are reviewed by the medical team and decision to admit or discharge the patient is made.

All patients had baseline observations (pulse, blood pressure, respiratory rate, temperature) and standard blood tests (full blood count, urea and electrolytes, liver function tests, coagulation profile and C-reactive protein) measured on admission. Blood culture requests were left to the discretion of the attending physician. All observations and blood tests were taken within 4 hours of hospital admission.

Subsequently, patients spend 12-24 hours in medical assessment Unit, from where they may be discharged or move on to a specialist ward. Critically ill patients may be admitted at any time to the Intensive Care Unit for invasive ventilation and/or inotropic support or to the High Dependency Unit, which provides intensive monitoring as well as non-invasive ventilation (bilevel or continuous positive airways pressure ventilation) and/or inotropic support. All patients received standard antibiotic therapy in accordance with British Thoracic Society guidelines [7].

**Glucose measurement**

All patients had plasma glucose measured on admission (all readings taken within 4 hours, prior to any corrective treatment).

The study cohort was divided into two groups on the basis of admission plasma glucose level:- Hypoglycaemic: Glucose < 4.4 mmol/L (< 79.0 mg/dL), as previously defined [8] and non-hypoglycaemic: Glucose ≥ 4.4 mmol/L (≥ 79.0 mg/dL).
The Hypoglycaemic group was then sub-divided further into the following groups:
mild hypoglycaemia: 3.9 – 4.39 mmol/L (70-78.9 mg/dL); moderate hypoglycaemia: 
3.4-3.89 mmol/L (61 – 69.9 mg/dL); severe hypoglycaemia: <3.4 mmol/L (<61 
mg/dL).

Severity Assessment scores on admission
The following severity scores were analysed for all patients on admission:

1). Pneumonia Severity Index
The Pneumonia Severity Index [4] is a well-validated prediction scale for 30-day 
mortality in CAP composed of the following twenty characteristics: demographics 
including age, sex and nursing home residence; co-morbid illness including neoplastic 
disease, cerebrovascular disease, congestive cardiac failure, chronic renal disease and 
chronic liver disease; physical examination findings including altered mental status, 
respiratory rate ≥ 30/min, systolic blood pressure <90mmHg, temperature <35°C or 
>40°C and pulse >125/min; laboratory findings including pH <7.35, blood urea >10.7 
mmol/L, sodium <130 mEq/L, glucose >13.9 mmol/L, haematocrit <30% and PaO2 
<60mmHg; radiographic findings including pleural effusion.

With use of these data, patients were classified into 5 risk classes (1–5) according the 
criteria created by Fine at al. [4]. In the original Pneumonia Patient Outcome Research 
Team cohort study, 30-day mortality ranged from 0.1% for patients with a class 1 
rating to 27% for patients with a class 5 rating.

2). CURB65
CURB65 is a validated method of predicting inpatient mortality associated with CAP 
that is recommended by the British Thoracic Society [7, 9]. It consists of new onset
mental confusion, urea > 7 mmol/L, respiratory rate ≥ 30 breaths/min, systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg and age ≥ 65 years.

British Thoracic Society guidelines suggest that patients with a CURB65 score of 0–1 be considered for outpatient treatment; that patients with a CURB65 score of 2 be considered for short inpatient hospital stay; and that patients with a CURB65 score ≥ 3 have severe pneumonia that requires inpatient management, and intensive care or high dependency environment care should be considered, particularly for patients with a CURB65 score ≥ 4 [7].

3) Systemic Inflammatory response syndrome (SIRS)

SIRS are well recognized criteria of the sepsis syndrome [10], defined as 2 of the following variables: temperature > 38°C or < 36°C, pulse rate > 90 beats/minute, respiratory rate ≥ 20 breaths/min or PaCO2 < 4.3 kPa (32 mmHg) and white cell count > 12,000 cells/mm³ or < 4,000 cells/mm³.

Severe sepsis is defined as SIRS with one or more organ failure, in the context of suspected or proven infection. Septic shock refers to SIRS with hypotension not responsive to adequate fluid resuscitation, also in the context of suspected or proven infection [10].

Outcomes

The outcomes of interest were 30-day mortality, need for mechanical ventilation and need for inotropic support. The indications for mechanical ventilation and inotropic support were left to the discretion of the attending physician.

Statistical analysis

All data were analysed using SPSS version 13 for windows (SPSS inc., Chicago, IL). Descriptive statistics of demographic and clinical variables are presented as median
(IQR) unless otherwise stated. The Chi-squared test was used to compare categorical data between groups. The Mann-Whitney $U$ test was used for comparison of 2 groups of continuous data and the Kruskal-Wallis test was used for comparison of more than 2 groups of continuous data. Kaplan Meier analysis was used for comparison of survival between hypoglycaemic and non-hypoglycaemic groups and between subdivisions of the hypoglycaemic group. The statistical significance was evaluated using the log-rank test.

Univariate analyses were performed for the outcomes of interest in hypoglycaemic patients, non hypoglycaemic patients and the sub-group of patients without a prior diagnosis of diabetes mellitus. We also performed separate univariate analyses comparing the outcomes of interest between mild, moderate and severely hypoglycaemic patients.

We used multivariable logistic regression to compare the outcomes of interest in patients with hypoglycaemia (plasma glucose <4.4 mmol/L or <79.0 mg/dL) compared to non-hypoglycaemic patients. To the baseline model we included prior diagnosis of diabetes mellitus, and pneumonia severity (PSI criteria)- non severe (≤3) versus severe (≥4). We also adjusted for prior statin use, as a previous analysis had found a significant association between statin use and reduced 30-day mortality in patients with CAP [11]. A 2 tailed p value <0.05 was considered statistically significant.

**Results**

1269 patients were considered for inclusion into the study. There were 1050 patients who met the criteria and were included in the study. A flow chart of patient enrolment
into the study is shown in figure 1. Baseline demographic characteristics of the study population and sub-groups are outlined in table 1.

### Table 1 Characteristics of study population

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>All patients n=1050</th>
<th>Non hypo glycaemic</th>
<th>Hypoglycaemic</th>
<th>Admission Glucose</th>
<th>Subdivisions of hypoglycaemic group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≥4.4 mmol/L (≥79.0 mg/dL) n=993</td>
<td>&lt;4.4 mmol/L (&lt;79.0 mg/dL) n= 57</td>
<td>Mild Hypoglycaemic 3.9-4.39 mmol/L (70-78.9 mg/dL) n=33</td>
<td>Moderate Hypoglycaemic 3.4-3.89 mmol/L (61-69.9 mg/dL) n=13</td>
</tr>
<tr>
<td>Gender (% males)</td>
<td>49.7% 50.2% 42.1%</td>
<td>0.28 54.5% 23.1%</td>
<td>27.3%</td>
<td>0.081</td>
<td></td>
</tr>
<tr>
<td>Median Age (IQR)</td>
<td>67 (51-78) 62 (52-75)</td>
<td>0.13 58 (56-64) 58 (49-68)</td>
<td>76 (50-79)</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>19.2% 19.5% 14.0%</td>
<td>0.39 12.1% 15.4%</td>
<td>18.2%</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>10.9% 11.0% 8.7%</td>
<td>0.83 9.1% 7.7%</td>
<td>9.1%</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>10.1% 10.2% 8.7%</td>
<td>0.83 12.1% 7.7%</td>
<td>0%</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Chronic renal impairment</td>
<td>5.6% 5.4% 8.7%</td>
<td>0.25 9.1% 7.7%</td>
<td>9.1%</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>5.0% 4.9% 5.3%</td>
<td>0.76 3.0% 15.4%</td>
<td>0%</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>20.2% 20.4% 15.8%</td>
<td>0.50 15.2% 23.1%</td>
<td>9.1%</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>13.7% 12.9% 28.1%</td>
<td>0.001 15.2% 38.5%</td>
<td>54.5%</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Temp &lt; 35°C or &gt;40°C</td>
<td>2.2% 2.1% 3.5%</td>
<td>0.48 0% 0%</td>
<td>18.2%</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>Pulse &gt;125/min</td>
<td>13.3% 12.4% 29.8%</td>
<td>&lt;0.0001 12.1% 46.2%</td>
<td>63.6%</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Resp rate&gt;30/min</td>
<td>36.0% 35.3% 47.4%</td>
<td>0.066 48.5% 61.5%</td>
<td>27.3%</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Haematocrit &lt;30%</td>
<td>4.3% 4.4% 1.8%</td>
<td>0.33 0% 0%</td>
<td>9.1%</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Systolic BP&lt;90mmHg</td>
<td>11.4% 10.8% 22.8%</td>
<td>0.005 12.1% 38.5%</td>
<td>36.4%</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>pH&lt;7.35</td>
<td>13.0% 12.0% 31.6%</td>
<td>&lt;0.0001 24.2% 23.1%</td>
<td>63.6%</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Blood urea &gt;10.7 mmol/L</td>
<td>20.5% 19.1% 43.9%</td>
<td>&lt;0.0001 39.4% 46.2%</td>
<td>54.5%</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Sodium &lt; 130 mEq/L</td>
<td>8.9% 8.6% 14.0%</td>
<td>0.16 9.1% 30.8%</td>
<td>9.1%</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>PaO2 &lt; 60mmHg</td>
<td>40.6% 40.1% 49.1%</td>
<td>0.18 36.4% 61.5%</td>
<td>72.7%</td>
<td>0.067</td>
<td></td>
</tr>
<tr>
<td>Statin Use</td>
<td>24.0% 24.6% 14.0%</td>
<td>0.07 21.2% 0%</td>
<td>9.1%</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Oral hypo glycaemic use</td>
<td>4.8% 4.9% 1.8%</td>
<td>0.27 0% 0%</td>
<td>3.0%</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>PSI risk class&gt;3</td>
<td>44.9% 43.5% 64.9%</td>
<td>0.002 57.6% 76.9%</td>
<td>72.7%</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>CURB65≥3</td>
<td>32.1% 30.8% 52.6%</td>
<td>0.001 39.4% 76.9%</td>
<td>63.6%</td>
<td>0.052</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as median (interquartile range) or % number of patients; † p value compares hypoglycaemic patients with non hypoglycaemic; * p value compares subdivisions of hypoglycaemic group
**Admission glucose level and outcome**

Overall 30-day mortality rate was 8.6%. Mechanical ventilation was required in 7.8% of patients and inotropic support was required in 5.7%. There were 181 patients (17.2%) discharged within 24 hours. Hypoglycaemic patients had increased risk of 30-day mortality, need for mechanical ventilation and inotropic support compared to those without hypoglycaemia (table 2). With increasing severity of hypoglycaemia, there was increased 30 day mortality. There were similar trends for mechanical ventilation and inotropic support, but this failed to reach statistical significance (see table 2).

**Table 2 Admission glucose level and outcome**

<table>
<thead>
<tr>
<th></th>
<th>Non hypoglycaemic (≥4.4 mmol/L (≥79.0mg/dL) n=993)</th>
<th>Hypoglycaemic (&lt;4.4 mmol/L (&lt;79.0mg/dL) n=57)</th>
<th>†P value</th>
<th>Mild 3.9-4.39 mmol/L (70-78.9mg/dL) n=33</th>
<th>Moderate 3.4-3.89 mmol/L (61-69.9mg/dL) n=13</th>
<th>Severe &lt;3.4 mmol/L (&lt; 61mg/dL) n=11</th>
<th>*P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day mortality</td>
<td>7.5%</td>
<td>28.1%</td>
<td>&lt;0.0001</td>
<td>12.1%</td>
<td>38.5%</td>
<td>54.5%</td>
<td>0.011</td>
</tr>
<tr>
<td>Need for mechanical ventilation</td>
<td>6.5%</td>
<td>29.8%</td>
<td>&lt;0.0001</td>
<td>15.2%</td>
<td>38.5%</td>
<td>36.4%</td>
<td>0.15</td>
</tr>
<tr>
<td>Need for inotropic support</td>
<td>4.8%</td>
<td>21.1%</td>
<td>&lt;0.0001</td>
<td>12.1%</td>
<td>23.1%</td>
<td>27.3%</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Data presented as % number of patients.
† p value compares hypoglycaemic patients with non hypoglycaemic.
* p value compares subdivisions of hypoglycaemic group
Kaplan Meier Survival analysis in hypoglycaemic and non-hypoglycaemic patients

Figure 2 shows survival analysis in hypoglycaemic and non-hypoglycaemic patients and in subdivisions of hypoglycaemic group, for 30 days post admission. In the hypoglycaemic patient group, mortality occurred earlier, in comparison to non-hypoglycaemic patients (Comparison of curves: Log rank = 15.1 on 1 degree of freedom; p < 0.0001). Survival analysis in subdivisions of the hypoglycaemic group is also shown in figure 2 (Comparison of curves: Log rank = 12.7 on 2 degrees of freedom. p =0.0018).

Admission glucose level and correlation with severity scores

A greater proportion of patients in PSI class IV or V was observed in the hypoglycaemic group compared to the non hypoglycaemic group (64.9% vs. 43.5%, p=0.002). Similar trends were seen with regards to the proportion of patients in CURB65 class 3-5 (52.6% vs. 30.8%. p=0.001) (table 1).

Analysis of outcome in hypoglycaemic and non hypoglycaemic patients, stratified by PSI risk class.

The rates of 30-day mortality, need for mechanical ventilation and need for inotropic support in hypoglycaemic and non hypoglycaemic patients, stratified according to PSI class is shown in table 3. In non hypoglycaemic patients, there were increasing rates of mortality, need for mechanical ventilation and inotropic support with increasing PSI class (see table 3). Trends towards increasing rates of mortality, need for mechanical ventilation and inotropic support were observed with increasing PSI class in hypoglycaemic patients, although this failed to reach statistical significance (see table 3).
Comparison of hypoglycaemic and non hypoglycaemic groups revealed significantly increased rates of mechanical ventilation in hypoglycaemic patients for PSI classes III and IV and significantly increased rates of inotropic support for PSI class IV. Otherwise, no significant differences were observed between the two groups when stratified according to PSI risk class (table 3).

### Table 3 Stratified outcome of hypoglycaemic and non hypoglycaemic patients according to PSI class

<table>
<thead>
<tr>
<th>PSI class</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>30 day mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemic</td>
<td>0%</td>
<td>25%</td>
<td>12.5%</td>
<td>18.2%</td>
<td>46.2%</td>
<td>0.065</td>
</tr>
<tr>
<td>Non Hypoglycaemic</td>
<td>1.8%</td>
<td>1.7%</td>
<td>2.8%</td>
<td>6.0%</td>
<td>29.9%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>†P value</td>
<td>1.00</td>
<td>0.080</td>
<td>0.23</td>
<td>0.15</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td><strong>Need for Mechanical Ventilation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemic</td>
<td>0%</td>
<td>25%</td>
<td>37.5%</td>
<td>36.4%</td>
<td>34.6%</td>
<td>0.32</td>
</tr>
<tr>
<td>Non Hypoglycaemic</td>
<td>0%</td>
<td>1.7%</td>
<td>1.4%</td>
<td>5.4%</td>
<td>31.3%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>†P value</td>
<td>1.00</td>
<td>0.080</td>
<td>0.0006</td>
<td>0.0032</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td><strong>Need for Inotropic Support</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemic</td>
<td>0%</td>
<td>25%</td>
<td>0%</td>
<td>27.3%</td>
<td>30.8%</td>
<td>0.20</td>
</tr>
<tr>
<td>Non Hypoglycaemic</td>
<td>0%</td>
<td>1.7%</td>
<td>1.4%</td>
<td>4.4%</td>
<td>20.9%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>†P value</td>
<td>1.00</td>
<td>0.080</td>
<td>1.00</td>
<td>0.015</td>
<td>0.31</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as % of each PSI group.
* p value compares rates between PSI risk classes
† p value compares hypoglycaemic patients with non hypoglycaemic

**Association of hypoglycaemia with sepsis**

The proportion of patients with severe sepsis or septic shock on admission (as defined by SIRS criteria) and proportion of positive blood cultures in each group is shown in table 4. A greater proportion of patients with severe sepsis or septic shock on admission was observed in the hypoglycaemic group compared to non-hypoglycaemic patients (40.4% vs 14.5%; p <0.0001). A higher proportion of hypoglycaemic patients also had positive blood cultures compared to non-hypoglycaemic patients (29.8% vs
6.8 %; \( p<0.0001 \) (see table 4). There were no significant differences between the mild, moderate and severe hypoglycaemic groups.

| Table 4 Admission glucose level and correlation with SIRS score and blood cultures |
|----------------------------------|------------------|----------------|----------------|----------------|----------------|
|                                   | Non hypoglycaemic ≥ 4.4 mmol/L (≥79.0 mg/dL) | Hypoglycaemic < 4.4 mmol/L (<79.0 mg/dL) | Subdivisions of Hypoglycaemic group | *P value |
|                                   | \( n=993 \) | \( n=57 \) | \( n=33 \) | \( n=13 \) | \( n=11 \) |
| Severe Sepsis or septic shock (SIRS criteria) | 14.5% | 40.4% | \(<0.0001\) | 24.2% | 53.8% | 54.5% | 0.069 |
| Positive Blood culture | 6.8% | 29.8% | \(<0.0001\) | 24.2% | 53.8% | 27.3% | 0.14 |

Data presented as % number of patients.  
† p value compares hypoglycaemic patients with non hypoglycaemic.  
* p value compares subdivisions of hypoglycaemic group.

**Influence of Plasma Glucose on outcome in patients without a prior diagnosis of diabetes mellitus**

At time of presentation, 10.1% of patients had a prior diagnosis of diabetes mellitus. Table 1 shows frequency of these patients in each group. Of the diabetic group, 28.3% were diet-controlled, 44.3% were on oral hypoglycaemic agents alone, 25.5% were on subcutaneous insulin alone and 1.9% were on a combination of insulin and oral agents. Analysis of patients without prior diagnosis of diabetes mellitus revealed similar trends to the whole cohort, with hypoglycaemic patients showing increased 30-day mortality (28.8% vs 6.6%; \( p<0.0001 \)), need for mechanical ventilation (32.7% vs 5.9%; \( p<0.0001 \)) and inotropic support (23.1% vs 4.5%; \( p<0.0001 \)), compared to non-hypoglycaemic patients.
**Multivariable Analysis**

On multivariable logistic regression, adjusting for variables in the PSI, diabetes mellitus and prior statin use, admission hypoglycaemia (<4.4 mmol/L or <79.0 mg/dL) was independently associated with increased 30-day mortality [OR 2.25 (95% CI 1.1-4.7, p=0.03], increased requirement for mechanical ventilation [OR 3.8 (95% CI 1.9-7.5, p=0.0002] and increased requirement for inotropic support [OR 2.9 (95% CI 1.4-6.3, p=0.0006].
Discussion

This study has found that patients who are hypoglycaemic on admission with CAP have significantly increased rates of 30-day mortality, need for mechanical ventilation and need for inotropic support. This effect was seen independently of prior diabetes mellitus diagnosis and after adjustment for prior statin use and pneumonia severity (PSI criteria). We are not aware of any previous study that has examined the association of hypoglycaemia with outcome in CAP.

Previous studies in patients with septicaemia have shown that hypoglycaemia is a late manifestation of septic shock [3] and is also associated with a high mortality rate (43-90%) [1,3,12]. In addition, interventional studies have shown that treating low blood glucose directly does not affect outcome in sepsis, suggesting that hypoglycaemia is a marker of adverse outcome rather than being directly responsible for increased mortality rates seen in these patients [13].

Although the direct pathophysiological relationship between hypoglycaemia and adverse outcome in CAP has not been characterised, studies into sepsis provide some insight. Animal studies have shown that endotoxin challenge induces hypoglycaemia in both dogs and rats [14-15]. Hepatic gluconeogenesis has been shown to be important in survival from septic shock and experimental models suggest that sepsis may induce hepatic dysfunction, leading to altered glucose homeostasis [16-17]. Poor perfusion, extensive anaerobic metabolism and increased peripheral glucose utilisation have also been proposed as causative pathophysiological factors involved in the hypoglycaemia observed in sepsis [3, 18]. In addition, studies have shown the presence of relative adrenal insufficiency in a proportion of patients with septicaemia [19-22] and this finding has been shown to correlate with adverse outcome [23]. This
may further explain the underlying cause for hypoglycaemia in CAP and also its influence on outcome.

We postulate that in CAP, similar to septicaemia, hypoglycaemia on admission reflects a sub-group of patients with severe physiological disturbance and subsequent increased rates of 30-day mortality, need for mechanical ventilation and inotropic support. This is supported by our finding that a greater proportion of hypoglycaemic patients had severe sepsis or septic shock, as defined by SIRS criteria.

Our results show that hypoglycaemia on admission is a relatively infrequent finding in patients with CAP (present in only 5.4% of our cohort). However, if present, it represents an additional marker of severity in CAP and such patients should be identified early as being at increased risk of complications. This is further confirmed by our finding that patients with hypoglycaemia were more likely to be classified in higher risk groups on the basis of admission severity scoring (PSI and CURB65). However, hypoglycaemia was a marker of poor outcome, independent of severity.

Kaplan Meier survival analysis of hypoglycaemic patients in our cohort indicated that the majority of deaths in this group occur early after admission (in the first 7 days). This reinforces that, in patients with CAP, admission hypoglycaemia should alert clinicians to a potential need for early aggressive management strategies.

Our findings also show that increasing levels of hypoglycaemia correlate with increasing risk of adverse outcome in CAP with severely hypoglycaemic patients (glucose <3.4 mmol/L or <61.0 mg/dL) showing the highest rates of 30-day mortality. Similar trends were seen for the need for mechanical ventilation and inotropic
support, although these endpoints failed to reach statistical significance, likely due to
the small numbers in the different subgroups of hypoglycaemia.

In conclusion on multivariable analysis, adjusting for diabetes mellitus diagnosis,
prior statin use and pneumonia severity index criteria, admission hypoglycaemia was
independently associated with increased risk of 30-day mortality, need for mechanical
ventilation and inotropic support in patients presenting with community-acquired
pneumonia.
References


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Figure 2 Kaplan Meier survival analysis in hypoglycaemic and non hypoglycaemic patients and in subdivisions of the hypoglycaemic group.