Impact of Obesity in Patients Infected With 2009 Influenza A(H1N1)

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In recent years, the prevalence of obesity in Spain has risen to 17%. The prevalence of patients who are obese is higher in the ICU than in the outpatient population, reaching approximately one-third of patients. In the last 2 years, two meta-analyses have examined the effect of obesity on outcomes in patients admitted to the ICU. In 2008, Akinnusi et al. reported an increase in the duration of mechanical ventilation (MV) and ICU stay in patients who are obese. In a meta-analysis carried out in 2009, Hogue et al. reported no differences in mortality in a pool of 88,501 patients from 22 studies.

Since the first reports of the pandemic due to 2009 influenza A(H1N1), obesity has been a leading comorbidity. Obesity has been seen as a possible mechanism for increased morbidity and mortality because of related physiologic changes such as proinflammatory states or insulin resistance. In addition, obesity has been associated with increases in serum titer values related to some viruses. The present study evaluates whether the presence of obesity in patients who are severely ill from A(H1N1) infection is associated with mortality and prolonged MV requirement, ICU length of stay (LOS), and hospitalization.

**Materials and Methods**

Study data were obtained from a voluntary registry created by the Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias (GTEI/SEMICYUC) registry. Adult patients with A(H1N1) that was confirmed by real-time polymerase chain reaction were included in the analysis. Patients who were obese (BMI > 30) were compared with patients who were nonobese. Cox regression analysis was used to determine adjusted mortality. Differences of \( P < .05 \) were considered significant.

**Objective:** A large proportion of patients infected with 2009 influenza A(H1N1) (A[H1N1]) are obese. Obesity has been proposed as a risk factor influencing outcome in these patients. However, its role remains unclear. We evaluate the outcome of patients who are obese and infected with A(H1N1) in the ICU, determining whether obesity is a risk factor for mortality.

**Methods:** This was a prospective, observational, and multicenter study performed in 144 ICUs in Spain. Data were obtained from the Grupo de Trabajo en Enfermedades Infecciosas de la Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias (GTEI/SEMICYUC) registry. Adult patients with A(H1N1) that was confirmed by real-time polymerase chain reaction were included in the analysis. Patients who were obese (BMI > 30) were compared with patients who were nonobese. Cox regression analysis was used to determine adjusted mortality. Differences of \( P < .05 \) were considered significant.

**Results:** In January 2010, the GTEI/SEMICYUC registry had complete records for 416 patients. One hundred and fifty patients (36.1%) were obese, of whom 67 (44.7%) were morbidly obese (BMI > 40). Mechanical ventilation (MV) was more frequently applied in patients who were obese (64% vs 52.4%, \( P < .01 \)). Patients with obesity remained on MV longer than patients who were nonobese (6.5 ± 10.3 days vs 9.3 ± 9.7 days, \( P = .02 \)), had longer ICU length of stay (10.8 ± 12.1 days vs 13.7 ± 11.7 days, \( P = .03 \)), and had longer hospitalization (18.2 ± 14.6 days vs 22.2 ± 16.5 days, \( P = .02 \)). Mortality adjusted by severity and potential confounders identified that obesity was not significantly associated with ICU mortality (hazard ratio, 1.1; 95% CI, 0.69-1.75; \( P = .68 \)).

**Conclusions:** In our cohort, patients who were obese and infected with A(H1N1) did not have increased mortality. However, there was an association between obesity and higher ICU resource consumption.
Coronarias (SEMICYUC) after the first reported ICU case. Inclusion criteria were: fever (>38°C); respiratory symptoms consistent with cough, sore throat, myalgia, or influenza-like illness; and acute respiratory failure requiring ICU admission; plus microbiologic confirmation of A(H1N1). Data were reported by the attending physician reviewing medical charts and radiologic and laboratory records. This study analyzes data from the first ICU case until January 31, 2010. Children < 15 years old were not enrolled in the study. The study was approved by the ethical board of Joan XXIII University Hospital in Tarragona, Spain. Patients remained anonymous, and the requirement for informed consent was waived because of the observational nature of the study. All tests and procedures were ordered by the attending physicians.

Data Collection

The following variables were recorded: demographic data, comorbidities, time of illness onset and hospital admission, time to delivery of first dose of antiviral medication, microbiologic findings, and chest radiologic findings at ICU admission. Intubation and MV requirements, adverse events during ICU stay (eg, need for vasopressor drugs or renal replacement therapies), and laboratory findings at ICU admission were also recorded. To determine the severity of illness, the Acute Physiology and Chronic Health Evaluation (APACHE) II score was determined in all patients within 24 h of ICU admission. Organ failure was assessed using the Sequential Organ Failure Assessment (SOFA) scoring system.

Patients who were obese were defined as those with a BMI > 30 kg/m², and patients with a BMI > 40 kg/m² at admission were considered morbidly obese. The definition of community-acquired pneumonia was based on current American Thoracic Society and Infectious Disease Society of America guidelines. Etiologic investigations for patients with community-acquired pneumonia included urinary tests for Streptococcus pneumoniae and Legionella pneumophila, examination of cultures from blood and respiratory samples, and examination of pleural fluid, if present.

RESULTS

On January 31, 2010, 872 patients were included in the registry; 416 had completed their ICU stay and were included in the current study. In this group, 150 (36%) patients presented with excess bodyweight: 83 (19.9%) patients were classified as obese, and 67 (16.1%) as morbidly obese. Of those patients with obesity (obese and morbidly obese), 83 (55.3%) were men, with a mean age of 43.1 ± 12.2 years and with an
APACHE II score at admission of 12 ± 5.2. Within comorbidities, only COPD (24% vs 11.7%; P < .01) was more often present in patients who were obese than in patients who were nonobese. Additional demographic data and clinical characteristics of patients with A(H1N1) with or without obesity are presented in Table 1.

Patients who were obese were comparable in terms of severity (APACHE II score and SOFA score) to patients who were nonobese. Invasive MV and prone positioning were more frequently implemented in patients who were obese. Corticosteroid use was administered in 167 patients; nevertheless, the indication for use (shock or pneumonia) was recorded in 163 patients (Table 2). All patients were administered oseltamivir; however, patients who were obese received higher doses of oseltamivir (up to 150 mg orally bid) more frequently than did patients who were nonobese (75.2% vs 63.8%, P < .02). CT scans were performed in 40 patients, and pulmonary embolism was diagnosed in two patients.

Among survivors, patients with obesity remained longer on MV than patients who were nonobese (6.5 ± 10.3 days vs 9.3 ± 9.7 days, P = .02), had longer ICU LOS (10.8 ± 12.1 days vs 13.7 ± 11.7 days, P = .03), and had longer hospitalization (18.2 ± 14.6 days vs 22.2 ± 16.5 days, P = .02).

Mortality in patients who were obese was not statistically different compared with patients who were nonobese (24.7% vs 17.4%; P = .07; OR = 1.56; 95% CI, 0.95-2.54). Only chronic renal failure and hematologic disease were associated with mortality in univariate analysis. A Cox regression analysis adjusted by severity (APACHE II score) and potential confounders (COPD, chronic renal failure, and hematologic disease) identified that obesity was not significantly associated with ICU mortality (HR, 1.1; 95% CI, 0.69-1.75; P = .68) (Fig 1). When these data were analyzed in patients with BMI > 40, similar results were found.

**Discussion**

The main finding of this study is that patients who were obese and infected with A(H1N1) necessitated higher resource consumption, as defined by longer ICU LOS and hospital LOS, although no significant differences in mortality were observed. In a review of influenza infection in special groups of patients in 2009, Kunisaki and Janoff concluded that populations of patients who were immunosuppressed were at a higher risk of influenza-associated complications but could be safely vaccinated. Obesity was not considered a risk factor for complications in seasonal influenza infection. Since the first series of pandemic A(H1N1) infection was reported, the medical research community has attempted to define people at risk for acquiring the infection or for poor outcomes if infected. Although between one-quarter and one-third of the infected population does not have a defined risk factor, people with previous respiratory disease or women during pregnancy seemed to be at higher risk for mortality. In a report by Jain et al., height and weight statistics were available for 100 patients: of those patients, 29% were obese and 26% morbidly obese. In June 2009, the University of Michigan reported severe pulmonary complications of A(H1N1) infection in 10 patients. All 10 patients had severe hypoxemia, and the major risk factor was obesity (for nine patients, of whom seven were morbidly obese). At the time the report was published, three patients had died, one patient was on extracorporeal membrane oxygenation, one was on MV, and the remaining five had been transferred back to the referring institutions.

In the first European series, Rello et al reported that 10 of 32 patients had a BMI > 30 kg/m², obesity being the most frequently described comorbidity. After 6 months of continued pandemics and > 400 cases with full follow-up, the presence of obesity remained at the same level. However, no association has been
In the Australian and New Zealand Intensive Care Society, especially in preparation for potential new waves. Although obesity has not been found to be a risk factor for mortality, another point to be considered is the use of critical care resources in A(H1N1) pandemic, especially in preparation for potential new waves. In their cohort, 72% of the patients without comorbid factors described by the CDC were obese.

Not all studies have found the increase in outcomes related to time on MV and ICU LOS that we report here. Gong et al23 showed that obesity was associated with ARDS but not with mortality. In an early 2009 meta-analysis by Hogue et al,3 pooled data did not demonstrate associations between mortality and obesity or morbid obesity, days on MV, ICU LOS, or hospital LOS.

This series describes new aspects of a novel disease, but some precautions should be noted. The series size is considerable, but other aspects of the study may explain the increase in outcomes parameters. The overall delay in antibiotic dosing may have negatively influenced the lack of mortality, but this delay was different between patients who were obese and nonobese. The effect of A(H1N1) infection was not analyzed in people who were underweight or of normal weight because the database design focused solely on the effect of obesity.

One important point to consider is that patients who were obese received higher doses of antiviral treatment than patients who were nonobese. Dosing of oseltamivir was left to the discretion of the attending physician and was not standardized. It is crucial to note that underdosing is a common problem in patients with severe sepsis, MV with high volume of distribution, and low enteral absorption.24 Ariano et al25 recently reported that the dosage of 150 mg daily achieved plasma levels that were far in excess of concentrations required to maximally inhibit the neuraminidase activity of the virus. Nevertheless, the two different regimens (150 mg daily vs 300 mg daily) of oseltamivir were included in the multivariate analysis, and no differences were found.

![Figure 1](image-url)

**Figure 1.** Survival graph for patients receiving mechanical ventilation with severe pandemic 2009 influenza A(H1N1) infection with and without obesity (censored at 60 days). Continuous line denotes patients without obesity, and dashed line denotes patients with obesity (hazard ratio 1.1; 95% CI, 0.69-1.75; P = .69).

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### Table 2—Initial Treatment and Outcomes Variables for Patients Infected With 2009 Influenza A(H1N1) Comparing Patients With and Without Obesity

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nonobesity (n = 265)</th>
<th>Obesity (n = 150)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive MV</td>
<td>139 (52.4)</td>
<td>96 (64.0)</td>
<td>.002</td>
</tr>
<tr>
<td>Vasopressor drugs</td>
<td>108 (40.7)</td>
<td>64 (42.6)</td>
<td>.7</td>
</tr>
<tr>
<td>Hemofiltration</td>
<td>20 (7.5)</td>
<td>13 (8.7)</td>
<td>.6</td>
</tr>
<tr>
<td>Dialysis</td>
<td>7 (2.6)</td>
<td>5 (3.3)</td>
<td>.6</td>
</tr>
<tr>
<td>Prone positioning</td>
<td>30 (11.3)</td>
<td>26 (17.3)</td>
<td>.08</td>
</tr>
<tr>
<td>Corticosteroid use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>19 (7.2)</td>
<td>12 (8.0)</td>
<td>.8</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>77 (29.1)</td>
<td>55 (36.7)</td>
<td>.1</td>
</tr>
<tr>
<td>VAP</td>
<td>18 (6.8)</td>
<td>14 (9.3)</td>
<td>.3</td>
</tr>
<tr>
<td>MV days</td>
<td></td>
<td></td>
<td>.02</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>13.2 (11.7)</td>
<td>15.2 (8.9)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>10 (5.25-16.75)</td>
<td>14 (9-19.75)</td>
<td></td>
</tr>
<tr>
<td>ICU LOS</td>
<td></td>
<td></td>
<td>.03</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>10.8 (12.1)</td>
<td>13.7 (11.7)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>6 (3-13)</td>
<td>11 (4-19.5)</td>
<td></td>
</tr>
<tr>
<td>Hospital LOS</td>
<td></td>
<td></td>
<td>.02</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>18.2 (14.6)</td>
<td>22.2 (16.5)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>13 (8-24)</td>
<td>16 (9-30)</td>
<td></td>
</tr>
</tbody>
</table>

Discrete variables are expressed as counts (percentage) and continuous variables as means ± SD or medians with 25th to 75th IQRs. Differences between groups were assessed using the \( \chi^2 \) test for categorical variables and the Mann-Whitney U test for continuous variables. LOS = length of stay; MV = mechanical ventilation; VAP = ventilator-associated pneumonia. See Table 1 for expansion of the other abbreviation.

Data extracted from 163 patients.

Only survivors who were mechanically ventilated.

Only survivors.
In conclusion, although no increase in mortality was observed in patients who were obese, this subgroup of patients required prolonged MV, ICU LOS, and hospitalization. The reasons for this consumption of ICU resources needs to be further elucidated.

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Additional information: The e-Appendix 1 can be found in the Online Supplement at http://chestjournal.chestpubs.org/content/139/2/382/suppl/DC1.

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