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

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

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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.**

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Abbreviations: A(H1N1) = 2009 influenza A(H1N1); APACHE II = Acute Physiology and Chronic Health Evaluation; CDC = US Centers for Disease Control and Prevention; HR = hazard ratio; IQR = interquartile range; LOS = length of stay; MV = mechanical ventilation; SOFA = Sequential Organ Failure Assessment

In recent years, the prevalence of obesity in Spain has risen to 17%.[1] 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 in the ICU. In 2008, Akinnusi et al[2] 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[3] 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) (A[H1N1]),[4-7] 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.[8] In addition, obesity has been associated with increases in serum titer values related to some viruses.[9] 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 (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[10] was determined in all patients within 24 h of ICU admission. Organ failure was assessed using the Sequential Organ Failure Assessment (SOFA) scoring system.[11]

Patients who were obese were defined as those with a BMI >30 kg/m^2, and patients with a BMI >40 kg/m^2 at admission were considered morbidly obese.[3] The definition of community-acquired pneumonia was based on current American Thoracic Society and Infectious Disease Society of America guidelines.[12] 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. BAL was not systematically performed because of the high risk of generating aerosols. Respiratory cultures were based on tracheal aspirates obtained immediately after intubation.

Nasopharyngeal-swab specimens were collected at admission, and lower respiratory secretions were also obtained in patients who had been intubated. Real-time polymerase chain reaction testing was performed in accordance with published guidelines from the US Centers for Disease Control and Prevention (CDC).[13] A(H1N1) testing was performed in each institution or centralized in a reference laboratory. A confirmed case was defined as an acute respiratory illness with laboratory-confirmed pandemic A(H1N1) virus infection identified by real-time polymerase chain reaction or viral culture test.[14] Only confirmed cases were included in the current study. Primary viral pneumonia was defined in patients presenting with acute respiratory distress and unequivocal alveolar opacities involving two or more lobes with negative respiratory and blood bacterial cultures during the acute phase of the influenza virus. Secondary bacterial pneumonia was considered in patients with confirmation of influenza virus infection showing recurrence of fever, increase in cough, and production of purulent sputum, plus positive bacterial respiratory or blood cultures.[15] Acute renal failure was defined as the need for renal replacement therapy, following the International Consensus Conference guidelines.[16] Systemic corticosteroid use was implemented when patients developed shock (hydrocortisone) or for pneumonia coadjuvant treatment (methylprednisolone). Oseltamivir was administered orally in accordance with CDC recommendations, and the regimen (150 mg/24 h or 300 mg/24 h) was chosen by the attending physician.[17] The ICU admission criteria and treatment decisions for all patients, including determination of the need for intubation and type of antibiotic and antiviral therapy administered, were not standardized and were decided by the attending physician.

Statistical Analysis

Discrete variables are expressed as counts (percentage) and continuous variables as means ± SD or medians with 25th to 75th interquartile ranges (IQRs). For the demographic and clinical characteristics of the patients, differences between groups were assessed using the χ^2 test and Fisher exact test for categorical variables and the Student *t* test or Mann-Whitney *U* test for continuous variables. Cox proportional-hazards regression analysis was used to assess the impact of independent variables on ICU mortality across time. Variables significantly associated with mortality in the univariate analysis were entered in the model. In order to avoid spurious associations, variables entered in the regression models were those with a relationship in the univariate analysis ($P \leq .05$) or a plausible relationship with the dependent variable. Results are presented as hazard ratio (HR) and 95% CI. Potential explanatory variables were checked for colinearity prior to inclusion in the regression models using the tolerance and variance inflation factor. Data analysis was performed using SPSS for Windows 15.0 (SPSS, Inc; Chicago, Illinois).

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

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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%, $P > .002$). CT scans were performed in 40 patients, and pulmonary embolism was diagnosed in two patients who were obese. Additional data based on therapy administered is detailed in Table 2.

Patients who were obese presented to the hospital after a mean of 4.7 ± 2.6 days of symptoms and were admitted to the ICU after a mean of 1.5 ± 1.7 days. 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, $P = .02$).

Table 1—*Comparison of Baseline Characteristics for Patients With and Without Obesity (Obesity and Morbid Obesity)*

Variables	Nonobesity (n = 265)	Obesity (n = 150)	*P* Value
Age, y			
Mean (SD)	43 (15.4)	43.9 (12.3)	.5
Median (IQR)	43 (31.2-53)	43 (34.7-52)	.55
Male sex, n (%)	158 (59.6)	83 (55.3)	.22
APACHE II score, mean (SD)	13.3 (7.4)	13.5 (6.5)	.76
SOFA score, mean (SD)	5.4 (3.8)	5.4 (3.2)	.97
Pregnancy	17 (6.4)	5 (3.3)	.17
COPD	31 (11.7)	36 (24.0)	.001
Asthma	33 (12.5)	25 (16.7)	.23
Heart failure	13 (4.9)	12 (8.0)	.20
Chronic renal disease	12 (4.5)	3 (2.0)	.18
Diabetes	26 (9.8)	24 (16.0)	.06
Immunosupression	8 (3.0)	4 (2.7)	.83
Hematologic disease	18 (6.8)	4 (2.7)	.07
Neuromuscular disease	12 (4.5)	3 (2.0)	.18
HIV infection	6 (2.3)	3 (2.0)	.8

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 χ^2 test for categorical variables and the Mann-Whitney *U* test for continuous variables. APACHE = Acute Physiology and Chronic Health Evaluation; IQR = interquartile range; SOFA = Sequential Organ Failure Assessment.

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[18] 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.[19] 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.[6] In a report by Jain et al,[6] 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.[20]

In the first European series, Rello et al[5] reported that 10 of 32 patients had a BMI > 30 kg/m^2, 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

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

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

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 χ^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.

[a]Data extracted from 163 patients.

[b]Only survivors who were mechanically ventilated.

[c]Only survivors.

found between mortality and patients with obesity or morbid obesity in this series.

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) pandemics, especially in preparation for potential new waves. In the Australian and New Zealand Intensive Care (ANZIC) Influenza Investigators study, which was designed to plan critical care needs, the median ICU LOS was 7 days (IQR, 2.7-13.4), and patients receiving MV remained ventilated for a median of 8 days (IQR, 4-16).[21] However, although 28.6% of the patients had a BMI >35, the authors did not analyze the effect of obesity. In our study, survivors underwent MV for 11 days (IQR, 7-18.5); the mean duration of MV was longer in patients who were obese than in patients who were nonobese (median 10 days; IQR, 5.25-16.75; vs median 14 days; IQR, 9-19.75; $P = .02$). The increase in ICU LOS with respect to the ANZIC study[21] was mainly the result of the presence of patients who were obese, who stayed a median of 11 days (IQR, 4-19.5) in the ICU compared with 6 days (IQR, 3-13, $P = .03$) for patients who were nonobese. Hospital LOS was also longer in patients with obesity: a median of 13 days (IQR, 8-24) compared with 16 days (IQR, 9-30, $P = .02$) in patients who were nonobese. More recently, Miller et al[22] reported that patients who were obese were more likely to be admitted to the ICU with A(H1N1) infection during a pandemic than would be expected among the general population. In their cohort, 72% of the patients without comorbid factors described by the CDC were obese.

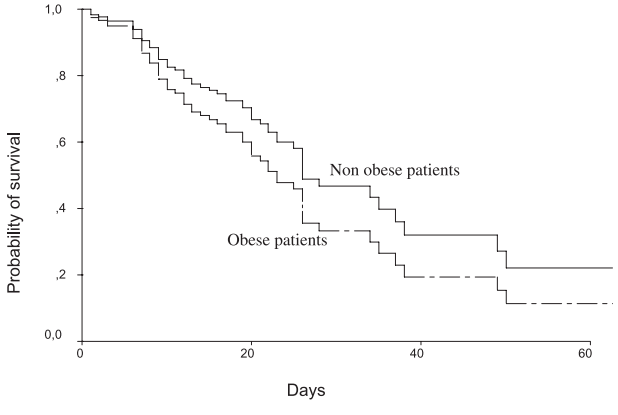

FIGURE 1. Survival graph for patients receiving mechanical ventilation with severe pandemic 2009 influenza A(H1N1) infection with and without obesity (censored at 60 days). Continuous line denotes patients without obesity, and dashed line denotes patients with obesity (hazard ratio 1.1; 95% CI, 0.69-1.75; $P = .68$).

Not all studies have found the increase in outcomes related to time on MV and ICU LOS that we report here. Gong et al[23] 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 al[25] 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.

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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Author contributions: *Dr Díaz:* contributed to study design, data analysis, drafting the manuscript, and discussion.
Dr Rodríguez: contributed to study design, analysis, writing, discussion, data collection and management, and revising the manuscript.
Dr Martin-Loeches: contributed to data analysis, drafting the manuscript, and discussion.
Dr Lorente: contributed to discussion, data collection, and revising the manuscript.
Dr Martín: contributed to discussion, data collection, and revising the manuscript.
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Dr Estella: contributed to discussion, data collection, and revising the manuscript.
Dr Arenzana: contributed to discussion, data collection, and revising the manuscript.
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