ORIGINAL ARTICLE

Obesity Paradox in Acute Pancreatitis

Raquel Barba[1], Asunción Gonzálvez-Gasch[2], Jesús Canora[3], Susana Plaza[4], Javier Marco[5], Miguel Yebra[1], Antonio Zapatero[3]

[1]Internal Medicine, Hospital Universitario Rey Juan Carlos, Spain

[2]Internal Medicine, Hospital General Villalba, Spain

[3]Internal Medicine, Hospital Universitario Fuenlabrada, Spain

[4]Internal Medicine, Hospital Universitario Severo Ochoa, Spain

[5]Internal Medicine, Hospital Clínico San Carlos, Spain

ABSTRACT

Background and Aim Obesity is an established risk factor for cardiovascular diseases, some types of cancer and mortality in general population. It is also considered a risk factor for poor outcome in acute pancreatitis. However, a reverse association between obesity and mortality has been reported in certain populations such as elderly, congestive heart failure and obstructive pulmonary disease showing that obesity might be protective for mortality. Along this same line, we aimed to further analyze the relationship between obesity and all-cause in-hospital mortality in patients with acute pancreatitis. **Methods** A retrospective chart review of consecutive patients admitted with acute pancreatitis as the primary reason for discharge in Spain between January 1st 2005 and December 31st 2013 was performed. Patients with a diagnosis of obesity in the hospital discharge clinical report were identified. The in-hospital mortality rate of obese patients with acute pancreatitis was compared with their non-obese counterparts. **Results** The medical records of 55285 patients with acute pancreatitis were retrospectively analyzed, 4594 (8.3%) being obese. In-hospital global mortality risk was 5.1%. Obese patients with acute pancreatitis showed lower in-hospital mortality risk (OR 0.62 IC 95% 0.53-0.73) than those non-obese. After adjusting for possible confounding factors, obese patients showed a significantly lower risk of death compared with non-obese subjects (OR 0.72 CI95% 0.61 -0.86). **Conclusions** The results of this report show a reverse association between obesity and all-cause in-hospital mortality among patients with acute pancreatitis.

INTRODUCTION

Early diagnosis and accurate prediction of acute pancreatitis (AP) severity is basic. Although most patients with AP run a benign course, up to 20% develop severe complications resulting in high mortality, ranging from 14 to 25% [1]. The severity of AP is a continuum from a mild, self-limiting pancreatic inflammation to severe disease with local and systemic complications. Identifying patients who are likely to present a complicated course helps the physician selecting those patients who will benefit from close monitoring and surveillance. To date, several objective and inexpensive multiple-choice score systems (APCAHE II, Ranson, Glasgow…) have been studied, neither one completely satisfactory. Obesity has been used as a covariate within a multiple clinical score [2] and has been linked to respiratory failure, local and systemic complications and death in patients with AP [3, 4, 5].

The prevalence of obesity has grown over the past two decades in most occidental countries and it is a well-recognized risk factor for cardiovascular diseases and mortality in general population [6, 7, 8]. However, during the past decade, there is emerging evidence that some obese patients with chronic diseases and acute decompensations, such as congestive heart failure in subjects with chronic heart failure [9, 10] or exacerbation of chronic obstructive pulmonary disease [11] may present lower mortality or readmissions compared with normal-weight patients. In addition, it has been reported that obese subjects might fare better after some surgical procedures, namely non-bariatric surgery [12], coronary artery bypass surgery [13] and decompressive laparotomy in patients with AP requiring Intensive Care Unit admission [14]. Such obese relationship has been termed as a phenomenon of obesity paradox and has never been stated among patients with AP. To address this question in patients with AP, we conducted a study to assess the relationship between overweight and obesity and in-hospital mortality.

Received October 08th, 2018 - Accepted December 18th, 2018
Keywords Mortality; Obesity; Pancreatitis
Correspondence Asunción Gonzálvez-Gasch
Internal Medicine, Hospital General Villalba
Carretera Alpedrete -Moralzarzal M-608 km 41
28400 Collado-Villalba, Madrid, Spain
Tel +718 270-1113
Fax +412-578-9487
E-mail asuncion.gonzalvez@hgvillalba.es

The aim of this study was to examine the association between obese individuals and all-cause in-hospital mortality among patients with AP.

PATIENTS AND METHODS

A retrospective chart review of consecutive patients with AP as the primary reason for discharge was performed. We identified every patient discharged from an Internal Medicine Department from hospitals in the Spanish Public Health Service (SPHS) between January 1st, 2005 and December 31st, 2013. Patients with AP and a diagnosis of obesity in the hospital discharge medical report were then identified. The in-hospital mortality in obese patients with AP was compared with their normal-weight counterparts to assess the effect of obesity on the final outcome.

Hospital discharge data were obtained from the Basic Minimum Data Set (BMDS) which is a compulsory registry for each patient admitted to a hospital in the SPHS, a system that cares for more than 90% of the country's population. All centers are requested to submit this information to the Spanish Health Ministry. BMDS contains sociodemographic and clinical data for every hospital discharge, including: gender and age, primary and secondary diagnoses according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code, primary and secondary procedures, admission and discharge status, inpatient stay from the time of admission to discharge and hospital characteristics (less than 200 beds; 200 to 500 beds; 500 to 1,000 beds; more than 1,000 beds).

Patients were selected if they were discharged with the diagnosis of pancreatitis (ICD-9-CM: 577.0). The patients above selected who also had a secondary diagnosis of obesity (ICD-9-CM: DRG 278.00. 278.01) were analyzed.

Definitions

Complications: The grading of the severity in AP has undergone significant recent changes [15, 16]. In the present study, disease severity was stratified as described in the Atlanta classification [17] because it reflects the criteria used in the medical reports and discharge files during the period of the study. Severe AP was defined by the presence of local complications (fluid collections or pancreatic necrosis) and/or organ failure, including shock, renal o respiratory failure or digestive hemorrhage. In our study, other conditions linked to a poor outcome were also considered as complications during admission.

In order to describe the complications above mentioned, we identified the following ICD-9-MC codes present in any secondary diagnosis field in the discharge medical reports: acute respiratory failure (ICD-9-CM: 518.82-518.84), acute renal failure (ICD-9-CM: 403.11, 403.91,404.12, 585-586), pneumonia (ICD-9-CM:480-486; 003.22, 507.0,510.0, 510.9, 513.0), bronchoaspiration (ICD-9-CM: 507.0), hypoglycemia (ICD-9-CM: 251.0-2, 250.30-1, 250.80-1, 249.80-1), decubitus ulcer (ICD-9-CM: 707.xx), urinary tract infection (ICD-9-CM: 599.00, 590.xx, 646.60-49, 601), deep venous thrombosis (ICD-9-CM: 415.1, 415.11, 415.19, 451.2, 451.81, 451.9, 453.40, 453.41, 453.42, 453.8, 453.9), sepsis (ICD-9-CM: 531-536, 537.83, 530.2, 530.82) 038. xx, 995.91, 995.92), gastrointestinal bleeding (ICD-9-MC: 530.21, 530.82, 531-535.00, 531-535.01, 531-535.20, 531-535.21, 531-535.40, 531-535.41, 531-535.60, 531-535.61), shock (ICD-9-CM: 785.50-59) and malnutrition (ICD-9-CM: 260-263.9). The presence or absence of complications has been shown in three different ways. Firstly, an item named "Any complication" which describes the presence of any of the complications mentioned above. Secondly, a composite variable named "Atlanta", which includes any complication linked to severe AP according to 1992 Atlanta consensus, and finally, each one of the different complications in a separate display.

Comorbidity: The Charlson Co-morbidity Index (CCI) [18] was computed for each patient. This index illustrates the number and relevance of co-morbid diseases according to ICD categories. It has been used in the present study to adequately depict the presence of additional co-occurring disorders, and thus appropriately adjust the results for the presence of diseases coexisting with AP and obesity that may affect mortality. The Charlson comorbidity index predicts the ten-year mortality for a patient who may have a range of comorbid conditions. Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one. Results provide a total score ranging between 0-37 to predict mortality. A grade higher than 2 is related to a mortality rate greater than 50% per year. Clinical conditions and associated scores are as follows:

1 each: Myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, diabetes.

2 each: Hemiplegia, moderate or severe kidney disease, diabetes with end organ damage, tumor, leukemia, lymphoma.

3 each: Moderate or severe liver disease.

6 each: Malignant tumor, metastasis, AIDS.

In addition, the following risk factors were identified using ICD-9-MC codes in any primary or secondary diagnosis field: diabetes (ICD-9-CM: 250.00-250.99), alcohol abuse (ICD-9-MC 305.00-305.03) and gallstones (ICD-9-CM: 575.xx).

Hospital Stay: Mean hospital stay was defined as the number of days that each patient spent at the medical center.

In-Hospital Mortality: Patients who died during admission were recorded. Deaths that might have occurred after patient´s discharge were not measured as these data were not available for the investigators.

Statistical Methods

A descriptive analysis was carried out in patients with AP. The demographic variables among patients with or

without obesity were compared. We used the chi-square test for categorical variables with the Yates correction, the Fisher`s exact test for dichotomous variables when the expected value of a cell was less than 5, and Student´s t-test or ANOVA for quantitative variables. All the univariate analyses were accomplished after having adjusted for age and gender. The Odds-Ratios (OR) and 95% Confidence Intervals (CI) were estimated from the regression coefficients.

A multivariate logistic regression analysis was performed in order to determine the excess of mortality owing to obesity, after the correction of possible confounding variables such as the age of the patient (in years, as a continuous variable), Charlson index (in points, as a continuous variable), sex and all variables that had demonstrated a statistically significant relationship in the univariate analysis with mortality (alcohol, gallstones, diabetes, acute respiratory failure, and acute renal failure). A logistic regression analysis with backward stepwise procedure and p>0.10 as the criterion for exclusion was used to find the best predictive model. Stratified analyses were performed to examine confounders and interactions. All statistical analyses were carried out with the Statistical Package for the Social Sciences (SPSS, version 16, Chicago, Illinois, SPSS Inc).

RESULTS

Within the study period, 55285 episodes of AP were included in the analysis. The average age was 64.1 years (SD 18.87 18-108); 56.3% of the patients were men. The median hospital stay was 10.9 days (SD, 12.72; range 0-849). A CCI ≥ 2 was present in 18.0% of the cases. Overall, a total of 4594 (8.3%) subjects were obese. During admission 2844 (5.1%) patients died, 4478 (8.1%) were readmitted at least once within 30 days of the index date of admission with the same Major Diagnostic Category as the main diagnosis, and a high proportion of patients developed complications 10339 (18,7%). Overall, 27% of patients were admitted in small size centers (<200 beds), 40% in medium size (200-500), 18.5% in big size (500-1000) and 14.5% in hospitals with more than 1000 beds.

Obese patients were more frequently women (54.6% *vs*. 42.7%; *P* <0.001), younger (62.9 *vs*. 64.1 years; p<0.001) and there was a less proportion of alcoholic intake (6.8% *vs*. 8.6%; *P* <0.001) than in non-obese patients. Diabetes and gallstones were more frequently found in obese patients than in non-obese (34.3% *vs*. 17.8% and 40.3% *vs*. 33.8% respectively, *P*<0.001). CCI was higher in non-obese patients (2.4 *vs*. 1.7; *P* <0.001). The mortality among obese patients was 3.4% versus 5.3% in non-obese patients, the unadjusted mortality rate was 0.62 IC 95% 0.53-0.573 **(Table 1)**.

Obese patients presented more hypoglycemia (1.5% *vs*. 0.7% p<0.001) than non-obese during admission. Bronchoaspiration (0.8% *vs*. 0.4%; *P* <0.001), pneumonia (2.3% *vs*. 1.5%; *P* <0.001), decubitus ulcer (0.6% *vs*. 0.3%; *P* =0.02), sepsis (2.7% *vs*. 2.2%; *P*=0.04), shock (1.5% *vs*. 0.8%; *P* <0.001), malnutrition (1.7% *vs*. 0.7%; *P* <0.007) or thrombosis (0.7% *vs*. 0.2%; *P*=0.04) were less frequent in obese patients than in non-obese subjects **(Table 2)**. The total rate of complications was slightly superior in non-obese patients than in obese patients (18.7% *vs*. 18.2%; OR 1.03 IC95% 0.96-1.10; P =0.395), but there were no statistical differences. Similarly, the presence of severe AP was slightly superior in non-obese patients than in obese (11.17% *vs*. 10.3%; OR 0.915 IC 95% 0.829-1.010, p= 0.082), but there were no statistical differences.

The following complications were significantly associated with higher risk of mortality in the univariate analysis in all patients with AP: acute renal failure, acute respiratory failure, acidosis, bronchoaspiration, pneumonia, hypoglycemia, decubitus ulcer, urinary tract infection, deep venous thrombosis, sepsis or shock **(Table 3)**.

Multivariate logistic regression analysis was performed to further assess which variables were independently associated with a higher mortality risk during hospital stay in all patients with AP). Age, gender (male), CCI≥ 2 and the presence of "All complications" and Atlanta composite variable were independent predictive factors of mortality in patients with AP **(Table 4 and 5)**. Obesity was found to have a lower mortality risk (OR 0.72 IC 95% 0.61-0.86). Acute renal and respiratory failure as well as the presence of shock correlate with in-hospital mortality **(Table 6)**.

DISCUSSION

Our data from a large series of medical records of patients admitted with AP reveal that there is an inverse relationship between obesity and mortality. The results from the analysis of 55285 charts show that obesity is an independent prognostic factor for lower in-hospital

Table 1. Demographic characteristics of patients in the data base.

	Normal-weight (N=50691)	Obese (N=4594)	OR (IC95%)	p
Age, years (SD)	64.15 (19.03)	62.91 (17.04)	-	<0.001
Gender (men)	29025 (57.3%)	2084 (45.4%)	1.61 (1.52-1.71)	<0.001
Length of stay, days (SD)	10.97 (12.94)	10.53 (9.9)	-	0.006
Death	2689 (5.3%)	155 (3.4%)	0.62 (0.53-0.73)	<0.001
Readmission	4535 (8.9%)	41 (9%)	1.0 (0.9-1.12)	0.93
Alcohol	4366 (8.6%)	311 (6.8%)	0.77 (0.68-0.86)	<0.001
Diabetes	9011 (17.8%)	1578 (34.3%)	2.42 (2.26-2.58)	<0.001
Gallstones	17115 (33.8%)	1853 (40.3%)	1.32 (1.25-1.41)	<0.001
CCI≥2	4716 (9.3%)	396 (8.6%)	0.92 (0.83-1.02)	0.131

Table 2. Complications during admission in obese patients with AP compared with non-obese.

	Normal-weight (N=50591)	Obese (N=4594)	OR (IC95%)	P
Acute respiratory failure	1992 (3.9%)	186 (4.0%)	1.03 (0.88-1.20)	0.695
Acute renal failure	3191 (6.3%)	283 (6.2%)	0.97 (0.86-1.10)	0.748
Pneumonia	1158 (2.3%)	67 (1.5%)	0.63 (0.49-0.81)	<0.001
Bronchoaspiration	406 (0.8%)	17 (0.4%)	0.46 (0.28-0.74)	0.001
Hypoglycemia	372 (0.7%)	69 (1.5%)	2.06 (1.59-2.67)	<0.001
Decubitus ulcer	303 (0.6%)	15 (0.3%)	0.54 (0.32-0.92)	0.023
Urinary tract infection	2413 (4.8%)	221 (4.8%)	1.01 (0.87-1.16)	0.888
Thromboembolic disease	375 (0.7%)	22 (0.2%)	0.64 (0.42-0.99)	0.018
Sepsis	1388 (2.7%)	103 (2.2%)	0.81 (0.66-0.99)	0.048
Shock	751 (1.5%)	39 (0.8%)	0.56 (0.41-0.78)	<0.001
Gastrointestinal bleeding	859 (1.7%)	38 (0.8%)	0.48 (0.35-0.67)	<0.001
Malnutrition	877 (1.7%)	32 (0.7%)	0.39 (0.25-0.56)	<0.001
Any Complications	9502 (18.7%)	837 (18.2%)	0.96 (0.89-1.04)	0.395
Atlanta	5638 (11.1%)	472 (10.3%)	0.915 (0.82-1.01)	0.082

Table 3. Mortality risk factors in acute pancreatitis.

	Death (N=2844)	Non-death (N=52441)	OR (IC95%)	p
Gender (% male)	1281 (45%)	29828 (56.9%)	0.63 (0.59-0.68)	<0.001
Age, years (SD)	80.5 (12.3)	63.1 (18.75)		<0.001
Acute respiratory failure (%)	660 (23.2%)	1518 (2.9%)	10.1 (9.2-11.2)	<0.001
Acute renal failure (%)	833 (29.3)	2641 (5.0%)	7.8 (7.1-8.5)	<0.001
Acidosis (%)	220 (2.7%)	558 (1.1%)	7.8 (6.6-9.1)	<0.001
Bronchoaspiration (%)	165 (5.8%)	258 (0.5%)	12.4 (10.2-15.2)	<0.001
Pneumonia (%)	284 (10%)	941 (1.8%)	6.1 (5.3-6.9)	<0.001
Hypoglucemia (%)	38 (1.3%)	403 (0.8%)	1.75 (1.2-2.4)	<0.001
Decubitus ulcer (%)	79 (2.8%)	239 (0.5%)	6.24 (4.8-8.0)	<0.001
Urinary tract infection (%)	224 (7.9%)	2410 (4.0%)	1.77 (1.54-2.04)	<0.001
Thromboembolic disease (%)	53 (1.9%)	344 (0.7%)	2.87 (2.15-3.81)	<0.001
Sepsis (%)	496 (17.4%)	995 (1.9%)	10.9 (9.71-12.23)	<0.001
Shock (%)	329 (11.6%)	461 (0.9%)	14.7 (12.7-17.1)	<0.001
CCI≥2 (%)	728 (25.6%)	4384 (8.4%)	3.77 (3.44-4.12)	<0.001

Table 4. Multivariate analysis evaluating variables independently associated with in-hospital mortality in all patients with AP (composite variable "Any complications").

	OR	95% CI		P
Gender (male)	1,053	,967	1,148	,235
Age (10y)	1,896	1,831	1,964	,000
CCI>2	2,549	2,307	2,817	,000
Gallstone	,454	,414	,497	,000
Alcohol	,702	,531	,926	,012
Any complications	5,383	4,954	5,849	,000
Obesity	,723	,607	,863	,000

Table 5. Multivariate analysis evaluating variables independently associated with in-hospital mortality in all patients with AP (composite variable Atlanta).

	OR	95% CI		P
Gender (male)	1,126	1,033	1,228	,007
Age (10y)	1,932	1,865	2,002	,000
CCI>2	2,484	2,246	2,748	,000
Gallstone	,449	,410	,493	,000
Alcohol	,686	,519	,906	,008
Atlanta	6,208	5,705	6,757	,000
Obesity	,707	,593	,844	,000

mortality in subjects with AP and that this association remains significant when controlled for confounding factors. The mechanisms that might account for lower risk of death in obese patients affected by AP remain unknown. The fact that patients may be beneficially affected by obesity is known as "obesity paradox" or "reverse epidemiology". Some authors claim that obese patients may have a more aggressive medical treatment and a closer surveillance than normal-weight groups. Also, it has been suggested that some obese patients may be on more cardioprotective

Table 6. Multivariate analysis evaluating variables independently associated with in-hospital mortality in all patients with AP (separately displayed variables).

	OR	95% CI		P
Gender (male)	1,111	1,018	1,212	,019
Age (10y)	1,978	1,908	2,050	,000
CCI>2	2,720	2,457	3,011	,000
Gallstone	,442	,403	,485	,000
Alcohol	,739	,559	,977	,034
Acute renal failure	3,073	2,768	3,412	,000
Acute respiratory failure	4,579	4,073	5,148	,000
Gastrointestinal bleeding	,948	,653	1,374	,777
Shock	5,941	4,980	7,088	,000
Obesity	,716	,598	,857	,000

medical therapy than other groups. These factors may lead to the false impression that obesity has a protective effect in some clinical conditions.

As for the physiologic mechanisms that may account for the obesity paradox, most of them are merely conjectures. Biochemical changes in obese patients may partly explain this benefit. A greater mobilization of endothelial progenitor cells has been found in obese patients with less coronary atherosclerosis [19]. Cardiovascular protection of obese patients may also be mediated by a decreased production of thromboxane [20]. Also, among subjects with heart failure, obese patients exhibit lower concentration of tumor necrosis factor receptor and this may cause a better outcome [21].

Controversies remain as to whether the obesity paradox is related to age. Most of the studies that confirm the obesity paradox have recruited cohorts of elderly subjects. It has been demonstrated that accumulation of intra-abdominal fat is significantly greater at younger ages compared with older ages, regardless of sex and race [22]. Thus, if visceral adiposity decreases with age, then higher BMI due to peripheral fat stores may be responsible for the observed protective effect of obesity in elderly patients. In the present analysis, no waist circumference measures have been registered and therefore no information can be obtained regarding fat distribution. However, obese subjects were significantly younger than those non-obese, 62.9 *vs*. 64.1 years respectively. Thus, the obesity paradox in our cohort does not seem to be related to changes in adiposity distribution linked to aged individuals. Furthermore, the reduction of mortality in obese patients with AP persisted after multivariate adjustment, including age.

Literature review shows that there are no studies to directly examine the paradoxal obesity in patients with AP. The results of this analysis apparently contradict current wisdom on obesity as a risk factor for severity in AP. Earlier work suggests obesity as a risk factor for severe AP [2, 3, 4, 5]. Two meta-analysis have examined the association between BMI and AP prognosis [23, 24]: compared with normal weight individuals, obese patients (BMI > 30 kg/m^2) developed significantly more severe AP and had a significantly increased risk of death. However, the rates of obesity in the studies were significantly heterogeneous, varying from 8% to 57%, and, as is usually the case in any meta-analysis, there were wide methodological variations. In addition, the possibility of publication bias is of concern. Conversely, in another systematic review, obesity was not found to be an independent prognostic factor for mortality and organ failure in patients with AP [25].

In two prospective reports, several parameters were investigated in patients suffering from AP to assess its prognostic role. Thandassery *et al*. [26] found that dynamic multiple organ failure over the first week (measured by multiple organ failure scoring system MOFS), higher APACHE II score and infected necrosis were independent predictors of mortality. Similarly, Gloor *et al*. [27] reported that the only parameter that proved to be an independent risk factor for death among patients with AP was infection of pancreatic necrosis. In both studies, univariate analysis revealed that BMI was a negative risk factor. However, after multivariate analyses with a stepwise forward regression, obesity did not prove to be an independent risk factor for death.

In our analysis, advanced age has shown to be a risk factor for higher mortality. In many but not all reports [28], older age has correlated with a more severe prognosis [29]. Some authors state that older individuals have a poor outcome because of comorbid disease rather than old age itself [30]. We have separately analyzed the influence of age and comorbidity in the evolution of AP and logistic regression failed to show significant association. Thus, in agreement with previous literature [31], we conclude that, in this cohort, advanced age worsens prognosis irrespective the comorbid diseases. Unfavorable outcome in older individuals could be put down to the diminished physiological response typical of elderly patients.

As for the outcome of AP according to the main causes, to date, the influence of etiology on the severity of AP has not been clearly stablished and the results differ depending on the various studies reviewed. Some authors emphasize that etiology is not linked to poor outcome in AP [31, 32]. On the contrary, previous studies confirm a more severe presentation in alcoholic AP [33], while others claim that biliary AP correlates with worse prognosis [34]. In our study, both etiologies were significantly associated to lower in-hospital mortality. This finding could probably be linked to current improvements in antibiotic therapy,

endoscopic retrograde biliary drainage followed by endoscopic sphincterotomy and specific care in critical units. It seems to be accepted that once the pathogenic mechanism has initiated the disease, the course of AP is no longer linked the initial cause.

As previously accepted [1], the rate of in-hospital mortality in our analysis was higher in patients with Atlanta complications. When examined separately, acute renal and respiratory failure as well as the presence of shock, correlates with in-hospital mortality. However, digestive hemorrhage was not an independent prognostic factor of mortality probably due to the reduced number of patients presenting this complication.

The strengths of our study include the large nationwide population (more than 55000 patients) allowing statistically precise estimates of the relationship between obesity and mortality in patients with AP. Compared with previous studies this is a large population-based analysis with much greater numbers of patients and thus adequately powered to detect differences between both groups.

There are however certain caveats that may affect the results of this report. Firstly, the main limitation of our analyses is that it is a retrospective study of the Basic Minimum Data Set (BMDS) administrative database and therefore subject to information bias. This database is applied nationwide and allows clustering of patients in medical codes that describe procedures and assistance in hospital inpatients. Medical indexing International Classification of Diseases, Ninth Revision, Clinical Modification (CIE-9-CM) and Diagnosis Related Group (GRD) obtained from BMDS were initially intended to define different categories that were clinically similar and expected to use the same level of hospital resources, therefore medical codes can sometimes be inaccurate concerning severity in some clinical conditions. However, this classification system has long been accepted and used throughout many different countries in our environment. We fully agree on the accuracy of these data and we retrospectively focused on the information displayed in the database.

We have not adjusted for edematous or necrotizing pancreatitis, thus, weather there are many more obese patients with edematous pancreatitis cannot be rule out. The ICD-9-CM code describes three different groups of patients with pancreatitis, namely, acute (577.0), chronic (577.1) and mumps pancreatitis (072.3). ICD-9-CM code 577.0 applies to abscess of pancreas, necrosis (sterile or infected) of pancreas, edematous, hemorrhagic and suppurate pancreatitis. Based on ICD-9-CM 577.0, a "grouper" program assigns a DRG 204 to all patients with acute pancreatitis, irrespective of the presence of necrosis. Both 577.0 medical code and DRG 204 can thus indicate a wide range of severity within patients admitted with acute pancreatitis. Being aware of the possible limitations of the DRG classification system to account adequately for severity of acute pancreatitis, we included ICD-9-CM medical codes describing complications related to acute pancreatitis according to Atlanta classification system as well as other medical complications not included in Atlanta criteria. We believe that such conditions can provide a more accurate spectrum of severity and sometimes indirectly reflect a possible underlying pancreatic necrosis, left underdiagnosed otherwise by means of ICD-9-CM codes.

There has only been limited evaluation on how frequently obesity is captured in administrative databases or how accurately is captured. A recent study by Martin *et al*. to assess the validity of obesity coding in administrative database [35], confirmed that obesity was poorly coded, however, when coded it was coded accurately.

Previous studies show that the relationship between mortality and obesity in patients with AP is not linear. Patients who are overweight and moderately obese have lower mortality risk than those with either normal or low BMI and those who are morbidly obese [36]. This is consistent with the "U" shaped curve concept that may explain the obesity paradox. No categories of BMI have been registered in our study, thus no conclusions can be dropped as whether different BMI ranges are protective from mortality in AP while others might be associated with worse outcome.

Finally, it should be emphasized the fact that BMI does not discriminate centrally distributed adiposity in upper body from lower-body obesity, the former being associated with poor outcome. A recent cohort study using dual-energy x-ray absorptiometry (DEXA) scans to estimate percent body fat reveals that higher BMI is not associated with high body-fat percentage, which might help explain the obesity paradox observed in some studies [37]. Neither waist circumferences measures nor percent body fat have been recorded in the present study.

It is well known that obesity is related to an overall decrease in lifetime survival and it is an increasingly major hazard in many developing countries. The discussion of the existence of the obesity paradox cannot lead to the underestimation for obesity as a crucial risk factor for the development of some cardiovascular and metabolic diseases, which requires appropriate prevention and specific management strategies. The results of the present study cannot be extrapolated to the general population. However, in certain clinical settings, obesity could confer survival advantage over non-obese individuals after all confounding factors are assessed.

CONCLUSION

This study highlights the need for further prospective studies to be undertaken to determine the potential contribution of obesity as a protective factor in patients with AP.

Contribution Statement

RB designs the study and made statistical analysis; AG wrote the article; JM and SP were the reviewers; AZ and JC made the data interpretation and de final revision; MY made the statistical analysis with RB

Acknowledgments

The authors thank the Spanish Minister or Hearth for the permission to use of the data.

Conflict of Interest

There is no potential source of financial or relationship conflict of interest.

References

1. Banks PA, Freeman ML, Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. Am J Gastroenterol 2006; 101:2379-400. [PMID: 17032204]

2. Johnson CD, Toh SK, Campbell MJ. Combination of APACHE-II score and an obesity score (APACHE-O) for the prediction of severe acute pancreatitis. Pancreatology 2004; 4:1-6. [PMID: 14988652]

3. Suazo-Baráhona J, Carmona-Sánchez R, Robles-Díaz G, Milke-García P, Vargas-Voráckova F, Uscanga-Domínguez L, et al. Obesity: a risk factor for severe acute biliary and alcoholic pancreatitis. Am J Gastroenterol 1998; 93:1324-8. [PMID: 9707059]

4. Mentula P, Kylänpää ML, Kemppainen E, Puolakkainen P. Obesity correlates with early hyperglycemia in patients with acute pancreatitis who developed organ failure. Pancreas 2008; 36:e21-5. [PMID: 18192869]

5. Sempere L, Martinez J, de Madaria E, Lozano B, Sanchez-Paya J, Jover R, et al. Obesity and fat distribution imply a greater systemic inflammatory response and a worse prognosis in acute pancreatitis. Pancreatology 2008; 8:257-64. [PMID: 18497538]

6. Hall JE. The kidney, hypertension, and obesity. Hypertension 2003; 41:625-33. [PMID: 12623970]

7. Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. Annu Rev Med 2010; 61:301-16. [PMID: 19824817]

8. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med 2006; 355:763-78. [PMID: 16926275]

9. Curtis JP, Selter JG, Wang Y, Rathore SS, Jovin IS, Jadbabaie F, et al. The obesity paradox: body mass index and outcomes in patients with heart failure. Arch Intern Med 2005; 165:55-61. [PMID: 15642875]

10. Zapatero A, Barba R, Gonzalez N, et al. Influence of obesity and malnutrition on acute heart failure. Rev Esp Cardiol (Engl Ed) 2012; 65:421-6. [PMID: 22133785]

11. Zapatero A, Barba R, Ruiz J, et al. Malnutrition and obesity: influence in mortality and readmissions in chronic obstructive pulmonary disease patients. J Hum Nutr Diet 2013; 26 Suppl 1:16-22. [PMID: 23656492]

12. Mullen JT, Moorman DW, Davenport DL. The obesity paradox: body mass index and outcomes in patients undergoing nonbariatric general surgery. Ann Surg 2009; 250:166-72. [PMID: 19561456]

13. Hastie CE, Padmanabhan S, Slack R, Pell AC, Oldroyd KG, Flapan AD, et al. Obesity paradox in a cohort of 4880 consecutive patients undergoing percutaneous coronary intervention. Eur Heart J 2010; 31:222-6. [PMID: 19687163]

14. Davis PJ, Eltawil KM, Abu-Wasel B, Walsh MJ, Topp T, Molinari M, et al. Effect of obesity and decompressive laparotomy on mortality in acute pancreatitis requiring intensive care unit admission. World J Surg 2013; 37:318-32. [PMID: 23052814]

15. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013; 62:102-11. [PMID: 23100216]

16. Dellinger EP, Forsmark CE, Layer P, Lévy P, Maraví-Poma E, Petrov MS, et al. Determinant-based classification of acute pancreatitis severity: an international multidisciplinary consultation. Ann Surg 2012; 256:875-80. [PMID: 22735715]

17. Bradley EL. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. Arch Surg 1993; 128:586-90. [PMID: 8489394]

18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40:373-83. [PMID: 3558716]

19. Fadini GP, Boscaro E, de Kreutzenberg S, Agostini C, Seeger F, Dimmeler S, et al. Time course and mechanisms of circulating progenitor cell reduction in the natural history of type 2 diabetes. Diabetes Care 2010; 33:1097-102. [PMID: 20150295]

20. Graziani F, Biasucci LM, Cialdella P, Liuzzo G, Giubilato S, Della Bona R, et al. Thromboxane production in morbidly obese subjects. Am J Cardiol 2011; 107:1656-61. [PMID: 21439532]

21. Feldman AM, Combes A, Wagner D, Kadakomi T, Kubota T, Li YY, et al. The role of tumor necrosis factor in the pathophysiology of heart failure. J Am Coll Cardiol 2000; 35:537-44. [PMID: 10716453]

22. Lee CG, Fujimoto WY, Brunzell JD, Kahn SE, McNeely MJ, Leonetti DL, et al. Intra-abdominal fat accumulation is greatest at younger ages in Japanese-American adults. Diabetes Res Clin Pract 2010; 89:58-64. [PMID: 20392506]

23. Hong S, Qiwen B, Ying J, Wei A, Chaoyang T. Body mass index and the risk and prognosis of acute pancreatitis: a meta-analysis. Eur J Gastroenterol Hepatol 2011; 23:1136-43. [PMID: 21904207]

24. Martinez J, Jonhson CD, Sanchez-Paya J, de Madaria E, Robles-Díaz G, Pérez-Mateo M. Obestiy is a definitive risk factor of severity and mortality in acute pancreatitis: an updated Meta-analysis. Pancreatology 2006; 6: 206-9. [PMID: 16549939]

25. Premkumar R, Phillips AR, Petrov MS, Windsor JA. The clinical relevance of obesity in acute pancreatitis: targeted systematic reviews Pancreatology 2015; 15:25-33. [PMID: 25464938]

26. Thandassery RB, Yadav TD, Dutta U, Appasani S, Singh K, Kochhar R. Dynamic nature of organ failure in severe acute pancreatitis: the impact of persistent and deteriorating organ failure. HPB (Oxford) 2013; 15:523-8. [PMID: 23750495]

27. Gloor B, Müller CA, Worni M, Martignoni ME, Uhl W, Büchler MW. Late mortality in patients with severe acute pancreatitis. Br J Surg 2001; 88:975-9. [PMID: 11442530]

28. Kaya E, Dervisoglu A, Polat C. Evaluation of diagnostic findings and scoring systems in outcome prediction in acute pancreatitis. World J Gastroenterol 2007; 13:3090–4. [PMID: 17589925]

29. Company L, Saez J, Martinez J, Aparicio JR, Laveda R, Griñó P, et al. Factors predicting mortality in severe acute pancreatitis. Pancreatology 2003; 3:144–8. [PMID: 12748423]

30. Blum T, Maisonneuve P, Lowenfels AB, Lankisch PG. Fatal outcome in acute pancreatitis: its occurrence and early prediction. Pancreatology 2001; 1:237–41. [PMID: 12120201]

31. Gonzálvez-Gasch A, García de Casasola G, Barba Martín R, et al. A simple prognostic score for risk assessment in patients with acute pancreatitis. Eur J Intern Med 2009; 20:43–8. [PMID: 19393477]

32. Uhl W, Isenmann R, Curti G. Influence of etiology on the course and outcome of acute pancreatitis. Pancreas 1996; 13:335–343. [PMID: 8899793]

33. Cho J, Kim T, Kim S. Comparison of clinical course and outcome of acute pancreatitis according to the two main etiologies: alcohol and gallstone. BMC Gastroenterol 2015; 15:1-7. [PMID: 26209440]

34. Zheng Y, Zhou Z, Li H, Li J, Li A, Ma B, et al. A multicenter study on etiology of acute pancreatitis in Beijing during 5 years. Pancreas 2015; 44:409-14. [PMID: 25438072]

35. Martin BJ, Chen G, Graham M, Quan H. Coding of obesity in administrative hospital discharge abstract data: accuracy and impact for future research studies. BMC Health Serv Res 2014; 14:70. [PMID: 24524687]

36. Gupta R, Villa M, Agaba E, Ritter G, Sison C, Marini CP, et al. The effect of body mass index on the outcome of critically ill surgical patients. JPEN J Parenter Enteral Nutr 2013; 37:368-74. [PMID: 23019130]

37. Padwal R, Leslie WD, Lix LM, Majumdar SR. Relationship Among Body Fat Percentage, Body Index, and All-Cause Mortality: A Cohort Study. Ann Intern Med 2016; 164:532-41. [PMID: 26954388]