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Type 2 diabetes is associated with in-hospital complications in women undergoing breast cancer surgical procedures

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ABSTRACT

Objectives: To assess type 2 diabetes (T2DM) and age-matched non-diabetic women hospitalized with breast cancer and to compare the type of surgical procedures used, comorbidities, in-hospital complications (IHC), and in-hospital outcomes. We aimed to identify factors associated with in-hospital complications in women with T2DM who underwent breast cancer surgical procedures.

Design: Retrospective study using National Hospital Discharge Database, 2013–2014.

Setting: Spain.

Participants: Women who were ≥40 years old with a primary diagnosis of breast cancer and had undergone a surgical procedure. We grouped admissions by T2DM status. We selected one age-matched control for each T2DM case.

Main outcome measures: The type of procedure (breast-conserving surgery (BCS) or mastectomy), clinical characteristics, complications, length of hospital stay and in-hospital-mortality were analyzed.

Results: We identified 41,458 admissions (9.23% with T2DM). Overall, and in addition to the surgical procedure, we found that comorbidity, hypertension and obesity were more common in patients with T2DM. We detected a higher use of mastectomy in women with T2DM (44.69% vs. 42.42%) and the greater use of BCS in patients without T2DM (57.58% vs. 55.31%). Overall, non-infectious complications showed a higher incidence among women with T2DM (8.08% vs. 6.12%). Among women who had undergone BCS, IHC were more frequent in those suffering diabetes (6.38% vs. 4.49%), and were equivalent for those who had received a mastectomy (11.99% vs. 10.04%). Comorbidity and obesity were significantly associated with a higher risk of IHC in women with diabetes independent of the procedure that was used.

Conclusions: Women with T2DM who undergo breast cancer surgical procedures have more comorbidity, risk factors and advanced cancer presentation than in similar non-T2DM patients. Mastectomy is more frequently used in diabetic women. Moreover, the procedures in women with T2DM were associated with more IHC. Comorbidity and obesity were strong predictors of IHC in women with T2DM.

Strengths and limitations of this study

- The strengths of our study lies its large simple size, standardized methodology, and use of age- and province-matched non-T2DM patients to control for the confounding effects of these variables.
- A limitation is the lack of information on chemotherapy or radiotherapy treatments prior to surgery, which may have affected our outcome variables.
- We lacked data such as breast cancer characteristics or time since diagnosis.

INTRODUCTION

Breast cancer is the most common type of cancer in women. [1] Recently, the Global Burden of Disease Cancer Collaboration reported that the incidence of breast cancer between 2005 and 2015 in Western Europe increased by 24%, from 100.6 to 124.7 cases per 100,000 individuals. Breast cancer was also the leading cause of cancer-related deaths in women. [1]

Breast-conserving surgery (BCS) and mastectomy remains the current therapeutic approach for breast cancer. Recently, the use of BCS has increased and become the primary surgical treatment for breast cancer. [2,3] In Spain, over 80% of women diagnosed with breast cancer underwent surgery, and among these patients, nearly 75% received BCS. [3] However, recent studies have shown an increased number of mastectomies in women candidates for BCS because of the rise of more cosmetically appealing techniques. [4]

Recently, a report using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database to study 30-day complication rates after breast operations concluded that BCS and mastectomy with implant reconstruction have low overall complication rates. Additionally, BCS in early stage breast cancer was associated with fewer overall early postoperative complications compared with mastectomy [OR 2.8; 95%CI 2.2–3.5, $p<0.01$]. [5]

Diabetes is a predictor associated with postoperative complications in women who undergo surgical procedures for breast cancer. [5-7] In women with early-stage breast cancer, diabetes has been found to be a risk factor for overall postoperative complications (OR 1.8; 95%CI 1.02–3.4, $p=0.04$). [5] De Blacam et al., using the NSQIP database, reported that independent risk factors for the development of infection of any wound in patients undergoing mastectomy included a high body mass index, smoking, and diabetes. [7]

To the best of our knowledge, no previous studies have investigated factors associated with in-hospital complications in women with diabetes undergoing breast cancer-related surgical procedures.

Using the Spanish national hospital discharge database for 2013–2014, we aim in this study to i) compare variables between type 2 diabetes (T2DM) and age-matched non-diabetes women hospitalized with breast cancer who underwent a surgical procedure, including the type of surgical procedure used (BCS or mastectomy), patient comorbidities, in-hospital complications and in-hospital outcomes (length of hospital stay and in-hospital mortality); and ii) identify factors associated with in-hospital complications in women with T2DM who underwent breast cancer surgical procedures.

METHODS

We performed a retrospective, observational study using the Spanish National Hospital Discharge Database (*Conjunto Mínimo Básico de Datos*, CMBD), which is managed by the Spanish Ministry of Health, Social Services and Equality (MHSSE) and compiles all public and private hospital data, which covers more than 98% of hospital admissions. [8] The CMBD includes patient variables (sex and date of birth), admission and discharge dates, and up to 14 diagnoses at discharge and up to 20 procedures performed during the hospital stay.

We analyzed data collected between January 1, 2013 and December 31, 2014 for women with and without T2DM who were aged 40 and over. In both groups, we selected patients with a primary diagnosis of breast cancer (ICD-9-MC codes: 174.0-174.9) and whose medical procedures included BCS (ICD-9-MC codes: 85.20-85.25) and/or mastectomy (ICD-9-MC codes: 85.41-85.48) in any procedure field of the database. If both types of procedures were recorded, that case was excluded.

We identified 41,458 admissions with breast cancer who underwent surgical procedures in 2013 and 2014 in Spain. Among those admissions, 3,882 (9.23%) had T2DM. Patients who underwent breast cancer surgical procedures in the non-diabetes group were selected to create a control group. Cases were matched with controls by age and province of residence; if more than one control was available for a case, the selection was conducted randomly. Ultimately, we identified 3,826 pairs of women.

In a second phase, to compare outcomes according to the type of procedure, we repeated the process and selected one non-diabetic woman (matched by age and province of residence) for each of 2,116 T2DM women who underwent BCS. We also selected 1,623 matched couples who underwent mastectomy. Clinical characteristics included data on overall comorbidities at the time of diagnosis, which were assessed by calculating the Charlson comorbidity index (CCI) and excluding cancer and diabetes as diseases. [9] We divided patients into three categories: CCI0, which corresponds to patients with no previously recorded disease; CCI1, patients with one disease category; and CCI≥2, patients with two or more disease categories.

We retrieved data about specific comorbidities, including acute myocardial infarction, congestive heart failure, renal disease, stroke/TIA/TEP and vascular disease, as described by Quan et al. and that were applied to ICD-9-CM. [10]

Tumor stage was classified as local (within the breast), regional (affecting the lymph nodes—primarily those in the armpit and/or upper arm) or distant (in other parts of the body) according to Escribà et al. using the enhanced ICD-9-CM. [3]

Specific risk factors considered in the data analysis included obesity (ICD-9-CM code: 278.xx), hypertension (ICD-9-CM codes: 401; 401.0; 401.1; 401.9) and current smoking (ICD-9-CM codes: 305.1;V15.82) recorded during hospitalization for breast cancer in any diagnostic position.

Additionally, we specifically recorded the following procedures: sentinel lymph node dissection (ICD-9-CM codes: 40.11; 40.19; 40.23) and axillary lymph node dissection (ICD-9-MC codes: 40.3; 40.50; 40.51).

Irrespective of the position at diagnoses or the procedure coding list, we retrieved data about in-hospital "infectious complications," such as pneumonia (ICD-9-CM codes: 997.39,480-488;507.0-507.8), sepsis (ICD-9-CM codes: 995.91, 995.92) and surgical site infection (breast specific infection, ICD-9-CM codes 611.0; postoperative infection, ICD-9-CM codes 998.5-998.59; cellulitis, ICD-9-CM codes 682.2, 682.9; Staphylococcus aureus, ICD-9-CM codes 041.1-041.19; incision/drainage, ICD-9-CM codes 85.0, 85.91. 83.44-83.49, 86.01, 86.04, 86.09, 86.22, 86.28). Additionally, we noted "non-infectious complications" after surgery that included postoperative hemorrhage/hematoma (ICD-9-CM codes 998.11, 998.12), fat necrosis (ICD-9-CM codes 567.82, 611.3), dehiscence (ICD-9-CM codes 875.0, 875.1, 879.0, 879.1, 998.3, 998.32) and necrosis (ICD-9-CM codes 998.83).

Hospital outcome variables included length of hospital stay (LOHS) and in-hospital mortality (IHM), which was defined as the proportion of patients who died during the admission.

Statistical analysis

A descriptive statistical analysis was performed for all continuous variables and categories by stratifying admissions for breast cancer according to diabetes status. Variables were expressed as proportions, either as the means with standard deviations or medians with interquartile ranges (LOHS). We performed bivariate conditional logistic regression models to compare the prevalence of clinical characteristics, risk factors, comorbidities, procedures, complications and in-hospital outcomes between T2DM patients and controls. The analysis was conducted for the entire sample and stratified according to the procedure type (i.e., BCS or mastectomy).

To identify variables associated with in-hospital complications among patients after breast cancer surgical procedures and T2DM, we performed a logistic regression analysis with any complication (infectious or non-infectious) as a binary outcome variable. Finally, we performed two logistic regression analyses to specifically identify variables associated with complications among patients suffering from diabetes who underwent BCS and mastectomy. Variables included in these models were those with significant results in the bivariate analysis and those considered relevant in other investigations. Estimates were described as an odds ratio (OR) with associated 95% confidence intervals.

Matching of cases with controls and all statistical analyses were performed using Stata version 10.1 (Stata, College Station, TX, USA). Statistical significance was set at $p<0.05$ (two-tailed).

Ethical aspects

Data confidentiality was maintained at all times in accordance with Spanish regulations. Given the anonymous and mandatory nature of the dataset, it was not deemed necessary to obtain informed consent. The study protocol was approved by the ethics committee of the Universidad Rey Juan Carlos.

RESULTS

Before matching was conducted, women with T2DM (3,882) were significantly older (70.66±10.24 vs. 60.2±12.71 years; p<0.001) than women without T2DM (37,576).

Table 1 shows the characteristics of hospital admissions for breast cancer patients who underwent a surgical procedure among women with T2DM and age-matched non-T2DM controls.

When we compared women with T2DM with matched controls, we found that patients with diabetes had more coexisting medical conditions according to the CCI ($p<0.001$). Specifically, T2DM women had a higher prevalence of vascular disease (8.86% vs. 6.51%), renal disease (4.10% vs. 1.49%), stroke (2.51% vs. 1.73%), congestive heart failure (2.01% vs. 1.05%) and acute myocardial infarction (0.99% vs. 0.42%). Additionally, the prevalence of hypertension (65.58% vs. 37.74%) and obesity (13.15% vs. 3.76%) were higher in T2DM patients.

In contrast, we found that a local tumor stage of the disease was more prevalent in non-T2DM women than in those with T2DM (73.86% vs. 71.33%; $p=0.020$).

Regarding the procedures that we analyzed, significant differences ($p=0.04$) were detected, with a higher use of mastectomy in women with T2DM compared with non-diabetic women (44.69% vs. 42.42%, $p<0.05$) and a greater use of BCS in patients without T2DM (57.58% vs. 55.31%).

As shown in Table 1, all types of in-hospital complications were more frequent among women with T2DM (8.89%) than in women without diabetes (6.85%; $p<0.05$). When the types of complication were analyzed, only non-infectious complications showed significant differences (8.08% vs. 6.12%).

Median LOHS and IHM values did not differ between diabetic and non-diabetic women.

Table 1. Clinical characteristics, type of surgical procedure, complications and hospital outcomes of hospital admissions for breast cancer among women suffering type 2 diabetes and age-matched non-type 2 diabetes controls.

	Both groups (n=7,652)		p-value
Age, mean (SD)	70.66 (10.24)		NA
40-59 years old, n (%)	547 (14.30)		
60-79 years old, n (%)	2435 (63.64)		
≥ 80 years old, n (%)	844 (22.06)		NA
	Diabetes (n=3,826)	No Diabetes (n=3,826)	
CCI0, n (%)	3119 (81.52)	3391(88.63)	
CCI1, n (%)	591 (15.45)	376 (9.83)	
CCI≥2, n (%)	116 (3.03)	59 (1.54)	<0.001
Vascular disease, n (%)	339 (8.86)	249(6.51)	<0.001
Renal disease, n (%)	157 (4.10)	57 (1.49)	<0.001
Stroke/TIA/TEP, n (%)	96 (2.51)	66 (1.73)	0.017
Congestive heart failure, n (%)	77 (2.01)	40 (1.05)	0.001
Acute myocardial infarction, n (%)	38 (0.99)	16 (0.42)	0.003
Obesity, n (%)	503 (13.15)	144 (3.76)	<0.001
Hypertension, n (%)	2509 (65.58)	1444 (37.74)	<0.001
Smoking, n (%)	183 (4.78)	213 (5.57)	0.112
Stage: Local, n(%)	2729 (71.33)	2826 (73.86)	
Stage: Regional, n(%)	986 (25.77)	896 (23.42)	
Stage: Distant, n (%)	111 (2.90)	104 (2.72)	0.020
Breast conservative surgical procedure, n (%)	2116 (55.31)	2203(57.58)	
Breast radical surgical procedure, n (%)	1710 (44.69)	1623 (42.42)	0.040
Infectious complications, n (%)	114 (2.98)	87 (2.27)	0.212
Non infectious complications, n (%)	309 (8.08)	234(6.12)	0.001
All complications (infectious and/or non infectious), n (%)	340 (8.89)	262 (6.85)	0.001
Length of stay, median (IQR)	3 (2-5)	3 (2-5)	0.070
In-hospital mortality, n (%)	6 (0.16)	1 (0.03)	0.097

CCI: Charlson Comorbidity Index. IQR: Interquartile range. P value for difference between T2DM sufferers and matched controls using bivariate conditional logistic regression.

Table 2 shows the characteristics of hospital admissions after BCS procedures in women suffering from T2DM and procedure- and age-matched non-T2DM controls.

Women with diabetes who underwent BCS were significantly younger than those who underwent a mastectomy (68.72 vs. 72.97 years; p<0.001).

Among those women who underwent a BSC, those with T2DM had higher frequencies of comorbidities according to the CCI compared with matched controls (p<0.001). Vascular disease, renal disease, acute myocardial infarction, obesity and hypertension were significantly more prevalent in patients with diabetes than in matched controls.

As shown in Table 2, we found a significantly lower use of sentinel lymph node dissection in T2DM patients compared with controls (62.62% vs. 66.18%).

Women with T2DM had a higher prevalence of all in-hospital complications (infectious and/or non-infectious) compared to those without diabetes (6.38% vs. 4.49%, respectively, p=0.006) and also for non-infectious complications alone (5.77% vs. 4.22%).

Table 2. Clinical characteristics, complications and hospital outcomes of hospital admissions for breast cancer among women suffering type 2 diabetes who underwent a breast conservative surgical procedure and procedure-age-matched non-type 2 diabetes controls

	Both groups (n=4,232)		p-value
Age, mean (SD)	68.72 (9.69)		NA
40-59 years old, n (%)	356 (16.82)		
59-79 years old, n (%)	1440 (68.05)		
≥ 80 years old, n (%)	320 (15.12)		NA
	Diabetes (n=2,116)	No Diabetes (n=2,116)	
CCI0, n (%)	1771(83.70)	1909 (90.24)	
CCI1, n (%)	299 (14.13)	182 (8.62)	
CCI≥2, n (%)	46 (2.17)	24 (1.14)	<0.001
Vascular disease, n(%)	175 (8.27)	112(5.31)	<0.001
Renal disease, n(%)	67 (3.17)	29 (1.36)	<0.001
Acute myocardial infarction, n (%)	25 (1.18)	6 (0.27)	<0.001
Stroke/TIA/TEP, n(%)	37 (1.75)	23 (1.09)	0.066
Congestive heart failure, n(%)	22 (1.04)	15 (0.73)	0.270
Hypertension, n (%)	1387 (65.55)	745 (35.22)	<0.001
Obesity, n (%)	288 (13.61)	82 (3.86)	<0.001
Smoking, n (%)	118 (5.58)	131 (6.17)	0.405
Stage: Local, n(%)	1622 (76.65)	1674 (79.12)	
Stage: Regional, n(%)	459 (21.69)	412 (19.47)	
Stage: Distant, n (%)	35 (1.65)	30 (1.41)	0.145
Sentinel lymph node dissection, n (%)	1325 (62.62)	1400 (66.18)	0.014
Axillary lymph node dissection, n (%)	443 (20.94)	397 (18.75)	0.071
Infectious complications, n (%)	39 (1.84)	25 (1.18)	0.074
Non infectious complications, n(%)	122 (5.77)	89 (4.22)	0.020
All complications (infectious and/or non infectious), n (%)	135 (6.38)	95 (4.49)	0.006
Length of stay, median (IQR)	2 (1-3)	2 (1-3)	0.062
In-hospital mortality, n (%)	2 (0.09)	0 (0.00)	0.149

CCI: Charlson Comorbidity Index. IQR: Interquartile range. P value for difference between T2DM sufferers and matched controls using bivariate conditional logistic regression.

Results obtained when we compared patients with T2DM who underwent mastectomy with age-matched controls who received this same procedure are shown in Table 3. Women with T2DM had more coexisting medical conditions according to the CCI and a higher prevalence of renal disease, congestive heart failure, obesity and hypertension than women without diabetes. Additionally, women with T2DM had a higher prevalence of in-hospital complications (infectious and/or non-infectious) that those without diabetes (11.99% vs. 10.04%, respectively; p=0.023). According to the type of complications, differences were only significant for non-infectious complications (10.94% vs. 8.69%; p=0.029).

Table 3. Clinical characteristics, complications and hospital outcomes of hospital admissions for breast cancer among women suffering type 2 diabetes who underwent a mastectomy and procedure-age-matched non-type 2 diabetes controls

	Both groups (n=3,246)		p-value
Age, mean (SD)	72.97 (10.64)		NA
40-59 years old, n (%)	184 (11.34)		
60-79 years old, n (%)	923 (56.87)		
≥ 80 years old, n (%)	516 (31.79)		NA
	Diabetes (n=1,623)	No Diabetes (n=1,623)	
CCI0, n (%)	1279 (78.83)	1403 (86.44)	
CCI1, n (%)	277 (17.08)	186 (11.46)	
CCI≥2, n (%)	66 (4.09)	34 (2.1)	<0.001
Renal disease, n(%)	85(5.26)	27(1.66)	<0.001
Congestive heart failure, n(%)	52 (3.22)	24(1.48)	0.001
Vascular disease, n(%)	156(9.59)	132(8.13)	0.139
Stroke/TIA/TEP, n(%)	56(3.45)	42(2.59)	0.147
Acute myocardial infarction, n (%)	12 (0.76)	10 (0.62)	0.615
Obesity, n (%)	204 (12.57)	59 (3.64)	<0.001
Hypertension, n (%)	1065 (65.61)	668 (41.16)	<0.001
Smoking, n (%)	62 (3.80)	77 (4.74)	0.178
Stage: Local, n(%)	1051 (64.74)	1083 (66.73)	
Stage: Regional, n(%)	500 (30.82)	467 (28.77)	
Stage: Distant, n (%)	72 (4.44)	73 (4.50)	0.433
Sentinel lymph node dissection, n (%)	544 (33.51)	586 (36.11)	0.116
Axillary lymph node dissection, n (%)	199 (12.28)	183 (11.28)	0.368
Infectious complications, n (%)	71 (4.39)	61 (3.76)	0.360
Non infectious complications, n(%)	177(10.94)	141(8.69)	0.029
All complications (infectious and/or non infectious), n (%)	195(11.99)	163 (10.04)	0.023
Length of stay, median (IQR)	4(3-6)	4(3-6)	0.074
In-hospital mortality, n (%)	4(0.23)	1 (0.06)	0.199

CCI: Charlson Comorbidity Index. IQR: Interquartile range. P value for difference between T2DM sufferers and matched controls using bivariate conditional logistic regression.

Table 4 shows the results of logistic regression analyses to assess those factors associated with in-hospital complications in patients with T2DM during hospital admission for breast cancer who underwent any breast surgical procedures and specifically according to the type of procedure. Among T2DM women with breast cancer and after any surgical procedure (i.e., conservative or mastectomy), comorbidity (OR 1.55, 95%CI 1.29–1.86) and obesity (OR 1.55, 95%CI 1.15–2.08) were the factors most strongly associated with a higher rate of in-hospital complications. These two factors also increased the risk of in-hospital complications for women who underwent BCS or mastectomy.

Table 4. Logistic regression analysis of the factor associated with in-hospital complications in women with type 2 diabetes during hospital admission for breast cancer and after any breast surgical procedures and according to the type of surgical procudure.

		OR (95%CI)
		Any breast cancer surgical procedure (Conservative or mastectomy)
Age groups, years	40-59	1
	60-79	0.98 (0.70-1.38)
	≥ 80	1.17 (0.79-1.72)
CCI, mean		1.55 (1.29-1.86)
Stage	Distant	1.21 (0.98-1.48)
Obesity	Yes	1.55 (1.15-2.08)
		Breast Conservative Surgery
Age groups, years	40-59	1
	60-79	0.79 (0.50-1.26)
	≥ 80	0.92 (0.50-1.67)
CCI, mean		1.71 (1.26-2.33)
Obesity	Yes	1.68 (1.08-2.61)
		Mastectomy
Age groups, years	40-59	1
	60-79	1.12 (0.67-1.87)
	≥ 80	1.21 (0.70-2.08)
CCI, mean		1.43 (1.14-1.80)
Obesity	Yes	1.48 (1.01-2.25)

CCI: Charlson Comorbidity Index. OR: Odds Ratio. 95%CI: 95% confidence intervals. Only those variables that showed a significant association are showed.

DISCUSSION

T2DM is considered to be a common comorbidity that is present in many breast cancer patients and correlates with poor clinical outcomes. [11,12] According to information obtained from the CMBD, compared with nondiabetic counterparts, women with T2DM undergoing breast cancer surgical procedures had more risk factors, comorbidities and advanced cancer presentations.

Several studies have reported that the presence of risk factors, such as hypertension and obesity, are common in both diabetes and breast cancer patients. [13,14] A recent meta-analysis that included 82 follow-up studies confirms the associations of obesity with an unfavorable overall and breast cancer survival rate in pre- and post-menopausal breast cancer. [15] Several hypotheses have been proposed to explain the poorer survival outcomes observed with increasing body mass index. [16] Obese patients may undergo less mammographic screening, and increased breast adiposity may delay tumor detection and diagnosis until the tumors grow larger. [17,18] Another possibility is that obese patients were undertreated compared to normal weight patients. [19]

In our present study, women with T2DM were significantly more likely to present with advanced-stage breast cancer compared with those women without diabetes. Our findings are consistent with other studies that demonstrated a more advanced stage of breast cancer among women with diabetes. [20, 21] A study conducted in Canada showed that diabetes was associated with more advanced-stage breast cancer, even after accounting for differences in screening mammogram use and other factors. [22] There are several possible explanations for this association, including that mammograms are less sensitive for the detection of early lesions in women with T2DM because of higher rates of obesity. [23] Finally, tumors may progress more rapidly in patients with diabetes, or diabetes may lead to a higher metastatic potential. [24]

We observed that mastectomy is more frequently used in diabetic women, which could be explained by several factors, including higher comorbidity, higher stage disease at diagnosis, the presence of more biologically aggressive tumors and that diabetes is an important risk factor for breast cancer recurrence. [3, 24] Kaplan et al. examined 483 breast cancer patients who had undergone a mastectomy that was completed between 1998 and 2010. They concluded that the recurrence of breast cancer was significantly increased in patients with diabetes (OR, 2.21; 95%CI 1.23–3.96; p=0.008). [25]

As expected, we observed that in-hospital mortality and complication rates in breast cancer surgery were low. This finding is consistent with de Blacam et al., who found in a multi-institutional study of patients undergoing mastectomy and BCS reported in the US that the overall 30-day morbidity rate was 5.6% for all procedures. [7]

We found that women with T2DM who underwent breast cancer surgical procedures had a higher frequency of overall in-hospital complications compared with those women without diabetes. Several studies have reported that diabetes is a risk factor for surgical site infections after breast operations. [7] A systematic review/meta-analysis concluded that patients with diabetes were more vulnerable to surgical site infections after breast cancer surgery (OR 1.88, 95%CI 1.47–2.39). [26]

In our present study, comorbidity was a strong predictor of in-hospital complications in women with T2DM who underwent surgical breast cancer-related procedures. Dehale et al. studied the impact of comorbidity using hospital discharge data from the "Health Care Utilization Project: Nationwide In-patient Sample" database in women with a primary diagnosis of breast cancer after undergoing breast surgery. Compared with patients without a comorbidity, they found that women with a severe (CCI score ≥3) comorbidity were 4.6-times more likely to develop a postoperative complication. [27]

Obesity was associated with an increased risk of surgical site infection, in accord with previous reports. [6] In our present study, obesity was a predictor of IHC in women with diabetes who underwent BCS and mastectomy. Overweight or obesity have been associated with higher rates of treatment-related sequelae, such as lymphedema, fatigue and arthralgia. [28] Helyer et al. concluded that obesity is a risk factor for the development of postoperative lymphedema in breast cancer patients (OR 1.8; 95%CI, 1.0004–1.165). [29] Excess adiposity may increase the risk of lymphedema by driving increased inflammation, adding stress to the lymphatic system, or slowing post-surgical healing times. [30]

The strengths of our study included its large simple size, standardized methodology, and use of age- and province-matched non-T2DM patients to control for the confounding effects of these variables. However, our study had several limitations. First, the database was designed for administrative rather than research purposes, and conditions such as infection, hypertension, obesity and smoking may not have been adequately recorded in the database. [8]

Second, the database that we used contained no information about chemotherapy or radiotherapy treatments prior to surgery, which may have affected our outcome variables.

Finally, we lacked data such as breast cancer characteristics or time since diagnosis.

CONCLUSIONS

We conclude that women with T2DM who undergo surgical procedures to treat breast cancer have more comorbidity, risk factors and advanced cancer presentation than non-T2DM patients. Mastectomy is more frequently performed in diabetic women. Moreover, procedures carried out in women with T2DM were associated with more in-hospital complications. Finally, comorbidity and obesity were strong predictors of in-hospital complications in women with T2DM.

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CONTRIBUTIONS

Ana López-de-Andres and Rodrigo Jiménez-Garcia participated in the conception and design, analysis, interpretation, and writing of the article. Valentín Hernández-Barrera and Isabel Jiménez-Trujillo contributed their statistical expertise and towards conception and design, interpretation and writing of the article. Javier de Miguel-Díez, Manuel Méndez-Bailón, José M de Miguel-Yanes, Napoleón Pérez-Farinós, Miguel-Angel Salinero-Fort, José L del Barrio and Martin Romero-Maroto were involved in the critical revision of the article, interpretation and design. All authors have seen and approved the final version.

COMPETING INTERESTS

The authors declare that they have no competing interests.

DATA SHARING STATEMENT

"No additional data available"

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	*6-8*
Study size	10	Explain how the study size was arrived at	6-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	8,9
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-17
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-17
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	9-17
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-17
		(*b*) Report category boundaries when continuous variables were categorized	9-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	18-20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20,21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

The effect of Type 2 diabetes on in-hospital complications among women undergoing breast cancer surgical procedures. A retrospective study using the Spanish National Hospital Discharge Database, 2013–2014.

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	Type 2 diabetes, Breast cancer, mastectomy, breast-conserving surgery, complications, hospitalizations

The effect of Type 2 diabetes on in-hospital complications among women undergoing breast cancer surgical procedures. A retrospective study using the Spanish National Hospital Discharge Database, 2013–2014.

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Key Words: Type 2 diabetes; breast cancer; mastectomy; breast-conserving surgery; complications; hospitalizations

Word count: 3447

ABSTRACT

Objectives: To compare the type of surgical procedures used, comorbidities, in-hospital complications (IHC), and in-hospital outcomes between women with type 2 diabetes (T2DM) and age-matched women without diabetes who were hospitalized with breast cancer. In addition we sought to identify factors associated with IHC in women with T2DM who had undergone surgical procedures for breast cancer.

Design: Retrospective study using the National Hospital Discharge Database, 2013–2014.

Setting: Spain.

Participants: Women who were ≥40 years old with a primary diagnosis of breast cancer and who had undergone a surgical procedure. We grouped admissions by T2DM status. We selected one matched control for each T2DM case.

Main outcome measures: The type of procedure (breast-conserving surgery (BCS) or mastectomy), clinical characteristics, complications, length of hospital stay and in-hospital-mortality.

Results: We identified 41,458 admissions (9.23% with T2DM). Overall, and in addition to the surgical procedure, we found that comorbidity, hypertension and obesity were more common among patients with T2DM. We also detected a higher incidence of mastectomy in women with T2DM (44.69% vs. 42.42%) and a greater rate of BCS in patients without T2DM (57.58% vs. 55.31%). Overall, non-infectious complications were more common among women with T2DM (6.40% vs. 4.56%). Among women who had undergone BCS or a mastectomy, IHC were more frequent among diabetics (5.57% vs. 3.04% and 10.60% vs. 8.24%, respectively). Comorbidity was significantly associated with a higher risk of IHC in women with diabetes, independent of the specific procedure used.

Conclusions: Women with T2DM who undergo surgical breast cancer procedures have more comorbidity, risk factors and advanced cancer presentations than matched patients without T2DM. Mastectomies are more common in women with T2DM. Moreover, the procedures among women with T2DM were associated with greater IHC. Comorbidity was a strong predictor of IHC in women with T2DM.

Strengths and limitations of this study

- The strengths of our study include the large sample size, the standardized methodology, and the use of age- province- surgical procedure and stage-matched women without T2DM to control for the confounding effects of these variables.
- A limitation of this study is the lack of information on chemotherapy or radiotherapy treatments prior to surgery, which may have affected our outcome variables.
- We lacked data such as specific breast cancer characteristics or accurate time frames since diagnosis.
- The effect of obesity on in-hospital complications must be interpreted with caution for the possible existence of a codification bias.

INTRODUCTION

Breast cancer is the most common type of cancer in women. [1] Recently, the Global Burden of Disease Cancer Collaboration reported that the incidence of breast cancer between 2005 and 2015 in Western Europe increased by 24%, from 100.6 to 124.7 cases per 100,000 individuals. Breast cancer was also the leading cause of cancer-related deaths in women. [1]

Breast-conserving surgery (BCS) and mastectomy still represent the current therapeutic approach for breast cancer. Recently, the use of BCS has increased and become the primary surgical treatment for breast cancer. [2,3] In Spain, over 80% of women diagnosed with breast cancer underwent surgery and, among these patients, nearly 75% received BCS. [3] However, recent studies have shown an increased number of mastectomies in women who are candidates for BCS because of the rise of more cosmetically appealing techniques. [4]

The Spanish Health Care System is public and offers universal coverage with no out-of-pocket expenses for patients.

Recently, a report using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database to study 30-day complication rates after breast operations concluded that, overall, BCS and mastectomy with implant reconstruction have low complication rates. Additionally, BCS in early stage breast cancer was associated with fewer overall early postoperative complications when compared with mastectomy [OR 2.8; 95%CI 2.2–3.5, $p<0.01$]. [5]

Diabetes is a predictor associated with postoperative complications in women who undergo surgical procedures for breast cancer. [5-7] In women with early-stage breast cancer, diabetes has been found to be a risk factor for overall postoperative complications (OR 1.8; 95%CI 1.02–3.4, $p=0.04$). [5] De Blacam et al., using the NSQIP database, reported that independent risk factors for the development of an infection of any surgical wound caused by a mastectomy included a high body mass index, smoking, and diabetes. [7]

To the best of our knowledge, no previous studies have investigated factors associated with in-hospital complications among women with diabetes undergoing breast cancer-related surgical procedures.

Using the Spanish national hospital discharge database (SNHDD) for 2013–2014, we aim in this study to i) compare variables between type 2 diabetes (T2DM) and matched women without diabetes hospitalized with breast cancer who underwent a surgical procedure, including the type of surgical procedure used (BCS or mastectomy), patient comorbidities, in-hospital complications and in-hospital outcomes (length of hospital stay and in-hospital mortality); and ii) identify factors associated with in-hospital complications in women with T2DM who underwent breast cancer surgical procedures.

METHODS

We performed a retrospective, observational study using the SNHDD, which is managed by the Spanish Ministry of Health, Social Services and Equality (MHSSE) and compiles all public and private hospital data covering more than 98% of hospital admissions. [8]

The SNHDD was implemented in 1987. According to Spanish legislation, all public and private Spanish hospitals must periodically submit data to the health authorities regarding those patients who have been hospitalized for at least 24 hours. The information required includes patient's characteristics such as their clinical history number, personal ID number, date of birth, sex, country of birth and address. Clinical variables include: admission and discharge dates, up to 14 diagnoses at discharge and up to 20 procedures performed during the hospital stay. The primary/main diagnosis is defined as the condition which, after proper investigation, is considered the reason why the patient was admitted to the hospital. The secondary diagnosis includes those diseases or risk factors that coexist with the primary diagnosis at the time of admission or were detected during the hospitalization and that, in the opinion of the treating physician, may have affected the patient's progress or treatment plan.

Procedures include those diagnostic or therapeutic procedures conducted during hospitalization. Information on the service where the patient has received care and the type of discharge (home, decease, voluntary discharge, other hospital, and social institution) is also collected.

All patients discharged from the hospital must have a discharge report signed by the physician discharging the patient that includes the above noted information. The Codification Unit of the hospital uses this discharge report and any additional information required by the hospital databases to complete the SNHDD. The database uses the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) for coding.

The Spanish Ministry of Health conducts regular audits to assess the accuracy of the SNHDD [8, 9]. Several studies have been conducted to assess the validity of the SNHDD for several conditions, including diabetes. [10-13]

We analyzed data collected between January 1, 2013 and December 31, 2014 for women with and without T2DM who were aged over 40 years old. In both groups, we selected patients with a primary diagnosis of breast cancer (ICD-9-MC codes: 174.0-174.9) and whose medical procedures included BCS (ICD-9-MC codes: 85.20-85.25) and/or mastectomy (ICD-9-MC codes: 85.41-85.48) in any procedure field of the database. If both types of procedures were recorded, that case was excluded (n=137).

We identified 41,458 admissions with breast cancer who had undergone surgical procedures in 2013 and 2014 in Spain. Among those admissions, 3,882 (9.23%) had T2DM. Patients who underwent surgical breast cancer procedures in the non-diabetes group were selected to create a control group. Cases were matched with controls by age and province of residence (n=50); if more than one control was available for a case, the selection was conducted randomly. Ultimately, we identified 3,826 pairs of women (98.6 % of cases matched).

In the second phase, we repeated the process and selected women without diabetes matched by age, province of residence, type of procedure and stage. Therefore, we matched 1,938 T2DM women who underwent BCS and 1,480 who underwent mastectomy (88% of cases matched). Clinical characteristics included data on overall comorbidities at the time of diagnosis, which were assessed by calculating the Charlson comorbidity index (CCI) and excluding both cancer and diabetes as diseases. [14] We divided patients into three categories: CCI0, as in those patients with no previously recorded disease; CCI1, patients with one disease category; and CCI≥2, patients with two or more disease categories.

We retrieved data concerning specific comorbidities, including acute myocardial infarction, congestive heart failure, renal disease, stroke/TIA/TEP and vascular disease, as described by Quan et al. and that were applied to ICD-9-CM. [15]

The tumor stage was classified as local (within the breast), regional (affecting the lymph nodes—primarily those in the armpit and/or upper arm) or distant (in other parts of the body) according to Escribà et al. using the enhanced ICD-9-CM. [3]

Specific risk factors considered in the data analysis included obesity (ICD-9-CM code: 278.xx), hypertension (ICD-9-CM codes: 401; 401.0; 401.1; 401.9) and current smoking (ICD-9-CM codes: 305.1;V15.82) recorded during hospitalization for breast cancer in any diagnostic position.

Additionally, we specifically recorded the following procedures: sentinel lymph node dissection (ICD-9-CM codes: 40.11; 40.19; 40.23) and axillary lymph node dissection (ICD-9-MC codes: 40.3; 40.50; 40.51).

Irrespective of the position at diagnosis or the procedure coding list, we retrieved data regarding in-hospital "infectious complications," such as pneumonia (ICD-9-CM codes: 997.39,480-488;507.0-507.8), sepsis (ICD-9-CM codes: 995.91, 995.92) and surgical site infection (breast specific infection, ICD-9-CM codes 611.0; postoperative infection, ICD-9-CM codes 998.5-998.59; cellulitis, ICD-9-CM codes 682.2, 682.9; Staphylococcus aureus, ICD-9-CM codes 041.1-041.19; incision/drainage, ICD-9-CM codes 85.0, 85.91. 83.44-83.49, 86.01, 86.04, 86.09, 86.22, 86.28). Additionally, we noted "non-infectious complications" after surgery, which included postoperative hemorrhage/hematoma (ICD-9-CM codes 998.11, 998.12), fat necrosis (ICD-9-CM codes 567.82, 611.3), dehiscence (ICD-9-CM codes 875.0, 875.1, 879.0, 879.1, 998.3, 998.32) and necrosis (ICD-9-CM codes 998.83).

Hospital outcome variables included the length of hospital stay (LOHS) and in-hospital mortality (IHM), the latter being defined as the percentage of patients who died during the admission.

Statistical analysis

A descriptive statistical analysis was performed for all continuous variables and categories by stratifying admissions for breast cancer according to diabetes status. Variables were expressed as proportions, either as the means with standard deviations or medians with interquartile ranges (LOHS). We performed bivariate conditional logistic regression models to compare the prevalence of clinical characteristics, risk factors, comorbidities, procedures, complications and in-hospital outcomes between T2DM patients and controls. The analysis was conducted for the entire sample and stratified according to the procedure type (i.e., BCS or mastectomy).

To identify variables associated with in-hospital complications among patients after breast cancer surgical procedures and T2DM, we performed a logistic regression analysis with any complication (infectious or non-infectious) as a binary outcome variable. Finally, we performed two logistic regression analyses to specifically identify variables associated with complications among patients suffering from diabetes who underwent BCS and mastectomy. The variables included in these models were those with significant results in the bivariate analysis ($p<0.05$) and those considered relevant in other investigations. The variables included in these models were, age, CCI, stage and obesity. The remaining variables were not significant in the bivariate analysis.

Estimates were described as the odds ratio (OR) with associated 95% confidence intervals.

The matching of cases with controls and all statistical analyses were performed using Stata version 10.1 (Stata, College Station, TX, USA). Statistical significance was set at $p<0.05$ (two-tailed).

Ethical aspects

Data confidentiality was maintained at all times, in accordance with Spanish law. Given the anonymous and mandatory nature of the dataset, the requirement for informed consent was deemed unnecessary. The study protocol was approved by the ethics committee of the Rey Juan Carlos University.

RESULTS

Before matching was conducted, women with T2DM (3,882) were significantly older (70.66±10.24 vs. 60.2±12.71 years; p<0.001) than women without T2DM (37,576).

Regarding the procedures that we analyzed, when we compared women with T2DM with matched controls by age and province of residence, significant differences (p=0.04) were detected, with a higher incidence of mastectomy in women with T2DM compared with those without diabetes (44.69% vs. 42.42%, p<0.05) and a greater rate of BCS in patients without T2DM (57.58% vs. 55.31%).

In contrast, we found that the local tumor stage of the disease was more prevalent in women without T2DM than in those with T2DM (73.86% vs. 71.33%; p=0.020).

Table 1 shows the characteristics of hospital admissions for breast cancer patients who underwent a surgical procedure and who underwent BCS procedures and mastectomy among women with T2DM and age-matched controls without T2DM.

When we compared women with T2DM with matched controls, by age, province of residence and tumor stage, we found that patients with diabetes had more coexisting medical conditions according to the CCI (p<0.001). Specifically, T2DM women had a higher prevalence of vascular disease (8.81% vs. 6.61%), renal disease (4.13% vs. 1.40%), stroke (2.40% vs. 1.61%), congestive heart failure (1.93% vs. 0.61%) and acute myocardial infarction (0.97% vs. 0.53%). Additionally, the prevalence of hypertension (65.54% vs. 36.22%) and obesity (13.17% vs. 3.63%) was higher in T2DM patients.

As shown in Table 1, all types of in-hospital complications were more frequent among women with T2DM (7.72%) than in women without diabetes (5.30%; p=0.003). When the types of complication were analyzed, only non-infectious complications showed significant differences (6.40% vs. 4.56%).

Median LOHS and IHM values did not differ between women with and without diabetes.

As can been seen in Table 1, women with diabetes who underwent BCS were significantly younger than those who underwent a mastectomy (68.18 vs. 72.71 years; p<0.001).

Among women who underwent a BSC, those with T2DM had higher frequencies of comorbidities according to the CCI, when compared with matched controls (p<0.001). Vascular disease, renal disease, acute myocardial infarction, obesity and hypertension were significantly more prevalent in patients with diabetes than in matched controls. We found a significantly lower rate of sentinel lymph node dissection in T2DM patients compared with controls (61.09% vs. 64.86%; p=0.032).

Women with T2DM who underwent a BSC had a higher prevalence of all in-hospital complications (infectious and/or non-infectious) compared to those without diabetes (5.57% vs. 3.04%, respectively, p=0.008) and also for non-infectious complications alone (4.80% vs. 2.73%).

Women with T2DM who underwent mastectomy had more coexisting medical conditions according to the CCI and a higher prevalence of vascular disease, renal disease, congestive heart failure, obesity and hypertension than women without diabetes. Additionally, women with T2DM had a higher prevalence of in-hospital complications (infectious and/or non-infectious) than those without diabetes (10.60% vs. 8.24%, respectively; p=0.029). According to the type of complications, differences were only significant for non-infectious complications (8.51% vs. 6.96%; p=0.032).

Table 2 shows the results of logistic regression analyses to assess those factors associated with in-hospital complications in patients with T2DM during hospital admission for breast cancer who underwent any breast surgical procedures and, more specifically, according to the type of procedure. Among T2DM women with breast cancer and after any surgical procedure (i.e., conservative or mastectomy), comorbidity (vs. no comorbidites, OR 1.72, 95%CI 1.30-2.27 for one comorbidity; OR 2.55, 95%CI 1.55-4.17 for two or more comorbidities) and obesity (OR 1.54, 95%CI 1.14–2.07) were the factors most strongly associated with a higher rate of in-hospital complications. These two factors also increased the risk of in-hospital complications for women who underwent BCS. However, among those who underwent mastectomy, only comorbidity was associated with a higher rate of in-hospital complications.

DISCUSSION

T2DM is considered to be a common comorbidity that is present in many breast cancer patients, correlating with poor clinical outcomes. [16,17] According to information obtained from the SNHDD, compared with nondiabetic counterparts, women with T2DM undergoing surgical breast cancer procedures have more risk factors, comorbidities and advanced cancer presentations.

Several studies have reported that the presence of risk factors, such as hypertension and obesity, are common in both patients with diabetes and those with breast cancer. [18,19]

However, in our study population, the prevalence of obesity is very low among women with diabetes, which is possibly a consequence of under-recording this condition. Previous studies conducted in Spain and other countries have also found an under-reporting of obesity in administrative data. [20-23] These authors suggest the following possible reasons to explain the low rates of obesity in administrative data: i) obesity is not explicitly mentioned in physician reports; ii) people who codify may not record obesity owing to time constraints when performing data abstraction; iii) when time for coding is limited, coders tend to include severe conditions but not risk factors and; iv) the diagnosis of obesity is often not based on the BMI, but rather on the subjective observation made by the clinician, which means that more severe obesity is over-codified [21-23] Furthermore, as described earlier, a possible differential information bias may occur and thus the misclassification of obesity may be related to the presence of diabetes. Thus, ICD codes for obesity may be more commonly assigned to patients suffering from other comorbidities (including diabetes) or postoperative complications. This suggests a greater association between obesity and adverse events than what is obtained based on the BMI calculations. [21, 23] As a result, any association between obesity and the presence of in-hospital complications must be interpreted with caution.

In our current study, women with T2DM were significantly more likely to suffer from advanced-stage breast cancer when compared with women without diabetes. Our findings are consistent with other studies demonstrating a more advanced stage of breast cancer among women with diabetes. [24, 25] A study conducted in Canada showed that diabetes was associated with more advanced-stage breast cancer, even after accounting for differences in screening mammogram use and other factors. [26] There are several possible explanations for this association, including the fact that mammograms are less sensitive for the detection of early lesions in women with T2DM because of higher rates of obesity. [27] Finally, tumors may progress more rapidly in patients with diabetes, or diabetes may lead to a higher metastatic potential. [28]

We observed that mastectomies are performed more frequently on diabetic women, which could be explained by several factors, including higher comorbidity, higher stage disease at diagnosis, the presence of more biologically aggressive tumors and the fact that diabetes is a major risk factor in breast cancer recurrence. [3, 28] Kaplan et al. examined 483 breast cancer patients who had undergone a mastectomy between 1998 and 2010. They concluded that the recurrence of breast cancer was significantly increased in patients with diabetes (OR, 2.21; 95%CI 1.23–3.96; p=0.008). [29]

As expected, we observed that in-hospital mortality and complication rates in breast cancer surgery were low. This finding is consistent with de Blacam et al., who, in a multi-institutional study of patients undergoing mastectomy and BCS in the US, found that the overall 30-day morbidity rate was 5.6% for all procedures. [7]

We found that women with T2DM who underwent breast cancer surgical procedures had a higher frequency of overall in-hospital complications compared with women without diabetes. Several studies have reported that diabetes is a risk factor for surgical site infections after breast operations. [7] A systematic review/meta-analysis concluded that patients with diabetes were more vulnerable to surgical site infections after breast cancer surgery (OR 1.88, 95%CI 1.47–2.39). [30]

In this study, comorbidity was a strong predictor of in-hospital complications in women with T2DM who underwent surgical breast cancer-related procedures. Dehale et al. studied the impact of comorbidity using hospital discharge data from the “Health Care Utilization Project: Nationwide In-patient Sample” database in women with a primary diagnosis of breast cancer after undergoing breast surgery. They found that women with a severe (CCI score ≥3) comorbidity were 4.6-times more likely to develop a postoperative complication when compared with patients without a comorbidity. [31]

In our present study, obesity was a predictor of IHC in women with diabetes who underwent BCS. Being overweight or obese has been associated with higher rates of treatment-related sequelae, such as lymphedema, fatigue and arthralgia. [32] Helyer et al. concluded that obesity is a risk factor for the development of postoperative lymphedema in breast cancer patients (OR 1.8; 95%CI, 1.0004–1.165). [33] Excess adiposity may increase the risk of lymphedema by driving increased inflammation, adding stress to the lymphatic system, or slowing post-surgical healing times. [34] However, as commented previously, the uncertainty regarding the validity of the obesity codification in the SNHDD requires caution when interpreting this result.

The strengths of our study included its large simple size, the standardized methodology, and use of age- and province-matched non-T2DM patients to control for the confounding effects of these variables. However, our study has several limitations. First, the validity of the T2DM must be discussed. In Spain, the diagnosis of type 2 diabetes is mainly performed in primary care centers. [35] Even if patients are diagnosed during hospitalization they are sent to their primary care center for the follow up and necessary medical prescriptions. A study conducted to validate the diabetes mellitus diagnosis in the computerized clinical records of primary health care, taking the 2003 American Diabetes Association Consensus Statement as the gold standard, found that the agreement was very high (κ=0.990), with a specificity of 99.49% and a sensitivity of 99.53%. [35] The validity of the diabetes diagnosis in the SNHDD has been assessed in two previous studies, revealing a sensitivity of 55% and 63.7% and a specificity of approximately 97%.[10,11]

The only moderate sensitivity found means that an important proportion of T2DM patients do not have this diagnosis codified in their discharge report. On the other hand, the very high specificity means that most patients without a T2DM diagnosis do not really have this disease; therefore, we think that the effect of this misclassification on our design is possibly very small. Furthermore, as commented previously regarding obesity, the database was designed for administrative rather than research purposes, therefore conditions such as infection, hypertension and smoking may not have been adequately recorded in the database. [8, 10, 11] Second, unfortunately the ICD 9 does not include information regarding whether a condition is part of the patient's past medical history or if this appeared during the hospitalization. Therefore, it is possible that a patient may first be diagnosed with diabetes or any other condition studied during the hospitalization. However, we think that this possibly affects a very small proportion of patients and thus the effect on our results would be minimal.

Third, the database that we used contained no information about chemotherapy or radiotherapy treatments prior to surgery, which may have affected our outcome variables.

Forth, we lacked data such as breast cancer characteristics or the time span since diagnosis.

Finally, other relevant variables such as laboratory results, BMI, medical treatments (e.g. glucose lowering drugs, insulin or antibiotics), patients who have undergone a prosthetic reconstruction and the eventual use of an acellular dermal matrix are not included in the SNHDD.

CONCLUSIONS

We conclude that women with T2DM who undergo surgical procedures to treat breast cancer have more comorbidities, risk factors and a more advanced cancer presentation than women without T2DM. Mastectomies are more frequently performed in diabetic women. Moreover, procedures carried out in women with T2DM were associated with greater in-hospital complications. Finally, comorbidity was a strong predictor of in-hospital complications in women with T2DM.

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CONTRIBUTIONS

Ana López-de-Andres and Rodrigo Jiménez-Garcia participated in the conception and design, analysis, interpretation, and writing of the manuscript. Valentín Hernández-Barrera and Isabel Jiménez-Trujillo contributed their statistical expertise and towards conception and design, interpretation and writing of the manuscript. Javier de Miguel-Díez, Manuel Méndez-Bailón, José M de Miguel-Yanes, Napoleón Pérez-Farinós, Miguel-Angel Salinero-Fort, José L del Barrio and Martin Romero-Maroto were involved in the critical revision of the manuscript, as well as the interpretation and design. All authors have seen and approved the final version.

COMPETING INTERESTS

The authors declare that they have no competing interests.

DATA SHARING STATEMENT

"No additional data available"

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Table 1. Clinical characteristics, complications and hospital outcomes of hospital admissions for breast cancer and according to type of surgical procedure among women suffering type 2 diabetes and matched women without type 2 diabetes.

	Total (n=6,836)			Breast conservative surgery (n=,3876)			Mastectomy (n=2,960)		
	Diabetes (n=3,418)	No diabetes (n=3,418)	p-value	Diabetes (n=1,938)	No diabetes (n=1,938)	p-value	Diabetes (n=1,480)	No diabetes (n=1,480)	p-value
Age, mean (SD)	70.14(10.22)	70.14(10.22)	NA	68.18(9.53)	68.18(9.53)	NA	72.71(10.51)	72.71(10.51)	NA
40-59 years old, n (%)	522(15.27)	522(15.27)		343(17.7)	343(17.7)		179(12.09)	179(12.09)	
60-79 years old, n (%)	2187(63.98)	2187(63.98)	NA	1335(68.89)	1335(68.89)	NA	852(57.57)	852(57.57)	NA
≥ 80 years old, n (%)	709(20.74)	709(20.74)		260(13.42)	260(13.42)		449(30.34)	449(30.34)	
Stage: Local, n (%)	2590(75.78)	2590(75.78)		1560(80.5)	1560(80.5)		1030(69.59)	1030(69.59)	
Stage: Regional, n (%)	799(23.38)	799(23.38)	NA	371(19.14)	371(19.14)	NA	428(28.92)	428(28.92)	NA
Stage: Distant, n (%)	29(0.85)	29(0.85)		7(0.36)	7(0.36)		22(1.49)	22(1.49)	
CCI0, n (%)	2798(81.86)	3050(89.23)		1627(83.95)	1763(90.97)		1171(79.12)	1287(86.96)	
CCI1, n (%)	522(15.27)	324(9.48)	<0.001	274(14.14)	155(8)	<0.001	248(16.76)	169(11.42)	<0.001
CCI≥2, n (%)	98(2.87)	44(1.29)		37(1.91)	20(1.03)		61(4.12)	24(1.62)	
Vascular disease, n (%)	301(8.81)	226(6.61)	<0.001	159(8.2)	119(6.14)	0.011	142(9.59)	107(7.23)	0.019
Renal disease, n (%)	141(4.13)	48(1.40)	<0.001	61(3.15)	24(1.24)	<0.001	80(5.41)	24(1.62)	<0.001
Stroke/TIA/TEP, n (%)	82(2.40)	55(1.61)	0.020	31(1.60)	22(1.14)	0.201	51(3.45)	33(2.23)	0.051
Congestive heart failure, n (%)	66(1.93)	21(0.61)	<0.001	21(1.08)	9(0.46)	0.020	45(3.04)	12(0.81)	<0.001
Acute myocardial infarction, n (%)	33(0.97)	18(0.53)	0.039	21(1.08)	7(0.36)	0.012	12(0.81)	11(0.74)	0.835
Obesity, n (%)	450(13.17)	124(3.63)	<0.001	267(13.78)	70(3.61)	<0.001	183(12.36)	54(3.65)	<0.001
Hypertension, n (%)	2240(65.54)	1238(36.22)	<0.001	1267(65.38)	654(33.75)	<0.001	973(65.74)	584(39.46)	<0.001
Smoking, n (%)	166(4.86)	185(5.41)	0.288	111(5.73)	121(6.24)	0.488	55(3.72)	64(4.32)	0.393
Sentinel lymph node dissection, n (%)	1697(49.65)	1795(52.52)	0.092	1184(61.09)	1257(64.86)	0.032	513(34.66)	538(36.35)	0.332
Axillary lymph node dissection, n (%)	560(16.38)	551(16.12)	0.747	375(19.35)	382(19.71)	0.752	185(12.5)	169(11.42)	0.349
Infectious complications, n (%)	95(2.78)	76(2.22)	0.138	35(1.81)	22(1.14)	0.088	60(4.05)	54(3.65)	0.560
Non infectious complications, n(%)	219(6.40)	156(4.56)	0.004	93(4.80)	53(2.73)	0.015	126(8.51)	103(6.96)	0.032
All complications (infectious and/or non infectious), n (%)	264(7.72)	181(5.30)	0.003	107(5.57)	59(3.04)	0.008	157(10.60)	122(8.24)	0.029
Length of stay, median (IQR)	3(2-5)	3(2-5)	0.070	2(1-3)	2(1-3)	0.065	4(3-6)	4(3-6)	0.062
In-hospital mortality, n (%)	5(0.15)	2(0.06)	0.277	2(0.1)	1(0.05)	0.571	3(0.2)	1(0.07)	0.341

CCI: Charlson Comorbidity Index. IQR: Interquartile range. P value for difference between T2DM sufferers and matched controls using bivariate conditional logistic regression. Matching was conducted by age, province of residence, type of surgical procedure and stage.

Table 2. Logistic regression analysis of the factor associated with in-hospital complications in women with type 2 diabetes during hospital admission for breast cancer according to the type of surgical procedure.

		Any breast cancer surgical procedure (Conservative or mastectomy) OR (95%CI)	Breast Conservative Surgery OR (95%CI)	Mastectomy OR (95%CI)
Age groups, years	40-59	1	1	1
	60-79	0.98 (0.70-1.37)	0.79 (0.50-1.26)	1.12 (0.67-1.86)
	≥ 80	1.16 (0.79-1.71)	0.92 (0.50-1.67)	1.22 (0.71-2.10)
CCI	0	1	1	1
	1	1.72(1.30-2.27)	1.75(1.12-2.71)	1.64(1.14-2.35)
	≥2	2.55(1.55-4.17)	3.33(1.48-7.48)	2.10(1.13-3.91)
Stage	Local	1	1	1
	Regional/distant	1.21 (0.98-1.48)	1.08(0.74-1.55)	1.19(0.93-1.52)
Obesity	Yes	1.54 (1.14-2.07)	1.68 (1.07-2.60)	1.46(0.98-2.19)

CCI: Charlson Comorbidity Index. OR: Odds Ratio. 95%CI: 95% confidence intervals. All variables included in the models are shown.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	*6-8*
Study size	10	Explain how the study size was arrived at	6-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	8,9
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-17
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-17
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	9-17
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-17
		(*b*) Report category boundaries when continuous variables were categorized	9-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	18-20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20,21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The association of Type 2 diabetes with in-hospital complications among women undergoing breast cancer surgical procedures. A retrospective study using the Spanish National Hospital Discharge Database, 2013–2014.

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The association of Type 2 diabetes with in-hospital complications among women undergoing breast cancer surgical procedures. A retrospective study using the Spanish National Hospital Discharge Database, 2013–2014.

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ABSTRACT

Objectives: To compare the type of surgical procedures used, comorbidities, in-hospital complications (IHC), and in-hospital outcomes between women with type 2 diabetes (T2DM) and age-matched women without diabetes who were hospitalized with breast cancer. In addition we sought to identify factors associated with IHC in women with T2DM who had undergone surgical procedures for breast cancer.

Design: Retrospective study using the National Hospital Discharge Database, 2013–2014.

Setting: Spain.

Participants: Women who were ≥40 years old with a primary diagnosis of breast cancer and who had undergone a surgical procedure. We grouped admissions by T2DM status. We selected one matched control for each T2DM case.

Main outcome measures: The type of procedure (breast-conserving surgery (BCS) or mastectomy), clinical characteristics, complications, length of hospital stay and in-hospital-mortality.

Results: We identified 41,458 admissions (9.23% with T2DM). Overall, and in addition to the surgical procedure, we found that comorbidity, hypertension and obesity were more common among patients with T2DM. We also detected a higher incidence of mastectomy in women with T2DM (44.69% vs. 42.42%) and a greater rate of BCS in patients without T2DM (57.58% vs. 55.31%). Overall, non-infectious complications were more common among women with T2DM (6.40% vs. 4.56%). Among women who had undergone BCS or a mastectomy, IHC were more frequent among diabetics (5.57% vs. 3.04% and 10.60% vs. 8.24%, respectively). Comorbidity was significantly associated with a higher risk of IHC in women with diabetes, independent of the specific procedure used.

Conclusions: Women with T2DM who undergo surgical breast cancer procedures have more comorbidity, risk factors and advanced cancer presentations than matched patients without T2DM. Mastectomies are more common in women with T2DM. Moreover, the procedures among women with T2DM were associated with greater IHC. Comorbidity was a strong predictor of IHC in women with T2DM.

Strengths and limitations of this study

- The strengths of our study include the large sample size, the standardized methodology, and the use of age- province- surgical procedure and stage-matched women without T2DM to control for the confounding effects of these variables.
- A limitation of this study is the lack of information on chemotherapy or radiotherapy treatments prior to surgery, which may have affected our outcome variables.
- We lacked data such as specific breast cancer characteristics or accurate time frames since diagnosis.
- The association of obesity on in-hospital complications must be interpreted with caution for the possible existence of a codification bias.

INTRODUCTION

Breast cancer is the most common type of cancer in women. [1] Recently, the Global Burden of Disease Cancer Collaboration reported that the incidence of breast cancer between 2005 and 2015 in Western Europe increased by 24%, from 100.6 to 124.7 cases per 100,000 individuals. Breast cancer was also the leading cause of cancer-related deaths in women. [1]

Breast-conserving surgery (BCS) and mastectomy still represent the current therapeutic approach for breast cancer. Recently, the use of BCS has increased and become the primary surgical treatment for breast cancer. [2,3] In Spain, over 80% of women diagnosed with breast cancer underwent surgery and, among these patients, nearly 75% received BCS. [3] However, recent studies have shown an increased number of mastectomies in women who are candidates for BCS because of the rise of more cosmetically appealing techniques. [4]

The Spanish Health Care System is public and offers universal coverage with no out-of-pocket expenses for patients.

Recently, a report using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database to study 30-day complication rates after breast operations concluded that, overall, BCS and mastectomy with implant reconstruction have low complication rates. Additionally, BCS in early stage breast cancer was associated with fewer overall early postoperative complications when compared with mastectomy [OR 2.8; 95%CI 2.2–3.5, $p<0.01$]. [5]

Diabetes is a predictor associated with postoperative complications in women who undergo surgical procedures for breast cancer. [5-7] In women with early-stage breast cancer, diabetes has been found to be a risk factor for overall postoperative complications (OR 1.8; 95%CI 1.02–3.4, $p=0.04$). [5] De Blacam et al., using the NSQIP database, reported that independent risk factors for the development of an infection of any surgical wound caused by a mastectomy included a high body mass index, smoking, and diabetes. [7]

To the best of our knowledge, no previous studies have investigated factors associated with in-hospital complications among women with diabetes undergoing breast cancer-related surgical procedures.

Using the Spanish national hospital discharge database (SNHDD) for 2013–2014, we aim in this study to i) compare variables between type 2 diabetes (T2DM) and matched women without diabetes hospitalized with breast cancer who underwent a surgical procedure, including the type of surgical procedure used (BCS or mastectomy), patient comorbidities, in-hospital complications and in-hospital outcomes (length of hospital stay and in-hospital mortality); and ii) identify factors associated with in-hospital complications in women with T2DM who underwent breast cancer surgical procedures.

METHODS

We performed a retrospective, observational study using the SNHDD, which is managed by the Spanish Ministry of Health, Social Services and Equality (MHSSE) and compiles all public and private hospital data covering more than 98% of hospital admissions. [8]

The SNHDD was implemented in 1987. According to Spanish legislation, all public and private Spanish hospitals must periodically submit data to the health authorities regarding those patients who have been hospitalized for at least 24 hours. The information required includes patient's characteristics such as their clinical history number, personal ID number, date of birth, sex, country of birth and address. Clinical variables include: admission and discharge dates, up to 14 diagnoses at discharge and up to 20 procedures performed during the hospital stay. The primary/main diagnosis is defined as the condition which, after proper investigation, is considered the reason why the patient was admitted to the hospital. The secondary diagnosis includes those diseases or risk factors that coexist with the primary diagnosis at the time of admission or were detected during the hospitalization and that, in the opinion of the treating physician, may have affected the patient's progress or treatment plan.

Procedures include those diagnostic or therapeutic procedures conducted during hospitalization. Information on the service where the patient has received care and the type of discharge (home, decease, voluntary discharge, other hospital, and social institution) is also collected.

All patients discharged from the hospital must have a discharge report signed by the physician discharging the patient that includes the above noted information. The Codification Unit of the hospital uses this discharge report and any additional information required by the hospital databases to complete the SNHDD. The database uses the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) for coding.

The Spanish Ministry of Health conducts regular audits to assess the accuracy of the SNHDD [8, 9]. Several studies have been conducted to assess the validity of the SNHDD for several conditions, including diabetes. [10-13]

In Spain, the diagnosis of type 2 diabetes is mainly performed in primary care centers using the American Diabetes Association (ADA) Consensus Statement. [14] Even if patients are diagnosed during hospitalization they are sent to their primary care center for the follow up and necessary medical prescriptions.

We analyzed data collected between January 1, 2013 and December 31, 2014 for women with and without T2DM who were aged over 40 years old. In both groups, we selected patients with a primary diagnosis of breast cancer (ICD-9-MC codes: 174.0-174.9) and whose medical procedures included BCS (ICD-9-MC codes: 85.20-85.25) and/or mastectomy (ICD-9-MC codes: 85.41-85.48) in any procedure field of the database. If both types of procedures were recorded, that case was excluded (n=137).

We identified 41,458 admissions with breast cancer who had undergone surgical procedures in 2013 and 2014 in Spain. Among those admissions, 3,882 (9.23%) had T2DM. Patients who underwent surgical breast cancer procedures in the non-diabetes group were selected to create a control group. Cases were matched with controls by age and province of residence (n=50); if more than one control was available for a case, the selection was conducted randomly. Ultimately, we identified 3,826 pairs of women (98.6 % of cases matched).

In the second phase, we repeated the process and selected women without diabetes matched by age, province of residence, type of procedure and stage. Therefore, we matched 1,938 T2DM women who underwent BCS and 1,480 who underwent mastectomy (88% of cases matched). Clinical characteristics included data on overall comorbidities at the time of diagnosis, which were assessed by calculating the Charlson comorbidity index (CCI) and excluding both cancer and diabetes as diseases. [15] We divided patients into three categories: CCI0, as in those patients with no previously recorded disease; CCI1, patients with one disease category; and CCI≥2, patients with two or more disease categories.

We retrieved data concerning specific comorbidities, including acute myocardial infarction, congestive heart failure, renal disease, stroke/TIA/TEP and vascular disease, as described by Quan et al. and that were applied to ICD-9-CM. [16]

The tumor stage was classified as local (within the breast), regional (affecting the lymph nodes—primarily those in the armpit and/or upper arm) or distant (in other parts of the body) according to Escribà et al. using the enhanced ICD-9-CM. [3]

Specific risk factors considered in the data analysis included obesity (ICD-9-CM code: 278.xx), hypertension (ICD-9-CM codes: 401; 401.0; 401.1; 401.9) and current smoking (ICD-9-CM codes: 305.1;V15.82) recorded during hospitalization for breast cancer in any diagnostic position.

Additionally, we specifically recorded the following procedures: sentinel lymph node dissection (ICD-9-CM codes: 40.11; 40.19; 40.23) and axillary lymph node dissection (ICD-9-MC codes: 40.3; 40.50; 40.51).

Irrespective of the position at diagnosis or the procedure coding list, we retrieved data regarding in-hospital "infectious complications," such as pneumonia (ICD-9-CM codes: 997.39,480-488;507.0-507.8), sepsis (ICD-9-CM codes: 995.91, 995.92) and surgical site infection (breast specific infection, ICD-9-CM codes 611.0; postoperative infection, ICD-9-CM codes 998.5-998.59; cellulitis, ICD-9-CM codes 682.2, 682.9; Staphylococcus aureus, ICD-9-CM codes 041.1-041.19; incision/drainage, ICD-9-CM codes 85.0, 85.91. 83.44-83.49, 86.01, 86.04, 86.09, 86.22, 86.28). Additionally, we noted "non-infectious complications" after surgery, which included postoperative hemorrhage/hematoma (ICD-9-CM codes 998.11, 998.12), fat necrosis (ICD-9-CM codes 567.82, 611.3), dehiscence (ICD-9-CM codes 875.0, 875.1, 879.0, 879.1, 998.3, 998.32) and necrosis (ICD-9-CM codes 998.83).

Hospital outcome variables included the length of hospital stay (LOHS) and in-hospital mortality (IHM), the latter being defined as the percentage of patients who died during the admission.

Statistical analysis

A descriptive statistical analysis was performed for all continuous variables and categories by stratifying admissions for breast cancer according to diabetes status. Variables were expressed as proportions, either as the means with standard deviations or medians with interquartile ranges (LOHS). We performed bivariate conditional logistic regression models to compare the prevalence of clinical characteristics, risk factors, comorbidities, procedures, complications and in-hospital outcomes between T2DM patients and controls. The analysis was conducted for the entire sample and stratified according to the procedure type (i.e., BCS or mastectomy).

To identify variables associated with in-hospital complications among patients after breast cancer surgical procedures and T2DM, we performed a logistic regression analysis with any complication (infectious or non-infectious) as a binary outcome variable. Finally, we performed two logistic regression analyses to specifically identify variables associated with complications among patients suffering from diabetes who underwent BCS and mastectomy. The variables included in these models were those with significant results in the bivariate analysis ($p<0.05$) and those considered relevant in other investigations. The variables included in these models were, age, CCI, stage and obesity. The remaining variables were not significant in the bivariate analysis.

Estimates were described as the odds ratio (OR) with associated 95% confidence intervals.

The matching of cases with controls and all statistical analyses were performed using Stata version 10.1 (Stata, College Station, TX, USA). Statistical significance was set at $p<0.05$ (two-tailed).

Ethical aspects

Data confidentiality was maintained at all times, in accordance with Spanish law. Given the anonymous and mandatory nature of the dataset, the requirement for informed consent was deemed unnecessary. The study protocol was approved by the ethics committee of the Rey Juan Carlos University.

RESULTS

Before matching was conducted, women with T2DM (3,882) were significantly older (70.66±10.24 vs. 60.2±12.71 years; $p<0.001$) than women without T2DM (37,576).

Regarding the procedures that we analyzed, when we compared women with T2DM with matched controls by age and province of residence, significant differences ($p=0.04$) were detected, with a higher incidence of mastectomy in women with T2DM compared with those without diabetes (44.69% vs. 42.42%, $p<0.05$) and a greater rate of BCS in patients without T2DM (57.58% vs. 55.31%).

In contrast, we found that the local tumor stage of the disease was more prevalent in women without T2DM than in those with T2DM (73.86% vs. 71.33%; $p=0.020$).

Table 1 shows the characteristics of hospital admissions for breast cancer patients who underwent a surgical procedure and who underwent BCS procedures and mastectomy among women with T2DM and age-matched controls without T2DM.

When we compared women with T2DM with matched controls, by age, province of residence and tumor stage, we found that patients with diabetes had more coexisting medical conditions according to the CCI ($p<0.001$). Specifically, T2DM women had a higher prevalence of vascular disease (8.81% vs. 6.61%), renal disease (4.13% vs. 1.40%), stroke (2.40% vs. 1.61%), congestive heart failure (1.93% vs. 0.61%) and acute myocardial infarction (0.97% vs. 0.53%). Additionally, the prevalence of hypertension (65.54% vs. 36.22%) and obesity (13.17% vs. 3.63%) was higher in T2DM patients.

As shown in Table 1, all types of in-hospital complications were more frequent among women with T2DM (7.72%) than in women without diabetes (5.30%; $p=0.003$). When the types of complication were analyzed, only non-infectious complications showed significant differences (6.40% vs. 4.56%).

Median LOHS and IHM values did not differ between women with and without diabetes.

As can been seen in Table 1, women with diabetes who underwent BCS were significantly younger than those who underwent a mastectomy (68.18 vs. 72.71 years; $p<0.001$).

Among women who underwent a BSC, those with T2DM had higher frequencies of comorbidities according to the CCI, when compared with matched controls ($p<0.001$). Vascular disease, renal disease, acute myocardial infarction, obesity and hypertension were significantly more prevalent in patients with diabetes than in matched controls. We found a significantly lower rate of sentinel lymph node dissection in T2DM patients compared with controls (61.09% vs. 64.86%; p=0.032).

Women with T2DM who underwent a BSC had a higher prevalence of all in-hospital complications (infectious and/or non-infectious) compared to those without diabetes (5.57% vs. 3.04%, respectively, p=0.008) and also for non-infectious complications alone (4.80% vs. 2.73%).

Women with T2DM who underwent mastectomy had more coexisting medical conditions according to the CCI and a higher prevalence of vascular disease, renal disease, congestive heart failure, obesity and hypertension than women without diabetes. Additionally, women with T2DM had a higher prevalence of in-hospital complications (infectious and/or non-infectious) than those without diabetes (10.60% vs. 8.24%, respectively; p=0.029). According to the type of complications, differences were only significant for non-infectious complications (8.51% vs. 6.96%; p=0.032).

Table 2 shows the results of logistic regression analyses to assess those factors associated with in-hospital complications in patients with T2DM during hospital admission for breast cancer who underwent any breast surgical procedures and, more specifically, according to the type of procedure. Among T2DM women with breast cancer and after any surgical procedure (i.e., conservative or mastectomy), comorbidity (vs. no comorbidites, OR 1.72, 95%CI 1.30-2.27 for one comorbidity; OR 2.55, 95%CI 1.55-4.17 for two or more comorbidities) and obesity (OR 1.54, 95%CI 1.14–2.07) were the factors most strongly associated with a higher rate of in-hospital complications. These two factors also increased the risk of in-hospital complications for women who underwent BCS. However, among those who underwent mastectomy, only comorbidity was associated with a higher rate of in-hospital complications.

DISCUSSION

T2DM is considered to be a common comorbidity that is present in many breast cancer patients, correlating with poor clinical outcomes. [17,18] According to information obtained from the SNHDD, compared with nondiabetic counterparts, women with T2DM undergoing surgical breast cancer procedures have more risk factors, comorbidities and advanced cancer presentations.

Several studies have reported that the presence of risk factors, such as hypertension and obesity, are common in both patients with diabetes and those with breast cancer. [19,20]

In our current study, women with T2DM were significantly more likely to suffer from advanced-stage breast cancer when compared with women without diabetes. Our findings are consistent with other studies demonstrating a more advanced stage of breast cancer among women with diabetes. [21, 22] A study conducted in Canada showed that diabetes was associated with more advanced-stage breast cancer, even after accounting for differences in screening mammogram use and other factors. [23] There are several possible explanations for this association, including the fact that mammograms are less sensitive for the detection of early lesions in women with T2DM because of higher rates of obesity. [24] Finally, tumors may progress more rapidly in patients with diabetes, or diabetes may lead to a higher metastatic potential. [25]

We observed that mastectomies are performed more frequently on diabetic women, which could be explained by several factors, including higher comorbidity, higher stage disease at diagnosis, the presence of more biologically aggressive tumors and the fact that diabetes is a major risk factor in breast cancer recurrence. [3, 25] Kaplan et al. examined 483 breast cancer patients who had undergone a mastectomy between 1998 and 2010. They concluded that the recurrence of breast cancer was significantly increased in patients with diabetes (OR, 2.21; 95%CI 1.23–3.96; p=0.008). [26]

As expected, we observed that in-hospital mortality and complication rates in breast cancer surgery were low. This finding is consistent with de Blacam et al., who, in a multi-institutional study of patients undergoing mastectomy and BCS in the US, found that the overall 30-day morbidity rate was 5.6% for all procedures. [7]

We found that women with T2DM who underwent breast cancer surgical procedures had a higher frequency of overall in-hospital complications compared with women without diabetes. Several studies have reported that diabetes is a risk factor for surgical site infections after breast operations. [7] A systematic review/meta-analysis concluded that patients with diabetes were more vulnerable to surgical site infections after breast cancer surgery (OR 1.88, 95%CI 1.47–2.39). [27]

In this study, comorbidity was a strong predictor of in-hospital complications in women with T2DM who underwent surgical breast cancer-related procedures. Dehal et al. studied the impact of comorbidity using hospital discharge data from the “Health Care Utilization Project: Nationwide In-patient Sample” database in women with a primary diagnosis of breast cancer after undergoing breast surgery. They found that women with a severe (CCI score ≥3) comorbidity were 4.6-times more likely to develop a postoperative complication when compared with patients without a comorbidity. [28]

In our present study, obesity was a predictor of IHC in women with diabetes who underwent BCS. Being overweight or obese has been associated with higher rates of treatment-related sequelae, such as lymphedema, fatigue and arthralgia. [29] Helyer et al. concluded that obesity is a risk factor for the development of postoperative lymphedema in breast cancer patients (OR 1.8; 95%CI, 1.0004–1.165). [30] Excess adiposity may increase the risk of lymphedema by driving increased inflammation, adding stress to the lymphatic system, or slowing post-surgical healing times. [31] However, as will be commented in the limitations section the uncertainty regarding the validity of the obesity codification in the SNHDD requires caution when interpreting this result.

The strengths of our study included its large simple size, the standardized methodology, and use of age- and province-matched non-T2DM patients to control for the confounding effects of these variables. However, our study has several limitations. First, the validity of the T2DM must be discussed. A study conducted to validate the diabetes mellitus diagnosis in the computerized clinical records of primary health care in Spain, taking the 2003 ADA Consensus Statement as the gold standard, found that the agreement was very high (κ=0.990), with a specificity of 99.49% and a sensitivity of 99.53%. [14] The validity of the diabetes diagnosis in the SNHDD has been assessed in two previous studies, revealing a sensitivity of 55% and 63.7% and a specificity of approximately 97%.[10,11]

The only moderate sensitivity found means that an important proportion of T2DM patients do not have this diagnosis codified in their discharge report. On the other hand, the very high specificity means that most patients without a T2DM diagnosis do not really have this disease; therefore, we think that the effect of this misclassification on our design is possibly very small. Furthermore, the database was designed for administrative rather than research purposes, therefore conditions such as obesity, infection, hypertension and smoking may not have been adequately recorded in the database. [8, 10, 11]

The validity of the variable "obesity" in our investigation must be discussed. In our study population, the prevalence of obesity is very low among women with diabetes, which is possibly a consequence of under-recording this condition. Previous studies conducted in Spain and other countries have also found an under-reporting of obesity in administrative data. [32-35] These authors suggest the following possible reasons to explain the low rates of obesity in administrative data: i) obesity is not explicitly mentioned in physician reports; ii) people who codify may not record obesity owing to time constraints when performing data abstraction; iii) when time for coding is limited, coders tend to include severe conditions but not risk factors and; iv) the diagnosis of obesity is often not based on the BMI, but rather on the subjective observation made by the clinician, which means that more severe obesity is over-codified [33-35] Furthermore, a possible differential information bias may occur and thus the misclassification of obesity may be related to the presence of diabetes. Thus, ICD codes for obesity may be more commonly assigned to patients suffering from other comorbidities (including diabetes) or postoperative complications. This suggests a greater association between obesity and adverse events than what is obtained based on the BMI calculations. [33, 35] As a result, any association between obesity and the presence of in-hospital complications must be interpreted with caution.

Second, unfortunately the ICD 9 does not include information regarding whether a condition is part of the patient's past medical history or if this appeared during the hospitalization. Therefore, it is possible that a patient may first be diagnosed with diabetes or any other condition studied during the hospitalization. However, we think that this possibly affects a very small proportion of patients and thus the effect on our results would be minimal.

Third, the database that we used contained no information about chemotherapy or radiotherapy treatments prior to surgery, which may have affected our outcome variables.

Forth, we lacked data such as breast cancer characteristics or the time span since diagnosis.

Finally, other relevant variables such as laboratory results, BMI, medical treatments (e.g. glucose lowering drugs, insulin or antibiotics), patients who have undergone a prosthetic reconstruction and the eventual use of an acellular dermal matrix are not included in the SNHDD.

CONCLUSIONS

We conclude that women with T2DM who undergo surgical procedures to treat breast cancer have more comorbidities, risk factors and a more advanced cancer presentation than women without T2DM. Mastectomies are more frequently performed in diabetic women. Moreover, procedures carried out in women with T2DM were associated with greater in-hospital complications. Finally, comorbidity was a strong predictor of in-hospital complications in women with T2DM.

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CONTRIBUTIONS

Ana López-de-Andres and Rodrigo Jiménez-Garcia participated in the conception and design, analysis, interpretation, and writing of the manuscript. Valentín Hernández-Barrera and Isabel Jiménez-Trujillo contributed their statistical expertise and towards conception and design, interpretation and writing of the manuscript. Javier de Miguel-Díez, Manuel Méndez-Bailón, José M de Miguel-Yanes, Napoleón Pérez-Farinós, Miguel-Angel Salinero-Fort, José L del Barrio and Martin Romero-Maroto were involved in the critical revision of the manuscript, as well as the interpretation and design. All authors have seen and approved the final version.

COMPETING INTERESTS

The authors declare that they have no competing interests.

DATA SHARING STATEMENT

"No additional data available"

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Table 1. Clinical characteristics, complications and hospital outcomes of hospital admissions for breast cancer and according to type of surgical procedure among women suffering type 2 diabetes and matched women without type 2 diabetes.

	Total (n=6,836)			Breast conservative surgery (n=,3876)			Mastectomy (n=2,960)		
	Diabetes (n=3,418)	No diabetes (n=3,418)	p-value	Diabetes (n=1,938)	No diabetes (n=1,938)	p-value	Diabetes (n=1,480)	No diabetes (n=1,480)	p-value
Age, mean (SD)	70.14(10.22)	70.14(10.22)	NA	68.18(9.53)	68.18(9.53)	NA	72.71(10.51)	72.71(10.51)	NA
40-59 years old, n (%)	522(15.27)	522(15.27)	NA	343(17.7)	343(17.7)	NA	179(12.09)	179(12.09)	NA
60-79 years old, n (%)	2187(63.98)	2187(63.98)		1335(68.89)	1335(68.89)		852(57.57)	852(57.57)	
≥ 80 years old, n (%)	709(20.74)	709(20.74)		260(13.42)	260(13.42)		449(30.34)	449(30.34)	
Stage: Local, n (%)	2590(75.78)	2590(75.78)	NA	1560(80.5)	1560(80.5)	NA	1030(69.59)	1030(69.59)	NA
Stage: Regional, n (%)	799(23.38)	799(23.38)		371(19.14)	371(19.14)		428(28.92)	428(28.92)	
Stage: Distant, n (%)	29(0.85)	29(0.85)		7(0.36)	7(0.36)		22(1.49)	22(1.49)	
CCI0, n (%)	2798(81.86)	3050(89.23)	<0.001	1627(83.95)	1763(90.97)	<0.001	1171(79.12)	1287(86.96)	<0.001
CCI1, n (%)	522(15.27)	324(9.48)		274(14.14)	155(8)		248(16.76)	169(11.42)	
CCI≥2, n (%)	98(2.87)	44(1.29)		37(1.91)	20(1.03)		61(4.12)	24(1.62)	
Vascular disease, n (%)	301(8.81)	226(6.61)	<0.001	159(8.2)	119(6.14)	0.011	142(9.59)	107(7.23)	0.019
Renal disease, n (%)	141(4.13)	48(1.40)	<0.001	61(3.15)	24(1.24)	<0.001	80(5.41)	24(1.62)	<0.001
Stroke/TIA/TEP, n (%)	82(2.40)	55(1.61)	0.020	31(1.60)	22(1.14)	0.201	51(3.45)	33(2.23)	0.051
Congestive heart failure, n (%)	66(1.93)	21(0.61)	<0.001	21(1.08)	9(0.46)	0.020	45(3.04)	12(0.81)	<0.001
Acute myocardial infarction, n (%)	33(0.97)	18(0.53)	0.039	21(1.08)	7(0.36)	0.012	12(0.81)	11(0.74)	0.835
Obesity, n (%)	450(13.17)	124(3.63)	<0.001	267(13.78)	70(3.61)	<0.001	183(12.36)	54(3.65)	<0.001
Hypertension, n (%)	2240(65.54)	1238(36.22)	<0.001	1267(65.38)	654(33.75)	<0.001	973(65.74)	584(39.46)	<0.001
Smoking, n (%)	166(4.86)	185(5.41)	0.288	111(5.73)	121(6.24)	0.488	55(3.72)	64(4.32)	0.393
Sentinel lymph node dissection, n (%)	1697(49.65)	1795(52.52)	0.092	1184(61.09)	1257(64.86)	0.032	513(34.66)	538(36.35)	0.332
Axillary lymph node dissection, n (%)	560(16.38)	551(16.12)	0.747	375(19.35)	382(19.71)	0.752	185(12.5)	169(11.42)	0.349
Infectious complications, n (%)	95(2.78)	76(2.22)	0.138	35(1.81)	22(1.14)	0.088	60(4.05)	54(3.65)	0.560
Non infectious complications, n(%)	219(6.40)	156(4.56)	0.004	93(4.80)	53(2.73)	0.015	126(8.51)	103(6.96)	0.032
All complications (infectious and/or non infectious), n (%)	264(7.72)	181(5.30)	0.003	107(5.57)	59(3.04)	0.008	157(10.60)	122(8.24)	0.029
Length of stay, median (IQR)	3(2-5)	3(2-5)	0.070	2(1-3)	2(1-3)	0.065	4(3-6)	4(3-6)	0.062
In-hospital mortality, n (%)	5(0.15)	2(0.06)	0.277	2(0.1)	1(0.05)	0.571	3(0.2)	1(0.07)	0.341

CCI: Charlson Comorbidity Index. IQR: Interquartile range. P value for difference between T2DM sufferers and matched controls using bivariate conditional logistic regression. Matching was conducted by age, province of residence, type of surgical procedure and stage.

Table 2. Logistic regression analysis of the factor associated with in-hospital complications in women with type 2 diabetes during hospital admission for breast cancer according to the type of surgical procedure.

		Any breast cancer surgical procedure (Conservative or mastectomy) OR (95%CI)	Breast Conservative Surgery OR (95%CI)	Mastectomy OR (95%CI)
Age groups, years	40-59	1	1	1
	60-79	0.98 (0.70-1.37)	0.79 (0.50-1.26)	1.12 (0.67-1.86)
	≥ 80	1.16 (0.79-1.71)	0.92 (0.50-1.67)	1.22 (0.71-2.10)
CCI	0	1	1	1
	1	1.72(1.30-2.27)	1.75(1.12-2.71)	1.64(1.14-2.35)
	≥2	2.55(1.55-4.17)	3.33(1.48-7.48)	2.10(1.13-3.91)
Stage	Local	1	1	1
	Regional/distant	1.21 (0.98-1.48)	1.08(0.74-1.55)	1.19(0.93-1.52)
Obesity	Yes	1.54 (1.14-2.07)	1.68 (1.07-2.60)	1.46(0.98-2.19)

CCI: Charlson Comorbidity Index. OR: Odds Ratio. 95%CI: 95% confidence intervals. All variables included in the models are shown.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	*6-8*
Study size	10	Explain how the study size was arrived at	6-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	8,9
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-17
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-17
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	9-17
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-17
		(*b*) Report category boundaries when continuous variables were categorized	9-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	18-20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20,21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.