Journal of Cardiothoracic and Vascular Anesthesia 38 (2024) 3134−3142

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Article

Sex Differences in Chronic Postsurgical Pain after Open Thoracotomy

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Study Objective: To determine the incidence of chronic postsurgical pain (CPSP) in women after open thoracotomy. Secondary objectives were to compare relevant patient and procedural variables between women and men.
Design: Observational cohort study.
Setting: Ten university-affiliated hospitals.
Subjects: Ninety-six women and 137 men.
Interventions: Scheduled open thoracotomy.
Measurements: Pain histories, psychological measures, and perceived health status and catastrophizing scores were obtained. The diagnosis of chronic postsurgical pain was by physical examination at 4 months. Standard preoperative, intraoperative, and postoperative data were also recorded.
Main Results: The chronic postsurgical pain incidence was significantly higher in women (53.1%) than in men (38.0%) ($p = 0.023$). At baseline, women had significantly worse scores on psychological measures (perception of mental state [$p = 0.01$], depression [$p = 0.006$], and catastrophizing [$p < 0.001$]). Women also reported more preoperative pain in the operative area ($p = 0.011$) and other areas ($p = 0.030$).
Conclusion: These findings show that the incidence of physician-diagnosed chronic postsurgical pain is higher in women than in men after surgeries involving thoracotomy. Sex and gender should be included in future clinical research on pain in surgical settings.

Key Words: chronic postsurgical pain; sex; gender

This work was supported by grant PI16/00279 from the Carlos III Institute of Health and the European Regional Development Fund (ERDF) channeled through the Spanish government's Ministry of Economy, Industry and Competitiveness.

ClinicalTrials.gov: NCT02991287; principal investigator, Antonio Montes; date of registration, December 13, 2016.

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https://doi.org/10.1053/j.jvca.2024.08.039
1053-0770/

Chronic pain continues to be reported after many types of surgery,[1,2] but is especially prevalent after open thoracotomy procedures.[3,4] How chronic postsurgical pain (CPSP) affects women in this setting, however, is poorly understood.

In a previous study by our group, we developed a chronic postsurgical pain (CPSP) risk model (GENDOLCAT) for use in 4 surgical settings: thoracotomy, inguinal hernia repair, abdominal hysterectomy, and vaginal hysterectomy.[5] Because genetic polymorphisms were investigated as possible risk factors, sex differentiation in the surgical cohorts was necessary. We recruited only men for the thoracotomy and hernia repair groups because they predominated among those undergoing these procedures at the time (2009-2011). Nonetheless, when we recruited a new cohort of patients to test the external validity of the risk model in 2017 to 2019,[6] we saw that the percentage of women undergoing open thoracotomy had increased considerably. This increase was unanticipated but consistent with observations of a rise in women undergoing open thoracotomy since the 1970s, especially in relation to surgical oncology.[7,8]

Biological sex has been studied in various pain syndromes to assess its influence on pain intensity, incidence, and response to analgesics.[9] Results have been contradictory, however, and when differences have been observed, they have been attributed to diverse factors, including genetic, social, hormonal, pharmacokinetic, and other influences.[9-13]

Female sex is recognized to be a risk factor for more intense pain after chest surgery.[14-17] Although some studies mention an association between sex and the development of chronic pain, the available studies are retrospective,[2,14] involve multiple types of surgeries (including reoperations),[14,16] and diagnose CPSP based on telephone interviews only. The studies also primarily include men, reflecting a historical bias in the surgical literature corroborated by meta-analysis.[18] Data on the incidence of CPSP in women after invasive procedures remain scarce and do not provide high levels of evidence.

We hypothesized that the incidence of CPSP might be higher in women than in men after open thoracotomy and sought and received approval for an amendment to the external validation study to allow us to recruit a parallel cohort of women following the same study design within the same time frame.[6] The primary objective was to determine the incidence of CPSP in women. The secondary objectives were (1) to compare the incidence of CPSP between women and men and (2) to compare patient and procedural characteristics according to biological sex in those with diagnosed CPSP, with an emphasis on quality of life and interference with function and other aspects related to quality of life.

Materials and Methods

Study Design, Participants, and Registration

This was a prospective, observational multicenter study conducted in parallel to the external validation[6] of the six-factor GENDOLCAT CPSP risk model[5] (ClinicalTrials.gov NCT02991287). (The factors in this model are surgical procedure, younger age, physical health [Short Form Health Survey 12 (SF-12)], mental health [SF-12], preoperative pain in the surgical field, and preoperative pain in another area.) Candidates for inclusion in the present study were being a woman scheduled for open thoracotomy under general anesthesia according to local clinical protocols. Exclusion criteria were the same as in the validation study: age under 18 years, reoperation due to surgical complications, a serious psychological disorder, a history of graft or organ transplantation, and evidence of oncologic involvement of the chest wall found during surgery.

The institutional review boards (IRBs) at 10 of the 17 hospitals approved a study to be conducted parallel to the validation trial in men that would enroll women undergoing open thoracotomy over a period of 24 months to determine the incidence of CPSP and other variables for comparison with men. Approval was received from the IRBs and the funding body (the Spanish Ministry of Health) by December 1, 2016. Scanned copies of the IRB decision letters were sent to the principal investigator, who stored all files.

Although the model development[5] and external validation[6] studies collected data for 4 surgical settings, the present study focused only on open thoracotomy in women for comparison with data being collected for men in the concurrent validation study. Enrollment of women began in July 2017 at the first center and ended in June 2019 (24 months), coinciding with the enrollment of men for the validation study.

Women scheduled for open thoracotomy were screened, contacted, and asked to provide consent for additional data collection, follow-up telephone contact, and a hospital appointment for a physical examination to confirm CPSP at 4 months. Otherwise, the women received routine care.

Data Collection

Designated anesthesiologists from each hospital attended training sessions on how to complete all the clinical questionnaires during the routine presurgical visit and to confirm CPSP at the hospital. Briefly, before surgery, the anesthesiologist administered the validated Spanish version of the Hospital Anxiety and Depression Scale (HADS) to screen all patients for these conditions.[19] The SF-12 questionnaire (Spanish version) was used to assess the physical and mental components of quality of life.[20] The validated Spanish version of the Pain Catastrophizing Scale was also administered.[21] Other data recorded at this time were physical status according to the American Society of Anesthesiologists' risk classification, the presence of prior pain in the area of surgery and in other parts of the body expressed on a verbal numerical rating scale of 0 to 10 (0 = no pain; 10 = the worst imaginable pain), history of treatment with analgesics, concomitant diseases, and any history of substance addiction. Surgical variables collected included diagnosis, planned approach, duration, techniques of regional and local anesthesia, doses of opioids and antihyperalgesic agents, and intraoperative complications. The structured telephone interview to screen for possible CPSP was done by one of the investigators (J.C.) 3 months after each patient's surgery. If pain was still present, the patient was given a hospital outpatient appointment for a physical examination at approximately 4 months after surgery to confirm or rule out CPSP. To check for neuropathic pain at this time, the examiner used the Douleur Neuropathique 4 tool (DN4).[22] If a patient was lost to follow-up, the Spanish National Health Service Death Register was checked.

Outcomes

The primary outcome was the incidence of CPSP in the enrolled women at 4 months. The diagnosis, which was made after physical examination by an anesthesiologist with expertise in chronic pain management, was based on the 2016 IASP criteria,[23] as follows: (1) the pain developed after a surgical procedure; (2) the duration of pain is of at least 3 months' duration; (3) other causes for the pain, such as continuing malignancy or chronic infection, can be excluded; and (4) the possibility that pain is continuing from a preexisting problem has been explored so that it can be excluded if possible.

To meet the secondary aims of comparing the incidence of CPSP in women and men and patient and procedural characteristics in those diagnosed with this condition, we extracted data for the thoracotomy subsample of men in the external validation study.[6]

Sample Size

It was assumed that the incidence of CPSP after thoracotomy would be at least as high as the 37% observed in men in the CPSP risk model development study.[5] Based on this premise and with an alpha error of 0.05 and a precision level of 10%, a sample size of 90 women was calculated. To account for potential loss to follow-up, an additional 20% was planned for recruitment if necessary.

Statistical Analysis

Categorical variables were expressed as the number of cases and percentage. Continuous variables were expressed as the median and 10th to 90th percentile range or mean (standard deviation), where appropriate. We also calculated 95% CIs for all measures. To compare demographic and clinical characteristics and the CPSP incidences between the women in this study and the men in the external validation cohort,[6] we used the *t* test for normally distributed continuous variables, the equivalent Mann-Whitney *U* test for nonparametric variables, or the χ^2 test for categorical variables. A mixed ANOVA with a sphericity test (nonsignificance, $p > 0.05$) and Bonferroni correction for multiple comparisons was carried out to analyze pre-post quality life according to biological sex.

A multivariable logistic regression was performed with CPSP as the dichotomous dependent variable. The independent variables were those significantly associated with biological sex in the univariable analysis. Odds ratios (OR) and their 95% confidence interval (CI) were also calculated.

Statistical analyses were performed using the R software, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria), and IBM SPSS software, version 20.

Results

Six of the 10 hospitals that participated in the present study analyzing CPSP in women following open thoracotomy enrolled women. A total of 101 women were enrolled in this cohort, recruited parallel to the men in the thoracotomy arm of the external validation study for the GENDOLCAT risk model for CPSP.[6] Five of the 101 women (5%) were lost to follow-up. The remaining 96 women (Fig 1) were screened for ongoing postsurgical pain in telephone interviews before they were scheduled for physical examination to confirm CPSP at 4 months.

The incidence of CPSP was statistically significantly ($p = 0.023$) higher in the cohort of women (53.1%) than in the parallel cohort of men who underwent the same type of surgery (38.0%) (Table 1).

Mental component scores on the SF-12 and depression scores on the HADS questionnaire indicated poorer status in women than in men (Table 1). The women also showed higher levels of catastrophizing for magnification of pain and helplessness but not for rumination. The prevalence of pain anywhere in the body was 2-fold higher at baseline, and the prevalence of pain in the surgical area was nearly 4-fold higher. In addition, we detected significant differences by sex in abuse of alcohol and drugs (higher in men). Significantly more women than men were never smokers.

The diagnoses that led to scheduling (Table 2) were similar in women and men ($p > 0.05$, all comparisons).

Table 3 shows the pain intensity, interference caused by it, and quality of life measures according to the SF-12 findings at 4 months after surgery in patients who developed CPSP. No differences were observed between women and men.

On comparing the quality of life of patients with CPSP before and after surgery, no significant interactions between sex and time were observed on the physical scale of the SF-12 ($F_{1,96} = 0.012$; $p = 0.914$). Although the mean score decreased 6.8 points (95% CI, 4.7-8.9 points) after surgery in those with CPSP, there was no difference between the sexes. The interaction between sex and scores on the mental scale was significant ($F_{1,96} = 5.075$; $p = 0.027$). In this case, the mean score increased 3 points in women (from 41.3 to 44.3) and decreased 2 points in men (from 46.6 to 44.6) (Fig 2).

The results of the univariable and multivariable analysis with CPSP as the dependent variable and variables significantly associated with sex as the independent variables are shown in Table 4. Significant effects were observed for body mass index (BMI) ($p = 0.04$) and preoperative pain in other areas ($p = 0.002$), indicating that patients of normal weight and those with pain in other areas before surgery are more likely to develop CPSP (OR 2.25 and 3.22, respectively).

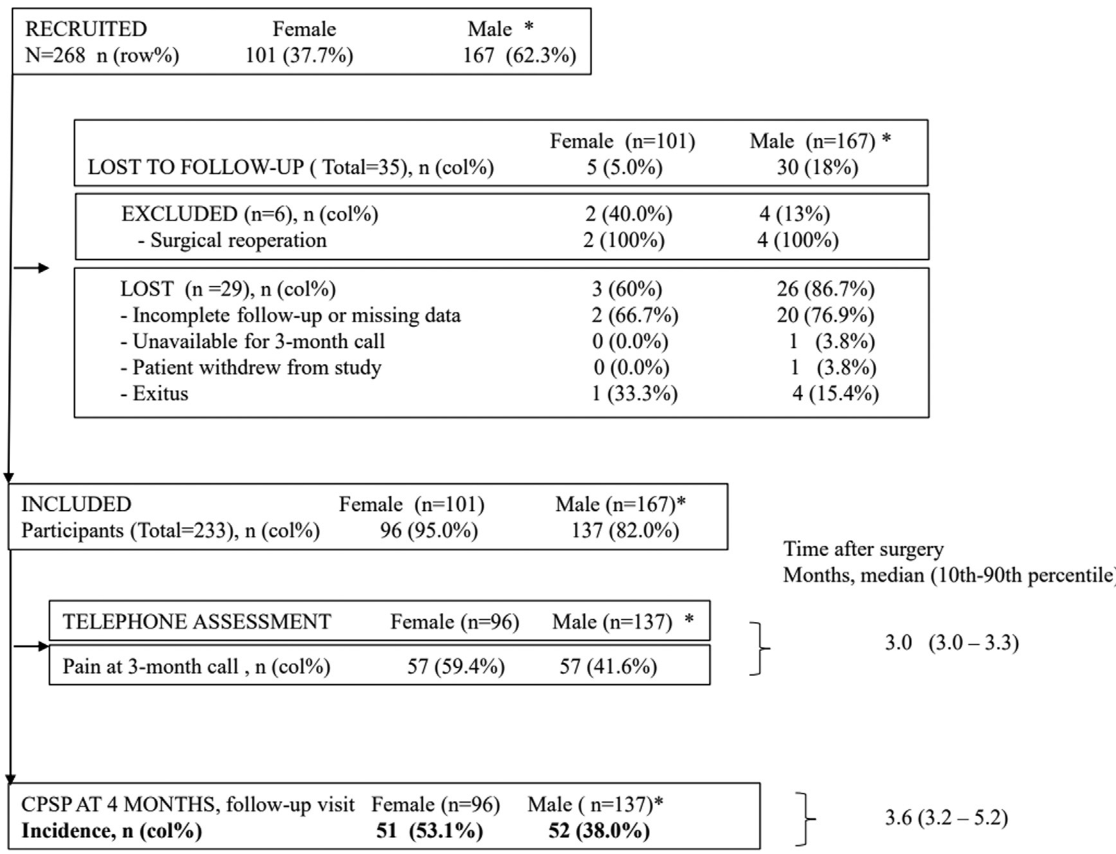

Fig 1. Recruitment flowchart, showing numbers of patients recruited by sex and those lost up until confirmation of chronic postsurgical pain (CPSP) at the follow-up visit at 4 months. Percentages are of the number shown at the head of each column (col%).* Data for the men were extracted from the external validation study[6] for the 6-factor CPSP model developed earlier.[5] The men and the women were recruited at the same time.

Discussion

This study reveals a significantly higher incidence of CPSP after open thoracotomy in women (53.1%) than in men (38.0%) (p = 0.023). At baseline, women had significantly worse scores on several psychological measures (perception of mental state [p = 0.01], depression [p = 0.006], and catastrophizing [p < 0.001]). They also reported more preoperative pain in the surgical area (p = 0.011) and other areas (p = 0.030). No differences in pain intensity or interference with activities after open thoracotomy were observed between women and men, with both sexes showing similar decreases in physical component scores on the SF-12. However, the interaction between sex and scores for the mental-component variables was significant (p = 0.027), with a mean increase of 3 points in women and a mean decrease of 2 points in men.

In our review of the literature on CPSP and open thoracotomies, we found just one study examining the effects of sex on the incidence of CPSP.[17] The study, however, did not control for potential confounders such as chest wall complications and reoperations, and follow-up was by telephone only. Our review confirmed the high prevalence of CPSP following open thoracotomy.

Depression and pain are known to be closely associated, and somatic symptoms in depression are known to be frequent in women.[15] Thus, the higher presurgical prevalence of pain in the area of surgery and other areas, both factors present in women in this study, could partially explain their higher prevalence of depression. These findings are consistent with the fact that the mental component of the SF-12 is one of the 6 risk factors in the validated CPSP risk model.[5,6] Pain catastrophizing, which was not considered when the study to develop the CPSP risk model was designed, might also have been a relevant predictor if we had been able to recruit women undergoing thoracotomy. However, when the validated model of the Spanish version of the catastrophizing scale was introduced after the development study had been registered,[21] we decided to measure it outside the study protocol during the external validation and therefore had data for men for comparison with the present study in women. Although relationships among pain intensity, catastrophizing, and sex have been reported in small studies,[9] contradictory ones were found in a large study.[24] Our findings nonetheless lead us to think that appropriately powered studies in the future may well be able to demonstrate that the catastrophizing scale is useful as a predictor for models of chronic pain development in some settings.

Like biological sex, none of the psychological variables with significant associations in the univariable analysis were predictors of CPSP in the logistic regression analysis. The only predictors that retained their significance were pain in

Table 1
Patient Characteristics at Baseline and the Incidence of CPSP in Women and Men after a Thoracotomy Procedure

	Thoracotomy			
	Women (n = 96)	Men* (n = 137)	Total (N = 233)	p
Patients with CPSP	51 (53.1)	52 (38.0)	103 (44.2)	0.023
Patients with neuropathic pain	37 (72.5)	32 (61.5)	69 (67.0)	0.235
Age (y)				0.506
18-51	17 (17.7)	18 (13.1)	35 (15.5)	
>51-64	37 (38.5)	48 (35.0)	85 (36.5)	
>64	42 (43.8)	71 (52.2)	113 (48.1)	
BMI				0.067
0-22.5	26 (27.1)	21 (15.3)	47 (20.2)	
>22.5-28.0	34 (35.4)	63 (46.0)	97 (41.6)	
>28.0	36 (37.5)	53 (38.7)	89 (38.2)	
SF-12 physical summary (mean [SD])	43.6 (8.1)	45.4 (8.5)	45.1 (8.9)	0.033
SF-12 physical summary (categorized)				0.088
0-33.5	17 (17.7)	12 (8.8)	29 (12.4)	
33.6-55.1	64 (66.7)	107 (78.1)	171 (73.4)	
>55.1	15 (15.6)	18 (13.1)	33 (14.2)	
SF-12 mental summary (mean [SD])	42.5 (11.3)	48.2 (10)	45.9 (10.9)	<0.01
SF-12 mental summary (categorized)				<0.01
0-44.8	54 (56.3)	41 (29.9)	95 (40.8)	
>44.8	42 (43.8)	96 (70.1)	138 (59.2)	
Anxiety (HADS) (mean [SD])	47 (49.0)	52 (38.2)	99 (42.7)	0.104
Depression (HADS) (mean [SD])	31 (32.3)	23 (16.8)	54 (23.2)	0.006
Pain Catastrophizing Scale				<0.001
0-1	7 (7.3)	25 (18.4)	32 (13.8)	
2-28	71 (74.0)	107 (78.7)	178 (76.7)	
>28	18 (18.8)	4 (2.9)	22 (9.5)	
Pain Catastrophizing Scale, rumination				0.060
0	14 (14.6)	36 (26.5)	50 (21.6)	
1-11	71 (74.0)	91 (66.9)	162 (69.8)	
>11	11 (11.5)	9 (6.6)	20 (8.6)	
Pain Catastrophizing Scale, magnification >3	58 (60.4)	51 (37.5)	109 (47.0)	0.001
Pain Catastrophizing Scale, helplessness				<0.001
0-3	35 (36.5)	89 (65.4)	124 (53.4)	
4-8	33 (34.4)	33 (24.3)	66 (28.4)	
>8	28 (29.2)	14 (10.3)	42 (18.1)	
Preoperative pain >3, surgical area	13 (13.5)	5 (3.6)	18 (7.7)	0.011
Preoperative pain >3, other areas	31 (32.3)	26 (19.0)	57 (24.5)	0.030
Anesthesia				0.687
General	7 (7.3)	12 (8.8)	19 (8.2)	
Combined	89 (92.7)	125 (91.2)	214 (91.8)	
Intraoperative intravenous opioid	96 (100.0)	135 (100.0)	231 (100.0)	1.000
Substance addiction	47 (49.0)	111 (81.0)	158 (67.8)	<0.001
Alcohol addiction	4 (4.2)	17 (12.4)	21 (9.0)	0.031
Smoking addiction				<0.001
Never	50 (52.1)	26 (19.0)	76 (33.0)	
Former	24 (25.0)	83 (60.6)	107 (45.5)	
Current	22 (22.9)	28 (20.4)	50 (21.5)	
Street-drug addiction	0 (0.0)	1 (0.7)	1 (0.4)	>0.999
ASA physical status >2	59 (61.5)	88 (65.0)	147 (63.5)	0.681
Intraoperative intravenous remifentanil	3 (3.1)	21 (15.7)	24 (10.4)	0.002
Postsurgical pain >3 at 24 h	18 (18.8)	18 (13.1)	36 (15.0)	0.273

Data are number of patients and the percentage of the number in each cohort shown at the top of the column.

* Data for the men were extracted from the external validation study[6] for the 6-factor CPSP model developed earlier.[5]

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CPSP, chronic postsurgical pain; HADS, Hospital Anxiety and Depression Score; SF-12, Short Form Health Survey-12.

other parts of the body and normal BMI. Pain catastrophizing might have been predictive with a larger sample, as a trend toward significance was observed (Table 4).

Pain in other parts of the body has been widely described as an independent risk factor for CPSP.[5,25,26] Chronic pain is thought to sensitize central pain pathways,[27,28] possibly explaining the increased risk of CPSP associated with preoperative pain. Higher rates of chronic pain in other parts of the body have been reported for women in developed and less developed countries.[29,30]

Table 2
ICD-9[*] Diagnostic and Procedure Codes Recorded for Enrolled Patients, According to Sex

Diagnostic codes		Women, n = 96 No. (%)	Men,[†] n = 137 No. (%)	p
162	Malignant neoplasm of trachea/bronchus or lung	65 (67.7)	93 (67.9)	1
195	Malignant neoplasm of the thorax	13 (13.5)	31 (22.6)	0.09
212	Benign neoplasm of trachea/bronchus or lung	9 (9.4)	5 (3.6)	0.09
	Other diagnoses[‡]	9 (9.4)	8 (5.8)	0.32
Procedure codes				
32.29	Excision of pulmonary nodule or atypical segmentectomy	9 (9.4)	20 (14.6)	0.31
21.3	Segmental lung resection	34 (35.4)	32 (23.4)	0.06
32.4	Lung lobectomy	41 (42.7)	74 (54.0)	0.11
	Other surgical procedures[°]	12 (12.5)	11 (8.0)	0.27

* ICD-9 codes were used during the GENDOLCAT study to develop the risk model for chronic postsurgical pain,[5] the validation study,[6] and the present study.
† Data for the men were extracted from the external validation study.[6]
‡ 163 (malignant neoplasm of pleura), 930.0/934.1/934.8 (foreign body in trachea/bronchus/lung).
° 32.1 (excision of bronchus), 32.5 (total pneumectomy), 34.02 (exploratory thoracotomy), 34.3 (excision destruction of lesion or tissue in the mediastinum), 34.51 (decortication of the lung), 34.81/34.82 (excision of lesion/suture or other operation on the diaphragm), 34.99 (other operation on the thorax).
Abbreviation: ICD, *International Classification of Diseases*.

Our observation of a significant association between normal BMI and the risk of CPSP contrasts with existing reports. One study found that obese patients experienced more postoperative pain than nonobese patients after lung cancer surgery,[31] whereas another study identified a high BMI as a risk factor for CPSP after thoracic surgery.[32] It has been postulated that the association between a high BMI and CPSP might be related to the proinflammatory cytokine resistin.[33,34]

Table 3
Pain and Interferences in Patients with CPSP at 4 Months, According to Sex

	Thoracotomy			
	Women (n = 51)	Men* (n = 52)	Total (n = 103)	p
Pain at its worst in the last 24 h	4.49 (2.29)	4.24 (2.51)		0.607
Pain at its least in the last 24 h	1.02 (1.49)	0.72 (1.29)		0.287
Pain on average	2.90 (1.87)	2.64 (1.71)		0.476
Pain right now	1.53 (2.25)	1.64 (2.14)		0.804
Pain interference >3, %*				
General activity	35.3	44.2		0.412
Mood	33.3	30.8		0.473
Walking ability	31.4	34.6		0.830
Normal work	43.2	42.3		1.000
Relations with others	21.6	25.0		0.810
Sleep	35.3	30.8		0.671
Enjoyment of life	35.3	30.8		0.6 71
SF-12 score, physical summary	(n = 49)	(n = 49)	(n = 98)	
Mean (SD)	37.0 (8.5)	39.02 (8.3)	38.2 (8.4)	0.198
0-33.5	20 (40.8)	13 (26.5)	33 (33.7)	
33.6-55.1	28 (57.1)	35 (71.4)	63 (64.3)	
>55.1	1 (2.0)	1 (2.0)	2 (2.0)	0.095
SF-12 score, mental summary	(n = 49)	(n = 49)	(n = 98)	
Mean (SD)	44.3 (9.5)	44.6 (11.6)	44.5 (10.5)	0.930
0-44.8	23 (46.9)	24 (49.0)	47 (48.0)	
>44.8	26 (53.1)	25 (51.0)	51 (52.0)	0.999

Data are number of patients and the percentage of the number in each cohort shown at the top of the column.
* Percentages of patients with a verbal numerical rating scale score >3 for pain.

Comparison of quality of life before and after surgery, as measured by the mental component of the SF-12, showed an improvement in men but a worsening in women. Our findings cannot be directly compared with others in the literature, as no studies have addressed this question in the field of open thoracotomy. Nonetheless, in a study of self-identified men and women undergoing lumbar decompression surgery, Jacob et al.[35] found that men had similar postoperative improvements and clinical outcomes to women but lower levels of postoperative satisfaction for disability, leg pain, back pain, and lifting. The authors suggested that gender might influence patient satisfaction and could be attributed to differing preoperative expectations at baseline for recovery. In more general terms, although exposure to adversity increases risk for poor mental outcomes, our results could be partly due to sex-related differences in stress responses between men and women.[36]

A noteworthy statistically significant difference between the care received by men and women in the 2 cohorts was related to anesthetic technique. Intraoperative remifentanil, a potent analgesic, was used much more often in men. This difference occurred even though no relevant hospital protocols related to that choice were in effect and even though the protocol for the use of general anesthesia was the same in both sexes. We surmise that anesthesiologists may unconsciously harbor a different attitude to male and female patients, possibly a marker of androcentric medicine, such as has been observed in the management of cardiovascular diseases.[37]

In addition, the higher incidence of CPSP in women cannot be explained by the lower use of remifentanil in this group, as this treatment has been associated with an increased rather than a decreased incidence of CPSP after thoracotomy.[38]

One strength of this study is that we based the CPSP diagnosis on physical examination of patients, not just a patient's report of pain in a telephone interview. The percentages of diagnosed CPSP on examination (at 4 months) fell below the percentages of pain reported by telephone (at 3 months) in both our cohorts, supporting the rigor of our diagnostic

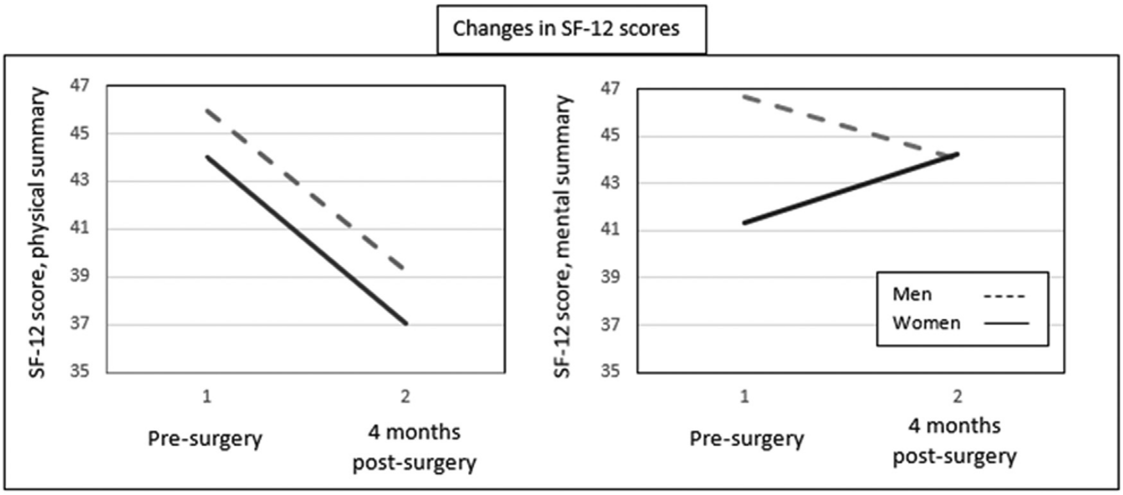

Fig 2. Direction and magnitude of changes in physical- and mental-component scores on the Short Form Health Survey 12 quality of life tool (SF-12) before open thoracotomy and 4 months later in patients with chronic postsurgical pain according to biological sex. The dashed and solid lines indicate changes in scores for men and women, respectively.

approach. The examining physician, who used the DN4 criteria, was an anesthesiologist experienced in chronic pain management, and the visit took place at least 4 months after surgery, the established period for defining chronic pain.[23] Another strength is that we excluded patients in whom evidence of oncologic involvement of the chest wall was found during surgery, thus eliminating a possible confounding factor that might have contributed to overestimating the incidence of CPSP. Finally, we recruited fewer-than-anticipated patients as the loss to follow-up was lower than expected.

Table 4
Univariable and Multivariable Analysis for CPSP (Dependent Variable) and Variables Significantly Associated with Sex

	Univariable Analysis				Multivariable Analysis			
	OR	IC		p	OR	IC		p
Sex	1.85	1.09	3.12	0.022				0.721
BMI				0.038				0.042
0-22.5	1.48	0.72	3.03	0.284	1.20	−2.74	0.53	0.661
>22.5-28.0	2.15	1.19	3.86	0.011	2.25	1.17	4.33	0.015
>28.0 (reference level)								
SF-12, physical summary				0.759				0.706
0-33.5	0.78	0.36	1.69	0.521				
33.6-55.1	0.70	0.26	1.88	0.480				
>55.1 (reference level)								
SF-12, mental summary	0.60	0.36	1.01	0.056				0.630
Anxiety (HADS)	1.50	0.89	2.32	0.126				0.561
Depression (HADS)	1.20	0.81	2.75	0.194				0.561
Pain Catastrophizing Scale, rumination				0.323				0.516
0	1.45	0.76	2.75	0.259				
1-11	2.12	0.75	6.04	0.159				
>11 (reference level)								
Pain Catastrophizing Scale, magnification >3	2.04	1.21	3.43	0.007				0.340
Pain Catastrophizing Scale, helplessness				0.004				0.117
0-3	1.86	1.02	3.4	0.042				
4-8	3.15	1.53	6.45	0.002				
>8 (reference level)								
Preoperative pain >3, surgical area	2.73	0.99	7.54	0.053				0.285
Preoperative pain >3, other areas	3.51	1.88	6.58	<0.01	3.22	1.53	6.78	0.002
Alcohol addiction	1.43	0.58	3.54	0.444				0.189
Smoking addiction				0.044				0.151
Never	1.64	0.81	3.33	0.174				
Current	0.70	0.38	1.26	0.231				
Former (reference level)								
Intraoperative intravenous remifentanil	0.98	0.42	2.25	0.958				0.851

Abbreviations: BMI, body mass index; CPSP, chronic postsurgical pain; HADS, Hospital Anxiety and Depression Score; SF-12, Short Form Health Survey-12.

A limitation is that we did not also ask about or record gender identification, a category with societal relevance. The terms "sex" and "gender," while related, are not synonymous.[39] We classified patients only according to biological characteristics, as is recommended when such parameters are suspected to be relevant.[40] However, we agree with researchers who have recently recommended using biopsychosocial approaches that look at both sex and gender when designing studies of chronic pain,[41] especially in surgical cohorts. Another limitation is that we did not study video-assisted thoracic surgery, which is gradually replacing open thoracotomy.[42,43] The impact of a shift to minimally invasive procedures on the development of chronic pain is still under debate.[44]

Our data for cohorts treated with similar surgical and anesthetic approaches show that the incidence of physician-diagnosed CPSP after thoracotomy seems to be higher in women, over half of whom might be expected to experience chronic pain according to our findings. However, this observation should be verified in other geographic settings.

Our study shows that independent of biological sex, women experience more pain than men after open thoracotomy, highlighting the importance of always implementing a biopsychosocial approach in clinical research in human patients, particularly in CPSP. Attention should be given to psychological perspectives, biological sex and gender, and in the case of CPSP, the higher prevalence of pain reported by women in other parts of the body. Another noteworthy finding is that while both men and women had worse physical component scores on the SF-12 after surgery, they had different mental component scores, with our interaction analysis showing an improvement in men but a worsening in women. While measures to prevent or reduce CPSP should benefit both men and women alike, we suggest heightened surveillance and treatment in women as they may be at greater risk for this condition. Future studies should aim to improve prediction models and develop advanced prevention strategies for CPSP. These studies should focus not only on pain intensity but also on other pain-related aspects, such as quality of life and physical and psychological well-being.

Declaration of competing interest

The authors declare the following financial interests/personal relationships, which may be considered as potential competing interests: A.M.P. reports financial support, administrative support, statistical analysis, and writing assistance were provided by Carlos III Institute of Health. A.M.P. reports a relationship with Carlos III Institute of Health that includes funding grants. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Gisela Roca: Writing − review & editing, Writing − original draft, Validation, Supervision, Methodology, Investigation, Conceptualization. **Sergi Sabate:** Writing − review & editing, Writing − original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Ancor Serrano:** Writing − review & editing, Writing − original draft, Supervision, Methodology, Conceptualization. **María Carmen Benito:** Writing − review & editing, Validation, Investigation. **María Pérez:** Writing − review & editing, Supervision, Investigation. **Miren Revuelta:** Writing − review & editing, Supervision, Investigation. **Ana Lorenzo:** Writing − review & editing, Supervision, Investigation. **Jordi Busquets:** Writing − review & editing, Validation, Investigation. **Gema Rodríguez:** Writing − review & editing, Supervision, Investigation. **David Sanz:** Writing − review & editing, Validation, Investigation. **Anabel Jiménez:** Writing − review & editing, Validation, Investigation. **Ana Parera:** Writing − review & editing, Validation, Investigation. **Francisco de la Gala:** Writing − review & editing, Supervision, Investigation. **Antonio Montes:** Writing − review & editing, Writing − original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

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Acknowledgments

Mary Ellen Kerans, MA, translated portions of the drafted manuscript and advised on English language expression in the authors' revisions.

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