Diagnosed and undiagnosed cough-related stress urinary incontinence in women with refractory or unexplained chronic cough: Its impact on general health status and quality of life

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Abstract

Background: Stress urinary incontinence (SUI) is common in women with chronic cough but may be overlooked. **Objective:** To determine the frequency of underdiagnosis of cough-related SUI and its impact on women's general health status and quality of life (QoL). **Methods:** Data were analyzed for 147 women with refractory/unexplained chronic cough. Relevant details were collected from clinical charts and a patient-completed survey. General health status was assessed using the EuroQoL visual analogue scale (EQ-VAS) and QoL with the cough-specific Leicester Cough Questionnaire (LCQ). **Results:** Women were classified into diagnosed (n = 32; 21.8%) or undiagnosed (n = 33; 22.4%) cough-related SUI, and no SUI (n = 82; 55.6%) groups. Women with versus without cough-related SUI perceived poorer health status and greater impact of cough on everyday lives. Mean LCQ scores were significantly lower in cough-related SUI groups versus no SUI group. In multivariate analysis, the presence of cough-related SUI was significantly associated with lower EQ-VAS and LCQ scores. **Conclusion:** In our cohort, 44% of women had cough-related SUI, and half were undiagnosed. Irrespective of diagnosis, impairment to everyday lives and QoL was similar. Diagnosing cough-related SUI may identify additional patients who can benefit from therapies to suppress cough and improve QoL.

Keywords

Chronic cough, stress urinary incontinence, cough-related quality of life, diagnosis, survey, Spain

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Introduction

Chronic cough (cough lasting >8 weeks) affects an estimated 5−10% of the world's population, predominantly women.[1] Chronic cough is a well-established risk factor for stress urinary incontinence (SUI) in women,[2–5] which is defined as the involuntary loss of urine due to a sudden increase in intra-abdominal pressure caused by effort, exertion or upon sneezing or coughing.[6] In populations with chronic cough or associated conditions such as chronic obstructive pulmonary disease (COPD), urinary incontinence was present in about half the women[7,8]; and in an even higher proportion (63%) when women were queried directly by their physician about cough-related SUI.[9] As chronic cough and SUI are both associated with anxiety, depression, social isolation and work limitations, there may be cumulative impairment to patients' quality of life (QoL).[10–12]

To understand the burden of cough for the health system and patients, we conducted an observational study of patients with refractory or unexplained chronic cough who attended outpatient clinics in Spanish hospitals. For context, refractory chronic cough (RCC) refers to a cough that persists despite optimal treatment for its presumed cause in a patient who is adherent to medical recommendations. Unexplained chronic cough (UCC) denotes cough when no diagnosable cause has been found despite extensive assessment for common and uncommon causes.[1] Cough-related SUI was documented in 18.4% of patients' clinical charts, with 2-fold greater frequency in women than men (21.1% vs. 9.1%).[13] In a parallel patient survey, 38.1% of women but the same percentage of men (9.1%) reported that cough-related SUI occurred 'frequently' or 'mostly/always',[14] further suggesting that cough-related SUI is underdiagnosed in women. This prompted us to examine the matter in greater detail. The current analysis aimed to determine the frequency of underdiagnosis of cough-related SUI, whether the profile of women with undiagnosed SUI is similar or different to that of women with diagnosed cough-related SUI, and the relationship between cough-related SUI and women's general health status and QoL.

Methods

The aforementioned retrospective, multicenter, non-interventional study focused on the burden of RCC and UCC to the healthcare system and patients. Methods and main outcomes have been reported previously.[13,14] Briefly, patients were recruited in allergy and pulmonology outpatient hospital clinics from the Spanish National Healthcare System. Consecutive adult patients (>18 years-old) with a diagnosis of RCC or UCC, who had cough of more than 1 year's duration, and who had cough on the day of the visit, were invited to participate. Active smokers or individuals who had stopped smoking in the previous

12 months were excluded. Other exclusion criteria were treatment with ACE inhibitors; chronic cough related to COPD, cancer, active infection, bronchiectasis, interstitial lung disease, cystic fibrosis, or Gilles de la Tourette syndrome; current participation in interventional studies; or conditions that, in the judgment of the treating physician, advised against participation (e.g., cognitive impairment, major depression, end-stage disease). The study protocol was reviewed and approved by the Research Ethic Committees of all participating hospitals. Enrolled patients provided signed informed consent before data collection began.

Information was collected from patients' clinical records and from a printed survey that patients and relatives completed without investigator or treating physician overview. Information collected from clinical charts comprised patients' characteristics, comorbidities, cough characteristics and cough-related diagnostic procedures and treatments. The predefined period for chart review was up to 3 years before study inclusion. Information collected from the printed patient survey included the impact of chronic cough on daily life activities, QoL, and a range of physical items.

The presence of cough-related SUI was explored either as a diagnosis documented in clinical charts and as a physical complication reported by patients in the printed survey. Women with a diagnosis of cough-related SUI in their clinical chart (yes/no) were considered to have 'Diagnosed cough-related SUI'. Women without a diagnosis of SUI in their clinical chart but who responded 'frequently' or 'mostly/always' to the survey question "*Do you ever have urinary incontinence (loss of urine) due to your cough?*" were considered to have 'Undiagnosed cough-related SUI'. Women without a diagnosis of SUI in their clinical chart and who did not select 'frequently' or 'mostly/always' in response to the survey question on cough-provoked urine incontinence were considered to have 'no SUI'.

As part of the printed survey, patients were asked a series of questions about the impact of cough on everyday life (e.g., home, work, social activities). The 15 items were adapted from questions reported in previous studies,[15,16] or were created ad hoc for study purposes under the guidance of cough experts. Patients were instructed to respond to the questions according to the impact of cough as a chronic condition in their everyday lives, and not to restrict their responses to a specific time interval. Response options ranged from 1 = Not at all to 7 = Extremely high.

Patients also completed the EQ-5D-5-L questionnaire (https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/), which is a generic measure of general health status. The EQ-5D descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Patients self-assess each dimension by selecting one of five levels ranging from 'no problems' to 'extreme problems'. The

accompanying EQ visual analogue scale (EQ-VAS) is labelled vertically from 0 = 'The worst health you can imagine' to 100 = 'The best health you can imagine', and is used as an overall quantitative measure of general health that reflects the patient's own judgement (https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/). A EQ-5Q index value for each patient was calculated using the value set for health states of the EQ-5D-5-L based on preferences of the Spanish population.[17]

Patients also completed the Leicester Cough Questionnaire (LCQ), a validated 19-item instrument used to assess the impact of cough on QoL.[18] The LCQ comprises three domains: physical, psychological, and social. Patients assess their cough symptoms and impact of cough on their QoL over the previous 2 weeks using a 7-point Likert-type scale for each item. Mean scores of each domain are calculated as the average of their items, yielding values from 1 to 7. The LCQ total score is the sum of the three individual mean scores, ranging from 3 to 21. Lower LCQ scores indicate poorer QoL due to cough. A change from baseline of 1.3 in the LCQ total score is the minimal clinically important difference.[19] The LCQ has been used in clinical trials of patients with RCC/UCC as a measure of cough-related QoL.[20,21]

Statistical analysis

Variables are summarized descriptively as mean ± standard deviation (SD) or as number and percentage. The impact of cough on women's everyday life is described according to the number (percentage) of women who responded 'quite a bit', 'very much' or 'extremely high' to each of the 15 items on the questionnaire. Differences between groups (diagnosed cough-related SUI, undiagnosed cough-related SUI, no SUI) were assessed using the chi-square test. General health status and QoL of respondents is described by the proportion of women who indicated any problem in the EQ-5D dimensions, and by the mean ± SD EQ-VAS score. The impact of cough on women's QoL is described according to mean ± SD LCQ scores (physical, psychological, social and total). Differences between the three groups were analyzed using the analysis of variance (ANOVA) test.

Multiple linear regression models were used to examine the relationship between cough-related SUI, general health status (EQ-VAS score) and cough-related QoL, with EQ-VAS and LCQ scores as dependent variables. Explanatory variables were those with potential to influence health status and cough-related QoL. Cough severity as perceived by patients was measured using a 100 mm cough severity VAS score from 'no cough' (0 mm) to 'worst cough' (100 mm) and was introduced into the model as a discreet variable by increments of 10 units. Beta coefficients ±SD with *p* values are provided.

All analyses were performed using the IBM SPSS 20.0.0 statistical program.

Results

Of 152 women who entered the study, five did not complete the printed survey. Data for 147 women were valid for the current analysis. Mean age was 57.9 ± 13.3 years and mean duration of cough was 6.2 ± 4.5 years. The number (%) of responses to the survey question "*Do you ever have urinary incontinence (loss of urine) due to your cough?*" were: never/hardly ever: 36 (24.5%); rarely: 17 (11.6%); sometimes: 38 (25.9%); frequently: 30 (20.4%) and mostly/always: 26 (17.7%).

Thirty-two women (21.8%) with a diagnosis of urinary incontinence documented in their clinical chart formed the diagnosed cough-related SUI group. Thirty-three women (22.4%) without a diagnosis of urinary incontinence in their clinical chart but who responded that their cough provoked urinary incontinence 'frequently' or 'mostly/always' constituted the undiagnosed cough-related SUI group. The remaining 82 women (55.6%) without a diagnosis of urinary incontinence in their clinical chart and who responded other than 'frequently' or 'mostly/always' to the question on cough-provoked urinary loss formed the 'no SUI' group.

Table 1 presents the characteristics of women according to their SUI diagnostic status. Mean body mass index (BMI) was higher in women with cough-related SUI than without SUI and the difference between the undiagnosed SUI group and the no SUI group was statistically significant (28.5 vs. 26.1 kg/m^2; *p* = .042). Cough characteristics were similar across the three diagnostic groups. The mean cough severity VAS score was similar between women with diagnosed and undiagnosed cough-related SUI, and was slightly but non-significantly lower in the no SUI group.

Women with diagnosed or undiagnosed cough-related SUI reported a larger impact of cough on their everyday lives (Table 2). Significantly higher proportions of women with diagnosed or undiagnosed cough-related SUI than no SUI chose the response 'quite a bit/very much/extremely high' to the items: cough impacts on quality of life (*p* = .005); cough makes me feel anxious or depressed (*p* = .006); cough affects everyday activities (*p* = .002); cough affects professional development (*p* = .006); cough requires extra pauses or slows work (*p* = .023); cough limits hobbies or leisure activities (*p* = .010); cough limits capacity to partake in sport or physical activities (*p* = .014); cough limits capacity to perform activities requiring concentration (*p* = .010). The proportions of women who responded 'quite a bit/very much/extremely high' to the statements were broadly similar in the diagnosed and undiagnosed cough-related SUI groups for most items.

The number and proportion of women who indicated any problem (slight problem, moderate problem, severe problem, extreme problem/unable to perform) in EQ-5D dimensions, mean EQ-VAS scores and mean EQ-5D indexes, are presented in Table 3. Percentages were numerically higher for all EQ-5D dimensions in women with diagnosed

Table 1. Characteristics of women with RCC or UCC according to diagnostic status of cough-related stress urinary incontinence.

Variable	Diagnosed cough-related SUI (n = 32)	Undiagnosed cough-related SUI (n = 33)	No SUI (n = 82)	p value
Age	61.7 ±10.9	57.9 ± 11.8	56.4 ± 14.5	.171
Body mass index, kg/m^2	28.1 ± 5.4	28.5 ± 5.9*	26.1 ± 4.8	.042
Duration of cough, years	6.0 ± 4.1	6.4 ± 5.4	6.2 ± 4.5	.959
Cough VAS severity score	65.9 ± 19.5	67.2 ± 20.7	60.9 ± 21.0	.247
Cough frequency[a]				
Continuous	27 (84.4)	27 (81.8)	65 (79.3)	.968
Intermittent, but not seasonal	4 (12.5)	5 (15.2)	15 (18.3)	
Intermittent, seasonal	1 (3.1)	1 (3.0)	2 (2.4)	
Classification of cough				
RCC	18 (56.2)	24 (72.7)	50 (61.0)	.352
UCC	14 (43.8)	9 (27.3)	32 (39.0)	
Attending clinic				
Pulmonology	28 (87.5)	28 (84.8)	69 (84.1)	.903
Allergy	4 (12.5)	5 (15.2)	13 (15.9)	

Data are expressed as mean ± SD or n (%).
*p < .05 compared to no SUI group in post hoc multiple comparisons.
RCC: refractory chronic cough; SD: standard deviation; SUI: stress urinary incontinence; UCC: unexplained chronic cough; VAS, visual analogue scale.
[a]Continuous: Patient suffers from cough every day or nearly every day. Intermittent, but not seasonal: Patient suffers periods of cough and periods of remission, but the cough is not present at specific periods in the year. Intermittent, seasonal: Patient has a chronic cough at specific times or seasons.

Table 2. Impact of cough on women's everyday life. Number (%) of women with RCC or UCC and diagnosed, undiagnosed or no cough-related stress urinary incontinence who selected the response options 'quite a bit/very much/extremely high' for each item.

Impact of cough in everyday life	Diagnosed cough-related SUI (n = 32)	Undiagnosed cough-related SUI (n = 33)	No SUI (n = 82)	p value
Cough impacts patient's quality of life (n = 147)	26 (81.2)	23 (69.7)	41 (50.0)	.005
Cough impairs patient's sleep (n = 147)	12 (37.5)	12 (36.4)	31 (37.8)	.990
Cough affects patient's mood or emotions (n = 147)	16 (50.0)	17 (51.5)	32 (39.0)	.360
Cough makes patient feel anxious or depressed (n = 147)	12 (37.5)	15 (45.5)	15 (18.3)	.006
Cough affects everyday activities (i.e., work, care of children or relatives, household) (n = 147)	15 (46.9)	20 (60.6)	22 (26.8)	.002
Cough has affected patient's professional development (difficulties to find a suitable job, need more time to do work due to cough) (n = 138)	8 (25.0)	11 (36.7)	8 (10.5)	.006
At work, patient needs extra pauses or works slower due to cough (n = 95)	6 (27.3)	5 (27.8)	4 (7.3)	.023
Patient has taken sick leave due to cough (with no other concurrent disease (n = 126)	3 (10.0)	6 (22.2)	7 (10.1)	.264
Cough affects patient's relationship with others (i.e., close friends, relatives) (n = 146)	10 (31.2)	12 (37.5)	15 (18.3)	.073
Cough limits hobbies or leisure (going to the cinema, theatre, restaurants) (n = 146)	15 (46.9)	16 (50.0)	20 (24.4)	.010
Cough limits patient's capacity to partake in sport or physical activity (n = 146)	17 (53.1)	16 (50.0)	23 (28.0)	.014
Cough limits patient's capacity to perform activities requiring concentration, like driving or riding a bike (n = 144)	11 (34.4)	12 (38.7)	12 (14.8)	.010
Patient's cough affects the quality of life of closer relatives (i.e., spouse, family) (n = 145)	11 (34.4)	12 (37.5)	17 (21.0)	.130
Patient's cough affects the sleep of closer relatives (n = 141)	11 (35.5)	14 (42.4)	18 (23.4)	.110
Cough affects patient's caring for his/her children (n = 115)	5 (17.2)	9 (31.0)	7 (12.3)	.102

Data are expressed as n (%). Not all patients responded to all items. Percentages are calculated according to the total number of respondents (as indicated) per item.
Response options per item were: (1) Not at all; (2) Slightly; (3) Somewhat; (4) Moderately; (5) Quite a bit; (6) Very much; (7) Extremely high.
RCC: refractory chronic cough; SUI: stress urinary incontinence; UCC: unexplained chronic cough.

Table 3. General health status. Number (%) of women with RCC or UCC and diagnosed, undiagnosed or no cough-related stress urinary incontinence who indicated any problem (slight problem, moderate problem, severe problem, extreme problem/unable to perform) in EQ-5D dimensions; mean EQ-VAS scores and mean EQ-5Q index values.

	Diagnosed cough-related SUI (n = 32)	Undiagnosed cough-related SUI (n = 33)	No SUI (n = 82)	p value
EQ-5D dimensions				
Mobility	16 (50.0)	17 (51.5)	28 (34.1)	.126
Self-care	9 (28.1)	8 (24.2)	6 (7.3)	.007
Usual activities	21 (65.6)	23 (69.7)	45 (55.6)	.310
Pain/discomfort	25 (78.1)	28 (84.8)	58 (70.7)	.261
Anxiety/depression	32 (75.0)	33 (72.7)	58 (56.1)	.082
EQ-VAS score	52.4 ± 22.9*	54.4 ± 22.6*	68.7 ± 18.5	.002
EQ-5Q index[a]	0.655 ± 0.254*	0.630 ± 0.253*	0.768 ± 0.199	.004

Data are expressed as n (%) and mean ± SD.
The EQ-5D-5L descriptive system of 5 health dimensions includes 5 response categories of no problem, slight problems, moderate problems, severe problems, and extreme problems/unable to perform. A lower EQ-VAS score indicates worse perceived general health status.
*p value <.05 compared to no SUI in post hoc multiple comparisons. For multiple comparisons between diagnosed and undiagnosed cough-related SUI groups, there were no significant differences.
EQ-VAS: EuroQoL visual analogue scale; RCC: refractory chronic cough; SUI: stress urinary incontinence; UCC: unexplained chronic cough.
[a]The EQ-5Q index was calculated based on data sets for Spain (value from 0 to 1, where 1 is the best state of health).

and undiagnosed cough-related SUI versus no SUI, and the difference was significant for the self-care dimension. The mean EQ-VAS score was significantly lower in diagnosed (p = .002) and undiagnosed (p = .009) cough-related SUI groups compared with the no SUI group, indicating poorer health status. The difference between the diagnosed and undiagnosed cough-related SUI groups was not significant (p = .696). Likewise, the mean EQ-5D index value was lower in diagnosed and undiagnosed cough-related SUI groups compared with the no SUI group (p = .017 and p = .003 respectively) but did not differ between women with diagnosed or undiagnosed cough-related SUI (Table 3).

LCQ domain and total scores were significantly lower in the diagnosed and undiagnosed cough-related SUI groups compared with the no SUI group, indicating poorer QoL due to cough (Table 4). There were no differences in mean LCQ domain and total scores between the diagnosed and undiagnosed cough-related SUI groups.

Multiple linear regression analysis was used to examine the impact of cough-related SUI on women's general health status (Table 5) and cough-related QoL (Table 6). Variables included in both the EQ-VAS and LCQ model were age, cough duration, cough diagnosis (RCC vs. UCC), cough severity by VAS and presence or absence of cough-related SUI. The EQ-VAS model also included the number of cardiovascular risk factors and the number of comorbidities. Due to the similarly in baseline characteristics, EQ-VAS score and LCQ scores between women with diagnosed or undiagnosed cough-related SUI, the two groups were combined. Greater cough severity VAS scores and the presence of cough-related SUI were each associated with a lower EQ-VAS score and lower LCQ total and domain scores, reflecting poorer health status and QoL. The presence of cough-related SUI was independently associated with reductions in the

Table 4. Quality of life as measured by the Leicester Cough Questionnaire in women with RCC or UCC and diagnosed, undiagnosed or no cough-related stress urinary incontinence.

LCQ domain	Diagnosed cough-related SUI (n = 32)	Undiagnosed cough-related SUI (n = 33)	No SUI (n = 82)	p value
Physical	3.9*	3.8*	4.4	.012
Psychological	3.1*	3.3*	4.1	.001
Social	3.6*	3.3*	4.4	<.001
Total score	10.3*	10.4*	12.5	.001

Lower LCQ scores indicate poorer quality of life due to cough.
*p value <.05 compared to no SUI in post hoc multiple comparisons. For multiple comparisons between diagnosed and undiagnosed cough-related SUI groups, there were no significant differences (all p values >.4).
LCQ: Leicester Cough Questionnaire; RCC: refractory chronic cough; SUI: stress urinary incontinence; UCC: unexplained chronic cough.

β coefficient of 10.62 for the EQ-VAS score and of 1.61 for the LCQ total score; and with corresponding decreases of 0.38, 0.61 and 0.79 in the physical, psychological and social LCQ domains (all p values <.02). These associations were independent of cough severity. The models explained about one-fifth of the variation in the EQ-VAS and about one-third of the variation in LCQ scores (goodness of fit [R^2]: 0.222 for EQ-VAS and 0.376, 0.321, 0.332 and 0.335 for LCQ scores respectively, Tables 5 and 6).

Discussion

Our analysis found that one in five women with RCC/UCC had diagnosed cough-related SUI as recorded in their

Table 5. Multivariate analysis: multiple linear regression model for the EuroQoL visual analogue scale (EQ-VAS).

Variables	β coefficient ± SD	p
Age (increment of 1 year)	0.01 ± 0.14	.965
Duration of cough (increment of 1 year)	0.06 ± 0.36	.858
Diagnosis (refractory vs. unexplained)	2.80 ± 3.42	.414
Cough severity visual analogue scale score (increment of 10 mm)	−3.53 ± 0.80	<.001
Cough-related stress urinary incontinence (present vs. absent)	−10.62 ± 3.33	.002
Number of cardiovascular risk factors[a]	−2.07 ± 2.19	.347
Number of comorbidities[b]	−4.95 ± 3.29	.135

Data are expressed as mean ± SD.
β coefficients indicate the extent to which the EQ-VAS score modifies with each variable versus its reference. Negative β coefficients indicate that the variable is associated with a decrease in the EQ-VAS score (indicating poorer perceived health status).
SD, standard deviation.
[a]Cardiovascular risk factors collected were arterial hyertension, obesity, and diabetes mellitus (smoking habit was an exclusion criterion for this study).
[b]Comorbidities collected were cardiovascular diseases heart failure, coronary artery disease or other), cerebrovascular diseases, chronic liver disease, cancer (not affecting respiratory system), neurodegenerative diseases and rheumatic diseases (respiratory diseases other than diseases related to refractory chronic cough were exclusion criteria). Goodness of fit (R^2): 0.222.

Table 6. Multivariate analysis: multiple linear regression model for Leicester Cough Questionnaire (LCQ) total and domain scores.

Variables	LCQ total score		Physical domain		Psychological domain		Social domain	
	β coefficient ± SD	p	β coefficient ± SD	p	β coefficient ± SD	p	β coefficient ± SD	p
Age (increment of 1 year)	−0.01 ± 0.18	.714	0.00 ± 0.01	.518	0.00 ± 0.01	.458	0.01 ± 0.01	.452
Duration of cough (increment of 1 year)	0.02 ± 0.05	.683	0.00 ± 0.02	.811	0.01 ± 0.02	.672	0.00 ± 0.02	.844
Diagnosis (refractory vs. unexplained)	−0.20 ± 0.49	.684	−0.17 ± 0.16	.299	−0.02 ± 0.19	.933	−0.13 ± 0.21	.539
Cough severity visual analogue scale score (increment of 10 mm)	−0.94 ± 0.12	<.001	−0.28 ± 0.04	<.001	−0.33 ± 0.05	<.001	−0.35 ± 0.05	<.001
Cough-related SUI (present vs. absent)	−1.61 ± 0.48	.001	−0.38 ± 0.16	.016	−0.61 ± 0.19	.001	−0.79 ± 0.21	<.001

Data are expressed as mean ± SD.
β coefficients indicate the extent to which the LCQ score modifies with each variable versus its reference. Negative β coefficients indicate that the variable is associated with a decrease on LCQ scores (indicating poorer quality of life). Goodness of fit (R^2) for the LCQ total score: 0.376; Physical domain: 0.321; Psychological domain: 0.332; Social domain: 0.335.
LCQ: Leicester Cough Questionnaire: SD, standard deviation; SUI: stress urinary incontinence.

clinical chart, while a similar proportion had undiagnosed cough-related SUI as reflected in the patient survey. The 44.2% total frequency of cough-related SUI in this patient cohort (65/147 women) is broadly in line with frequencies reported in other chronic cough populations.[7–9] The total number of women with SUI ($n = 65$) is higher than the sum of women who responded 'frequently' or 'mostly/always' to the question on cough related SUI ($n = 56$) because nine patients in the diagnosed SUI group responded 'sometimes'. As the study focused mainly on the identification and description of diagnosed and undiagnosed cough-related SUI, these nine women were retained in the diagnosed group for analysis. A major finding of the study was that, independently of cough severity, the presence of diagnosed or undiagnosed cough-related SUI was associated with significantly worse general health status and worse cough-related QoL.

The absence of a diagnosis in half the women with cough-related SUI in our cohort is of concern given the substantial impact of SUI on women's health status and QoL.[10–12] Potential reasons for SUI to be undiagnosed in women, including those with chronic cough, are the associated embarrassment or stigma (preventing women from coming forward), a lack of active screening by the treating physician, and the perception by many women that incontinence is a normal consequence of aging or childbirth.[3,22] The finding that general health status and cough-related QoL are similarly impacted in undiagnosed and diagnosed women is relevant since cough-related SUI

can benefit from new cough-specific therapies,[23] suggesting value in screening women for this complication.

The additional mental and physical burden of cough-related SUI was clearly exposed by investigating the impact of cough on patients' everyday lives according to diagnosis. Compared to the no SUI group, significantly more women with cough-related SUI, whether diagnosed or not, reported that cough made them feel anxious or depressed, and that it interfered with everyday activities, professional development, leisure time activities, and ability to perform tasks requiring concentration. The presence of cough-related SUI was also associated with poorer QoL due to cough as evidenced by significantly lower mean LCQ scores in diagnosed and undiagnosed SUI groups compared with the no SUI group. Numerically, the largest difference in QoL was in the LCQ social domain, consistent with the social and recreational withdrawal that is known to occur in women with SUI.[24] The extent of impairment to general health status, daily life and QoL was similar between the diagnosed and undiagnosed cough-related SUI groups, suggesting that a relevant proportion of female patients with chronic cough 'suffer in silence' about their SUI and are potentially missing opportunities for effective management.

In multivariate analysis, greater cough severity (VAS) and the presence of SUI were key factors associated with lower EQ-VAS and LCQ scores. The association of cough-related SUI with poorer health status and poorer QoL was independent of cough severity. This finding emphasizes the importance that patients place on the secondary physical effects of cough such as SUI relative to more simple measures such as cough frequency or severity.[25]

The current range of treatment options for cough-related SUI is limited, underlying the need for new therapeutic approaches.[26] Alleviating repetitive daily cough-induced increases in intra-abdominal pressure may reduce episodes of incontinence. An interesting observation was that BMI was approximately 2 kg/m^2 higher in women with than without cough-related SUI. A high BMI was identified as a risk factor for de novo SUI in a large longitudinal study involving 25,000 Chinese women,[6] and was associated with a greater likelihood of cough-induced SUI in a cohort of female patients with chronic cough.[9] Since BMI is a modifiable risk factor, reducing BMI among women in the overweight/obese range, may improve SUI. As regards pharmacological therapies, the efficacy and safety of the cough-specific P2X3 antagonist gefapixant was evaluated in 375 women with RCC/UCC and cough-related SUI. At week 12, gefapixant-treated participants experienced a greater percentage reduction in mean self-reported daily cough-related SUI episodes compared with placebo recipients.[23,27]

Limitations of observational studies include the absence of a control group, incomplete or missing data, and potential for selection bias. Specific to the current study, cough-related SUI was diagnosed based on information recorded in clinical charts or by patient self-reporting and was not verified by specific SUI diagnostic tests. Although the survey question posed to women specified a relationship between cough and urinary incontinence, we cannot exclude that some cases of urge urinary incontinence may have been mislabeled as SUI. No data were collected about potential pharmacological or non-pharmacological measures to relieve urinary incontinence in women with diagnosed SUI. The fact that all women had a cough duration >1 year and cough on the day of the visit (inclusion criteria), and that there were no differences in the cough severity VAS between those with diagnosed and undiagnosed SUI, suggests that cough is the driver of urinary incontinence in these women. Some data regarding the impact of cough were collected using validated instruments (e.g., EQ-5D-5 L for general health status and LCQ for QoL), whereas other data were derived from unvalidated sources. Questions to assess the impact of cough on everyday life activities were developed specifically for study purposes; validated patient-reported instruments to assess anxiety and depression were not used. Although the questions and instruments were intended to assess the impact of cough on SUI, the contribution of other risk factors to SUI is uncertain. As some instruments assessed only the moment that patients responded (VAS cough severity score, EQ-VAS), or the previous 2 weeks (LCQ), we acknowledge that a longitudinal study may provide a more complete picture of the impact of cough-related SUI on everyday life and QoL. Statistical comparisons must be interpreted with caution given that the 147 women included in this analysis represented a subgroup of the total number of patients required to provide statistical power ($n = 196$) as reported previously.[13] Results of multivariate analyses should be considered descriptive in nature and fundamentally as hypotheses generators of factors that may influence the health status and QoL of women with RCC/UCC. Lastly, because the study involved outpatients attended at cough clinics with potentially greater symptomatology, the results may not be generalizable across the wider RCC/UCC population.

Conclusions

A substantial proportion of women with RCC or UCC have cough-related SUI. Current practice suggests that about half the women with RCC or UCC managed at outpatient hospital clinics in Spain have undiagnosed cough-related SUI. SUI associated with RCC and UCC adversely impacts women's general health status, QoL and ability to perform everyday life activities. Since the burden of cough-related SUI is the same irrespective of diagnostic status, removing obstacles to a SUI diagnosis is essential to identify patients with unmet needs who can benefit from new therapies to

suppress cough. Educational campaigns may increase awareness of cough-related SUI in general and instill women with the confidence to come forward about their condition. Women with chronic cough should be screened regularly for SUI.

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Author contributions

Ebymar Arismendi participated in data collection, data interpretation and drafting and editing of the manuscript. Luis Puente-Maestu, Christian Domingo, Ignacio Dávila and Santiago Quirce participated in study design, data collection, study analysis and editing of the manuscript. Francisco Javier González-Barcala and Astrid Crespo-Lessmann participated in data collection, data interpretation and drafting and editing of the manuscript. Marta Sánchez-Jareño, Cristina Rivas-Pardiñas and Luis Cea-Calvo participated in study design, study analysis, data interpretation and drafting and editing of the manuscript. All authors approved the final version.

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