



Cancer-Related Lymphedema: Clinical and Epidemiological Features in Mexico

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: There is a lack of clinical and epidemiological knowledge about cancer-related lymphedema in Mexico. The objective of this study is to present a broad and deep report of cancer-related lymphedema's clinical characteristics and epidemiological features based on the analysis of CRL patients' data, collected from a specialized rehabilitation clinic in Mexico.

Methods: This is a cohort study based on the analysis of clinical data gathered between 2015 and 2022. The study was developed in a private clinic that specializes in oncological patients' rehabilitation. Clinical assessments and interviews were performed to collect each case's clinical history, considering diverse clinical characteristics and demographic information, classified in a matrix, and statistically evaluated.

Results: Among 307 lymphedema patients, gender distribution was represented by 87.9% (270) female and 12.1% (37) male; mean age of 54.5 years (\pm 32.5); 79.8% of the patients corresponded to breast cancer diagnosis, the rest of them were associated with other 19 different types of cancer. 90.2% of patients underwent some lymph node removal procedure, 68.1% of patients received fractionated radiotherapy sessions, and 87.7% received some chemotherapy scheme treatment. 64% of patients had a diagnosis of lymphedema and had onset symptoms of lymphedema in the first 5 years after oncological interventions and/or cancer diagnosis, most of them during the first 2 years.

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The general distribution of clinical staging was: 23.7% in stage 0; 20.1% in stage I; 44.6% in stage II, and in stage III 11.4%. Regarding body mass index, it was found a mean of 26.7 BMI. 61.2% of patients ranged between overweight and obesity. 43.3% of patients with CRL reported a disability to perform one or more activities due to lymphedema. 80% of patients had no physical activity or performed under the minimal physical activity recommended for the population group they belong.

Conclusion: This study reports broad epidemiological and clinical features of a group of cancer-related lymphedema patients in Mexico, it was possible to identify diverse potential factors and relations that influence the clinical features of CRL; it is necessary to explore all factors and the interactions among them for a better understanding of CRL patients in the country.

Keywords: lymphedema; secondary lymphedema; cancer-related lymphedema; lymphedema in Mexico.

1. INTRODUCTION

Lymphedema is a chronic-progressive disease that produces rich protein edema, caused by the obstruction of lymph vessels, lymph nodes, or by lymphatic function disorders [1-3]. It may occur due to congenital malformations of the lymphatic and venous system, or secondary to different agents that damage lymphatic structures. It is estimated that more than 250 million patients around the world, and 5 million in Mexico, suffer a lymphatic disease [2,4].

Lymphedema is classified into two types according to its general etiology: primary and secondary lymphedema. Primary is due to congenital lymphatic anomalies and secondary includes all cases provoked by external factors or because of a principal disease; in this second category, CRL is found, which may be developed due to a neoplasm or tumor blocking lymph nodes or lymph vessels, lymph node removal surgery, and/or radiotherapy, being possible one or multiple oncologic factors in absence of a primary lymphatic alteration [2, 5].

1.1 Background

The clinical and epidemiological data about patients with cancer-related lymphedema (CRL) in Mexico is limited [2]. Clinical guidelines of Mexican public health services barely suggest lymphedema management as a consequence of breast cancer processes [6], which is the most studied type of lymphedema in the country, however, these guidelines are based on foreign epidemiological and clinical data; this may be influenced by the absence of local data that targets this population.

In 2019 and 2020 the Mexican Consensus about diagnosis and treatment of breast cancer dedicates a chapter to physical therapy for breast

cancer patients and includes suggestions about lymphedema management, but the cited data is based on foreign epidemiological studies. This information is limited to breast cancer related lymphedema [7, 8].

Previously, in 2014, Gutierrez-Pérez and Avalos-Nuño reported a prevalence of 41% of lymphedema among breast cancer patients that underwent breast cancer treatment in Mexico [9] while in 2019, Chavira et. al reported a 23% prevalence of lymphedema in breast cancer patients that underwent mastectomy [10].

Recently in 2022 was reported that CRL in Mexico is associated to 19 different cancer diagnoses [2] thus, it was decided to explore the clinical and epidemiological features of this population.

1.2 Objective

The purpose of this study is to report epidemiological and clinical features of Cancer-Related lymphedema population and to define its characteristics.

2. MATERIALS AND METHODS

This study aims to obtain epidemiological and clinical information about Mexican lymphedema patients, using information collected via direct clinical interview and physical examinations with previous written and verbal informed consent signed by patients or primary caregivers who agreed to share and use the data in the study while keeping their privacy.

Between January 2015 and June 2022, 380 Mexican patients went to rehabilitation service due to oncologic process and/or CRL (in risk or onset). They were clinically assessed and interviewed in Fi Fisioterapia Integral S.C., a

private physiotherapy clinic that provides specialized rehabilitation services for patients with lymphedema and cancer processes.

The information was collected during clinical assessment appointments directed by lymphedema specialized clinicians employing a clinical datasheet file tool which included complete clinical history, clinical characteristics, socio-demographic data, and physical functional status.

A digital spreadsheet matrix was created employing all data and set to order, to classify and to organize diverse items and information gathered, to later analyze it statistically employing both Excel software and manual calculations to identify and limit mistakes.

2.1 Patient Inclusion Criteria

1. The patient or primary caregiver signed informed consent to employ clinical history, clinical characteristics, and sociodemographic data for the study.
2. Patients with previous cancer treatments, such as lymphadenectomy and radiotherapy without lymphedema onset, but at risk of developing it (stage 0).
3. Patients undergoing cancer treatments that put them at risk of developing lymphedema or undergoing cancer treatments with lymphedema onset.
4. Patients with cancer diagnosis, without cancer treatment, but with lymphedema onset.
5. Patients previously diagnosed with cancer-related lymphedema, and cancer in complete remission, or post-cancer surveillance.

2.2 Exclusion Criteria

1. Patients unwilling or unable to participate for any reason.
2. Denial to sign consent letter or approval to share information by patient or primary caregiver.
3. Acute edema (less than 12 weeks) due to cardiac, hepatic, nephrotic, pharmacological, orthostatic edema or undetermined causes unrelated to cancer treatments or tumoral compression.
4. Any patient not meeting inclusion criteria.

Out of 380 assessed patients, 307 met the inclusion criteria.

The following items were included in the clinical file datasheet and spreadsheet:

Gender, age, height and weight measured at clinic, body mass index, evolution time until lymphedema diagnosis and its clinical stage based on the International Society of Lymphology clinical staging, Table 1; affected segments, circumferential measures of segments (sum of arm circumferences), comorbidities history, surgery history, previous and ongoing treatments and their characteristics, pain (analogous visual scale employed), infection history, physical activity level (minutes per week and sessions per week), reported disability for daily living activities, amount of fractioned radiotherapy sessions, amount of lymph nodes removed, occupation, among others for further studies. Concrete questions for each item were made when patient did not mention the information by himself.

3. RESULTS

A total of 307 patients were included in the analysis; 87.9% (270) female and 12.1% (37) male; age of 54.5 years old (± 32.5), male's mean age of 60.7 years (± 19.3), and female's mean age of 53.3 years (± 29.7).

According to the age distribution, only 32% (97) of patients were elderly adults, while 68% (210) was under 60 years old.

Among the 307 patients with cancer related lymphedema, 79.8% of them corresponded to breast cancer diagnosis, the rest were associated with other 19 different types of cancer diagnosis. The most prevalent diagnoses were breast cancer-related lymphedema (79.8%), prostate-CRL (3.2%) and womb-CRL (2.9%) Table 2.

As for lymph node removal, 9.7% (30) of patients with CRL did not have any lymph node removed, 9.7% (30) had only 1-9 lymph nodes removed; while 74% (129) of patients had more than 10 lymph nodes removed; 6% (18) 6% of patients were unable to report this information or it was unable to access by any available source by any available source (clinical file, patient referenced, or primary caregiver reference) Table 3.

Table 1. ISL Lymphedema Staging

Stage	Characteristics
0	No clinical evidence of increased volume, patent damage reported in clinical history (e.g.: lymph node removal, lymph node biopsy, radiotherapy).
I	Reversible discreet edema, soft and tender, that increases along the day, disappears completely during the night, while at rest, or at elevation of the limb; differences between limbs is more than 2 cm or 200 mL volume.
II	Irreversible edema that does not improve or minimally improves during night, rest or elevation; tends to go worse. Fibrosclerotic changes begin to be evident due to skin thickening and color changes, differential volume is evident at single sight, diameter of limbs is equal or superior to 2cm or 200mL volume.
III	Presents important or massive deformities due to increased volume of the extremity or a segment of it, present skinfolds, articular sulcus, big fibrotic areas, thickened skin, color changes, sometimes presents papillomatosis or lymphatic cysts, lymphorrea and wounds; recurrent or frequent skin infection is usual. Limited functionality of the limb and disability are present.

Table 2. CRL Diagnoses prevalence

Cancer-related lymphedema	Patients	%Prevalence
Breast cancer	245	79.8%
Prostate cancer	10	3.2%
Womb cancer	9	2.9%
Metastatic cancer	8	2.6%
Sarcoma	6	1.9%
Melanoma	4	1.3%
Hodgkin Lymphoma	4	1.3%
Penis cancer	3	0.9%
Head and neck cancer	3	0.9%
Colon cancer	3	0.9%
Osteosarcoma	2	0.6%
Condrosarcoma	2	0.6%
Lymphoma	2	0.6%
Hepatic cancer	1	0.3%
Periphereal Nervous System	1	0.3%
Bladder cancer	1	0.3%
Liposarcoma	1	0.3%
No-Hodgkin Lymphoma	1	0.3%
Serous epithelial cancer	1	0.3%

Table 3. CRL patients' lymph nodes removed

Lymph nodes removed	% Patients
0	9.7% (30)
1-9	9.7% (30)
10-15	31.9% (98)
16+	42.6% (131)
Unknown amount	6% (18)

Regarding radiotherapy, only 31.9% (98) did not receive any fraction-session or did not undergo radiotherapy until the assessment date, while most patients (53.4%) received more than 20 fractioned radiotherapy sessions Table 4.

As for chemotherapy (infusion or pills), it was found that 87.7% (269) received a chemotherapy scheme treatment.

It was considered the time span of lymphedema symptoms beginning after the oncological relevant treatments, like lymph node removal and/or radiotherapy. 64% (196) of patients had a diagnosis of lymphedema and had onset symptoms of lymphedema progression in the first 5 years after oncological interventions and/or cancer diagnosis; most of them (51.3%) during the first year. Almost ¼ of the patients remained in a subclinical stage Table 5.

Table 4. CRL patients' radiotherapy sessions

Fractionated radiotherapy sessions / Gy's range	%Patients
0/0	31.9% (98)
1-15/ up-to 30Gy	6.5% (20)
16-20 / up to 50Gy	4.8% (15)
21-30/ up-to 60Gy	35.5% (109)
31+ / >60Gy	17.9% (55)
Unknown amount	3.2% (10)

Table 5. CRL Lymphedema beginning

Onset lymphedema time span	%Patients
1 – 6 months	34.3% (105)
7 months – 23 months	17% (52)
2 – 5 years	12.7% (39)
More than 5 years	9.7% (30)
Subclinical	23.1% (71)
Not reported	3.2% (10)

The distribution of affected segments was very symmetrical for upper limbs. The top 3 affected limbs were the following: 38.7% (119) for upper right extremity, 38.1% (117) for upper left extremity and 6.5% (20) for lower left extremity. The less frequent were head, face, neck, and genital areas with a sum of 3.2% (10) Table 6.

Table 6. CRL Lymphedema affected segment distribution

Affected segment	% Patients
Upper right extremity	38.7% (119)
Upper left extremity	38.1% (117)
Lower left extremity	6.5% (20)
Bilateral lower extremities	4.8% (15)
Bilateral upper extremities	4.5% (14)
Lower right extremity	3.9% (12)
Genital	1.9% (6)
Head, face and neck	1.4% (4)

The general distribution of clinical staging is as follows: 23.7% (73) of patients in stage 0; 20.1% (62) in stage I; 44.6% (137) in stage II, and in stage III 11.4% (35). Distribution by gender is detailed in Table 7.

Table 7. CRL Lymphedem Stage by gender

Stage	Male % (37)	Female % (270)
0	0	27% (73)
I	8.1% (3)	21.8% (59)
II	83.7% (31)	39.2% (106)
III	8.1% (3)	11.8% (32)

About the clinical details of the patients' affected limb, Godette's sign was present in 54.7% (168) of patients while Stemmer sign was present in 56.3% (173). Only 3.9% (12) patients had a history of lymphorrea and 0.6% (2) of lymphatic cysts or lymphatic papillomatoses.

Regarding body mass index, it was found a mean of 26.7 BMI. 61.2% (188) of patients ranged in overweight and obesity. The following distribution of BMI was found: 1.6% (5) in <18.5 BMI or low weight; 28.3% (87) 18.5–24.9 BMI in normal weight range; 36.8% (113) 25-29.9 in overweight range; 24.4% (75) >30 BMI in obesity range; 7.8% (35) were unable to evaluate due to clinical difficulties during assessments such as extreme mobility limitation to measure weight and/or height. 64% (286) of patients ranged above ideal BMI Table 8.

Table 8. CRL patient's BMI distribution

BMI	% Patients
Low weight (<18.5)	1.6% (5)
Normal (18.5-24.9)	28.3% (87)
Overweight (25-29.9)	36.8% (113)
Obesity (30)	24.4% (75)
Not Reported	8.7% (27)

Only 45.9% (141) of patients had no other comorbidities other than cancer; the most referred comorbidities were related to chronic diseases like diabetes and cardiac pathology. An antecedent of recurrent regional or local infection such a bacterial cellulitis, lymphangitis and/or dermatolymphangioadenitis in lymphedema affected limb was reported by 15.3% (47) of patients.

A 4.8% (15) of patients had a record of a thrombotic event in affected limb. While 2.9% (9) of patients had an ulcer in the affected limb or in the ipsilateral adjacent segment; the causes were associated to radiodermatitis, skin metastasis, tumors, or non-healed surgical wounds. History of surgery in limb or side affected by lymphedema was overall 94.4% (290); this includes mastectomy with or without lymphadenectomy, biopsy, and sentinel lymph node procedures.

In 0.65% (2) of the cases, patients referred to have had a previous surgical procedure to prevent lymphedema, being lympho-venous anastomoses (LVA) in the context of Lymphatic Preventive Healing Approach (LYMPHA

acronym). Cases were in clinical stage 0 prior to surgery.

A 43.3% (133) of participants reported history of pain experience in limbs affected by lymphedema, all patients associated their pain experience to their condition or stated that their pain was caused by this condition.

The 43.3% (133) of patients with CRL reported disability to perform one or more activities related to the condition of lymphedema; this included its signs, symptoms, volume, and/or fear of worsening their limb's condition or even developing lymphedema in those at stage 0. Difficulties to perform daily tasks and chores were referred: some of them like moving the limb, moving objects, wearing clothes, independent personal care, eating, walking, climbing stairs, working, getting up from a chair or a bed, changing position, participating in social and family activities, lifting objects, exercising. This was classified according to the clinical stage of patient's lymphedema Table 9.

Table 9. CRL Distribution of reported disability

Stage	Reported disability % Patients
0	32.4% (24)
I	27.8% (17)
II	44.1% (60)
III	80% (29)

Concerning physical activity, patients' activity level and exercise habits were classified into 3 groups, these are: below minimum, minimum physical activity, and above the minimum recommended physical activity for their age group.

The recommendations were taken from American College of Sports Medicine (ACSM) *Exercise prescription guideline for cancer patients*: 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity activity, or an equivalent combination, and muscle-strengthening activities at least 2 days/week for each major muscle group [11].

Only 13% (41) of all patients performed at or above minimum physical activity recommended for cancer patients, 80% (248) of patients had no physical activity or performed under the proper population group's recommendation. The rest was unable to be classified or did not answer Table 10.

As for their occupations, there is the following information: 49.1% (151) of patients only performed home chores, 14% (43) did work that involves high physical effort, 21.1% (65) did office work, 1.9% (6) are health care professionals and the same amount are retired, 7.1% (22) are students, and 4.5% (14) did not answer.

4. DISCUSSION

Regardless of selecting a population in the category of cancer-related lymphedema, this is still a highly heterogeneous population due to the existence of a prevalence of 20 different kinds of cancer involved, each with its own specific treatments and population characteristics; however, this report provides a solid background in Mexico to begin the study and understanding of CRL beyond only breast cancer-related. In the country's context any information documented is helpful in an understudied topic. And especially, the antecedent of evidence-based population approaches and the understanding of this health condition.

All diagnoses were clinically determined. Due to the nature of clinical and physical assessments and the unavailability of image studies like Near-Infra-Red lymphatic imaging, data of those "at-risk" of developing lymphedema or stage 0 may not be accurate, since it is needed to assume a lymphedema stage 0 in the absence of an image study that demonstrated lymphatic damage, the valid criteria still being considering the existence of a clinical history of radiotherapy and/or ablative procedures of regional lymph nodes. That is why it was needed to employ screening strategies that include NIR lymphatic imaging for those at risk of developing CRL [2,3,12].

Table 10. CRL physical activity level distribution by clinical stage

Clinical Stage	Above recommended	Reccomended	Below recommended
0	6.7% (5)	13.5% (10)	74.3% (55)
I	0% (0)	9.6% (6)	87% (54)
II	1.4% (2)	11.7% (16)	79.4% (108)
III	0% (0)	5.7% (2)	88.5% (31)

It has been reported a prevalence of onset lymphedema (not stage 0) in different oncological populations ranging from 8% up to 83% [13] our study, excluding stage 0 patients, reached 76.22% of this cohort, which is a remarkably high rate, highest than that previously reported by Chavira and Avalos-Nuño for Mexican population [9,10]. Considering that around a third of them presented symptoms along the first year after cancer diagnosis and/or treatment, we suggest that early identification is a priority problem to solve that may impact its clinical evolution.

A bias identified in the study was the small samples relating to the 19 types of cancer-related lymphedema other than breast cancer. Sharing our findings about CRL, other to breast cancer, is our responsibility; we hope this is a call to continue the study of lymphedema as a prevalent consequence of different type of cancer.

Regarding cancer treatment, it is noted that 90.2% of patients underwent procedures where more than 1 lymph node was removed, 68.1% received regional radiotherapy (most with 20+ fractioned sessions). Along with other risk factors for lymphedema development, it is known that a high BMI represents a strong risk factor for CRL development which was prevalent in more than 60% of patients [13-17]. During lymphedema management, these risk factors should be considered to prescribe and decide for an appropriate, effective, and sustainable approach; this information should be considered also for proper educational and preventive strategies for practitioners, health care services, and patients.

The 56% of patients were in clinical stages II and III, stages where not only control treatment is needed, but also interventions seeking to revert volume increasing which makes evident the need for treatment; this means that at least around 44% of patients still had the possibility of preventing lymphedema progression through timely diagnosis and preventive strategies.

Clinicians should be ready to solve complex scenarios, such as: secondary symptoms of standard oncological treatments, comorbidities (especially cardiac, and metabolic), chronic wounds, regional infections, thrombosis, and recent surgeries.

A 43.3% of patients experienced pain; also, a total of 43.3% experienced some disability. It is a simplistic to say that pain will necessarily cause disability; it is known that CRL represents high

psychosocial distress [18-21], and pain as a complex experience may be related to a framework where the burden of suffering and disability play a key role in these painful experiences. This puts pain phenomenon beyond a merely tissue's interaction. It is necessary to explore mechanisms, factors, and relationships among them on pain in CRL.

It is important to address that 80% of patients had no physical activity at all or performed under the proper population group's recommendation. The rate in each stage is concerning considering that a patient in stage 0 or I should not have a physical limitation to perform any activity related to lymphedema volume; however, it is highly prevalent for those in stage 0 and gets worse once it comes to stage I, and as for stage III gets worse compared to stage II.

It was not surprising to identify as one of the principal causes of disability and limited physical activity for all patients with CRL, in all clinical stages, the fear-avoidance behaviors related to health care practitioners and patients' support groups explicitly indicating and recommending avoiding every physical effort, activity, exercise, and daily chores that involve the use of the affected limb to either prevent lymphedema development or to avoid its worsening once onset. These are not evidence-based recommendations, and in fact, there is strong evidence contradicting them; also exists worldwide evidence that shows there is a general lack of information of lymphedema prevention and management, and of appropriate clinical practice standards in the healthcare professionals [22-24]. The health care providers and support groups spreading these recommendations may be representing a factor that complicates this scenario, this favors lymphedema progression, disability, and a barrier to the rehabilitation of these patients. We consider that education and research about lymphedema are the best solution.

We hypothesize, that this phenomenon may explain in part the high rate of sedentary behavior in the patient population in all clinical stages, added to the physical complications of patients undergoing or that underwent oncological processes; this might be as well a relevant explanatory factor in the high BMI prevalence e.g, causing patients to abandon active lifestyles or continue with avoidance of active lifestyle behaviors in the long term; and as a consequence of this cluster, worsening disability rates and pain related to it.

It is needed to consider the progressive nature of lymphedema, it was found to have an increased prevalence in disability report as the stage was higher, (Table 9) this certainly also correlates to limb volume increase and the proper physical limitations it causes, plus the complexity of oncological contexts [25-27].

Understanding the clinical features of CRL as well as its epidemiological data in Mexican population will help to acknowledge factors that might be key to develop better strategies for improved public healthcare practices, develop precise clinical guidelines, treatment options and new research lines build on the understanding of CRL, but also to solve the clinical scenarios that these patients and clinicians treating CRL face daily.

5. CONCLUSION

This study reports broad clinical and epidemiological data from a group of cancer-related lymphedema patients in Mexico. Further studies are needed and encouraged to improve and broaden the understanding of the findings and their correlations.

CONSENT

As per international standards or university standards, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards, written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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