***Original Research Article***

**Cancer-Related Lymphedema: Clinical and epidemiological features in Mexico**


## 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 (± 32.5); 79.8% of the patients corresponded to breast cancer diagnosis, the rest of them were associated with other 19 different kinds of cancer diagnosis. 90.2% of patients underwent some lymph node removal procedure, 68.1% of patients received 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. The general distribution of clinical staging was: 23.7% in stage 0; 20.1% in stage I; 44.6% in stage II, and 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 disability to perform one or more activities related to lymphedema. 80% of patients had no physical activity or performed under the minimal physical activity recommended for the proper population group.

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



**Keywords:** lymphedema, secondary lymphedema, cancer-related lymphedema, lymphedema in Mexico

## Introduction

Lymphedema is a chronic progressive disease that produces rich protein edema, caused due to the obstruction of lymph vessels, lymph nodes, or 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; here is included the Cancer-Related Lymphedema 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 simultaneous oncologic factors in absence of lymphatic a primary disease. **[2, 5]**

## 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 target 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 still 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 a mastectomy. **[10]**

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

**Objective**

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

**Materials and methods**

This study aimed to attain epidemiological and clinical characteristics data of Mexican lymphedema patients. Employing 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 this information to use such data in the study while keeping its 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 offers specialized rehabilitation services for patients with lymphedema and cancer processes.

The data were 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, classify and organize diverse items and information gathered, to later analyze it statistically employing both excel software and manually calculated to identify and limit mistakes.

*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 him at risk of developing lymphedema or undergoing cancer treatments with lymphedema onset.
4. Patient 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.

*Exclusion criteria*

1. Patient 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, immobility, or undetermined causes not related 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 the clinic, body mass index, evolution time until diagnosis lymphedema diagnosis and its clinical staging based on 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 its 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 radiotherapy sessions, amount of lymph nodes removed, occupation, among others for further studies. Concrete questions for each item were made when a patient did not refer by himself to this information.

| Stage | Characteristics |
|---|---|
| 0 | No clinical evidence of increased volume or patent damage was reported in clinical history (i,e: lymph node removal, lymph node biopsy, radiotherapy). |
| I | Reversible discreet edema, soft and tender that increases along the day, disappears completely during the night, rest, or elevation of the limb; differences between limbs not above 2 cm or 200 mL volume. |
| II | Irreversible edema that does not improve o minimally improves during the 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, and the 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 1.** — ISL *Lymphedema Staging*

## Results

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

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

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

| 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% |
| Liver | 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 2.**— CRL *Diagnoses prevalence*

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 and 6% (18) were not reported by the patient or was not able to be known by any available mean (clinical file, patient referenced, or primary caregiver reference. **Table 3**

| **Lymph nodes removed** | **% Patients** |
|---|---|
| 0 | 9.7% (30) |
| 1-9 | 9.7% (30) |
| 10-15 | 31.9% (98) |
| 16+ | 42.6% (131) |
| Removed but not reported amount | 6% (18) |

**Table 3.** —*CRL patients' lymph nodes removed*

Regarding radiotherapy, only 31.9% (98) did not receive any session or didn't undergo radiotherapy until the assessment date so far, while most patients (53.4%) received more than 20 sessions. **Table 4**

| **Radiotherapy sessions** | **%Patients** |
|---|---|
| 0 | 31.9% (98) |
| 1-15 | 6.5% (20) |
| 16-20 | 4.8% (15) |
| 21-30 | 35.5% (109) |
| 31+ | 17.9 (55) |
| Had RT, but it was not able to determine the amount of sessions | 3.2% (10) |

***Table 4.***—*CRL patients' radiotherapy sessions.*

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

It was considered during the assessment period of lymphedema symptoms onset 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**

| **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) |

**Table 5.—** CRL *Lymphedema beginning*

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

| **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) |

**Table 6.—** CRL *Lymphedema limbs distribution*

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 the 11.4% (35). Distribution by gender is detailed in Table 4. **Table 7**

| 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) |

**Table 7.** — CRL *Lymphedem Stage by gender*

About clinical details of the patients' affected limb: Godette's sign was present in 54.7% (168) of patients while Stemmer's 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 between 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**

| 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) |

**Table 8.**— *CRL patient's BMI distribution*

Only 45.9% (141) of patients had no other comorbidities other than cancer, most referred comorbidities were related to chronic diseases like diabetes and cardiac pathology. The antecedent of recurrent regional or local infection such as bacterial cellulitis, lymphangitis,

and/or dermatolymphangioadenitis in lymphedema affected limb was reported by 15.3% (47) of patients.

4.8% (15) of patients had a record of a thrombotic event in the affected limb. While 2.9% (9) of patients had an ulcer in the affected limb or the ipsilateral adjacent segment; the causes were associated with radiodermatitis, skin metastasis, tumor, or non-healed surgical wounds. History of surgery in limb or side affected by lymphedema was overall 94.4% (290); included 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 the 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 with their condition or stated that their pain was caused by this condition.

43.3% (133) of patients with CRL reported disability to perform one or more activities related to the condition of lymphedema, its signs, symptoms, volume, and/or fear of worsening their limb's condition or even developing lymphedema. Difficulties to develop daily living tasks and chores were referred: to moving the limb, moving objects, wearing clothes, independent personal care, eating, walking, climbing stairs, working, waking up from a chair or a bed, changing his position, participating in social and familiar activities, lifting objects, or exercising; all were considered and classified by the clinical staging of lymphedema. **Table 9.**

| Stage | Disability report<br>% Patients |
|---|---|
| 0 | 32.4% (24) |
| I | 27.8% (17) |
| II | 44.1% (60) |
| III | 80% (29) |

**Table 9.** — *CRL Distribution of reported disability*

Concerning physical activity, patients' activity level and exercise habits were classified into 3 groups, the ones doing minimum or above minimum physical activity recommended for its population group, and those doing below physical activity recommended, in which we included sedentary patients.

The recommendations were taken from the 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]**

In the general account, only 13% (41) of all patients performed at or above the minimum physical activity recommended for cancer patients, and 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**

| Clinical Stage | Above recommended | Recommended | 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) |

**Table 10.** — *CRL Activity Level distribution by clinical stage.*

As for their occupations, the findings are the following: 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 for retired, 7.1% (22) are students, and 4.5% (14) did not answer.

## Discussion

Regardless of selecting a population with the category of cancer-related lymphedema, this is still a highly heterogeneous population due to the fact of the existence of a prevalence of 20 different kinds of cancer involved, each, with its specificity of treatments and population

characteristics; even though, this study will work as a solid background to begin the study and understanding of lymphedema related each kind of cancer in Mexico beyond solely breast cancer. Any information documented is useful in an understudied population in this country. And especially will be the antecedent of evidence-based population approaches and 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 represent the reality, given it is still needed to assume a lymphedema stage 0 in absence of an imaging study that demonstrates lymphatic damage only with the existence of a clinical history of radiotherapy and/or ablative procedures of regional lymph nodes. That is why it needed to employ screening strategies that include NIR lymphatic imaging for those at risk of developing CRL. **[2, 3, 12]**

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 and highest than that previously reported by Chavira and Avalos-Nuño for Mexican population **[9, 10]**. Considering that around a third of them presented symptoms during the first year after cancer diagnosis and/or treatment, should be taken into count that early identification is a priority problem to solve that may impact its clinical evolution.

A bias identified in the study was that the source of the analysis is mainly based on women and with BCRL, the data of the broadest sample including more patients belonging to other 19 types of cancer-related lymphedema is needed. Anyhow it is a victory to make visible lymphedema related to other kinds of cancer different from the breast; we hope this raises attention to the consideration of lymphedema as a prevalent consequence of other cancers that are also needed to be identified, treated, and investigated.

Regarding cancer treatment, it is noted that 90.2% of patients underwent procedures where more than 1 lymph node was removed, and 68.1% received regional radiotherapy (most with 20+ sessions). Along with these risk factors for lymphedema development, it is known that

high BMI represents a strong risk factor for CRL development which was especially prevalent in more than 60% of patients. **[13-17]** During lymphedema management, these risk factors should be considered to prescribe and decide the appropriate, effective, and sustainable approach; this information should be considered also for proper educational and preventive strategies for practitioners, and health care services, and patients.

56% of patients were in clinical stages II and III, stages where it is needed not only to control treatment but interventions seeking to revert volume increasing which makes visible a need to be solved: treatment; that means that at least around 44% of patients is possible to avoid lymphedema progression strategies, which makes possible another important need to be solved: opportune diagnosis and prevention.

Related to additional features, clinicians should be ready to solve complex scenarios: secondary symptoms of standard oncological treatments, comorbidities (especially cardiac, and metabolic), chronic wounds, regional infections, thrombosis, recent surgeries; even infrequent, not impossible to represent a conditional of the clinical scenarios and prognosis.

A very peculiar data was obtained 43.3% of patients experienced pain; but also, a total of 43.3% experienced some disability. It is 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 plays a role in these painful experiences as a key factor, this puts pain phenomenon beyond a merely a tissue's interaction. It is necessary to explore the pain mechanisms, factors, and relationships among them on pain related to CRL.

Related to physical activity level it is especially important to put on the table the fact 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 worrying considering that a patient in stage 0 or I should not have a physical limitation to perform any activity related to lymphedema volume, regardless, it is highly prevalent for those in stage 0 and gets worse once it goes stage I; as for stage III gets worse compared to stage III.

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 indicating and recommending patients explicitly avoid every physical effort, activity, exercise, and daily chores that implicates the use of the affected arm; for either prevent lymphedema development or avoid its worsening once onset. These are not evidence-based recommendations, and in fact, exists strong evidence contradicting those; also exists worldwide evidence about the low knowledge about lymphedema prevention and management worldwide, as the lack of appropriate clinical practice standards. **[22-24]** The health care providers and support groups spreading these recommendations may be representing a factor that complicates this scenario, favors lymphedema progression, disability, and a barrier to the rehabilitation of these patients. We consider education and research about lymphedema as the best solution.

We hypothesize, that this phenomenon may explain in part the high rate of sedentary behavior in this 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 i,e. 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, there was found a disability increased prevalence as the clinical stage is higher (Table 9) this certainly also correlates to the fact of limb volume increases 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 the Mexican population will help to understand factors that may represent a key to developing better strategies to bring better public healthcare practices, develop precise clinical guidelines, treatment options, and new research lines to improve not only the understanding of CRL but also solve the clinical scenarios that this patients and clinicians dealing with CRL face daily.

**Conclusion**

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

## Consent

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

## Ethical approval

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



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