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# A Scoping Review of Lymphedema in Iran

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Despite significant publications in cancer survivorship, a scoping review was needed to picture the current interests and achievements of lymphedema research, as well as gaps and opportunities in Iran. Databases such as PubMed, Scopus, Google Scholar, and Persian databases (SID and MagIran) were searched to collect data. The main topics were divided into four major categories: treatment, prevention, diagnosis, and complications. Moreover, the level of evidence (LoE) was determined based on the Oxford Criteria 2009. After screening, of the 105 articles included in this study, 68 (64.7%) were English. The number of published articles increased to 14 (13.3%) and 56 (53.3%) during the first (2000-2009) and second (2010-2019) decades, respectively. In addition, 32 (30.4%) articles were published during 2020-2023. The majority of articles were related to breast cancer-related lymphedema (64.7%) and interventional trials (46.6%, 18.1% were RCTs), with the LoE of 1 and 2 (44.7%). The topic of treatment was the most investigated topic among the included articles (51.6%), and valuable studies were recently published about the prediction of lymphedema using machine learning and artificial intelligence. This scoping review showed an increasing trend of lymphedema research in Iran during the past years. Most of the research output is focused on the treatment of breast cancer-related lymphedema (BCRL) and studies on animal models and epidemiology of lymphedema are the main gaps in this field.

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## INTRODUCTION

Lymphedema is a condition of lymphatic circulation malfunction with a wide variety of presentations and clinical types. Primary lymphedema, alone or in combination with specific syndromes, is caused due to genetic defects and has a low prevalence [1]. While secondary lymphedema, such as lymphatic filariasis, has a great burden and high prevalence in geographically susceptible areas [2]. Anyhow, the most well-known type of lymphedema, which has gained even more credit in research during the past years, is secondary lymphedema due to surgery, radiotherapy, and other interventions, especially among cancer survivors [3]. Although there has been no informative epidemiological study, breast cancer-related lymphedema (BCRL) is probably the most prevalent type of lymphedema in developed

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and many other countries, including Iran. BCRL and other types of lymphedemas have somehow been neglected in medical research, and despite well-recognized animal studies in the past decade, limited data is available on its pathophysiology [4, 5]. The psychological impact of lymphedema has been addressed in research frequently; however, many other aspects of this disease remain to be investigated [6]. Research on lymphedema has been mainly focused on BCRL, and no attempt has ever been made to highlight research gaps in this field in Iran. The research output eventually needs to be directed toward evidence-based medicine (EBM) and be used in producing high-quality guidelines for lymphedema management like in other countries [7]. Therefore, this scoping review attempted to address three objectives: 1) to determine the lymphedema research trend and outcomes in Iran, 2) to shed light on evidence gaps in lymphedema management, and 3) to suggest research priorities for future investigations in Iran.

## METHODS

This scoping review was done based on the Arksey and O'Malley method and Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR), including different steps as elaborated in the following [8, 9].

### Identifying the Research Question and Relevant Studies

The main research question was "what are the achievements and shortcomings of lymphedema research in Iran?" Therefore, to get accurate results from research databases –PubMed and Scopus- we used keywords, such as lymphedema", "lymphoedema", and "Iran", in the title and abstract of articles published till the end of 2023 without any limitation on publication date or language. Meanwhile, Persian databases (including SID and MagIran) were used to gather all relevant publications as much as possible. All types of papers focusing on lymphedema, including original articles, reviews, book chapters, conference abstracts, letters, editorials, and other types of research articles, were eligible to be selected in the screening process. English and Persian articles published till the end of 2023 were included. The study design was not limited, and all kinds of studies were included, such as reviews, randomized clinical trials (RCTs), uncontrolled interventional studies, cohort, case-control, cross-sectional, case studies, and animal studies. In addition, there was no restriction on the type of lymphedema, as both primary and secondary were eligible. Lymphedema should have been the main objective of the article to be included. Therefore, articles that lymphedema was not the main focus were excluded as in those papers that were mainly focused on breast cancer survivors and their overall outcomes. Titles and abstracts were screened by two investigators independently, with the collaboration of the third investigator in the case of disagreement. The full text of the remaining articles was screened in the same way. Finally, data were extracted from the included studies.

### Charting the Data

The title, year, journal, authors and affiliations, and language of each included article were extracted. Lymphedema was classified into primary, secondary, or mixed based on the study population. The anatomical site of lymphedema was at extremities, genital, head, and neck or any other site. Given that BCRL is the most prevalent type of lymphedema in Iran, its lymphedema was even more categorized based on etiology to BCRL, filariasis, and genetics. The study design of included articles were RCTs, other interventional studies, cohort, case-control, cross-sectional, case studies, reviews, such as narrative or systematic reviews and meta-analyses, and statistical studies. The last-mentioned group meaning statistical studies was added for articles that used data mining, machine learning, statistical modeling, artificial intelligence (AI), or other engineering methods. Due to the recent increasing interest in such methods in biomedical research, these articles were highlighted in a distinct methodology. The main topics were determined as follows:

Treatment: Complete decongestive therapy (CDT), manual lymphatic drainage, pneumatic pressure, surgery, cell therapies, genetic studies and drugs, laser therapy, yoga, diet intervention, exercise, and weight reduction

Prevention: epidemiology, risk factors, education

Diagnosis: lymphoscintigraphy and other diagnostic methods, prediction, devices, and applications, rare diseases

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Complications: Quality of Life (QoL), pain, and, musculoskeletal disorders such as carpal tunnel syndrome

The levels of evidence (LoE) were defined based on the Oxford categories 2009 [10]. Based on the Oxford LoE criteria, there are several categories based on the purpose of the study, such as therapy, prevention, diagnosis, and other topics. Included articles were divided based on these categories, and the LoE was determined according to the quality and methodology of the study. The LoE contains the range of 1a to 5 from the highest to the lowest level in most Oxford categories. All data were imported to individual spreadsheets by two investigators independently, with the help of the third investigator as needed.

### Collating, Summarizing, and Reporting the Results, With Expert Consultation

Data were used to calculate the number and percent of language, type of lymphedema, anatomical site, study design, main topic, and LoE. Moreover, the trend of publication was charted based on four major timings: 1) articles published before 2000, 2) articles published during 2000-2009, 3) articles published during 2010-2019, and 4) articles published between 2020 and 2023. The names of authors and journals were listed and the most active authors and journals that published articles on lymphedema were specified. All author affiliations were reviewed in a similar method and finally, the most mentioned affiliations, most productive universities, research institutes, and also the collaborations with other countries were determined based on affiliations.

## RESULTS

The list of all reviewed articles, including their title, year of publication, journal, and other characteristics, is provided in the supplementary file. The PRISMA flow diagram illustrates the number of excluded and included articles in Figure 1.

### Trend of Publication

Of 105 reviewed articles, 68 (64.7%) were English, and 37 (35.3%) were Persian. As shown in Figure 2, the overall trend of published articles increased from 2000 to 2019. Only 3 (3%) articles were published before 2000. The number of publications increased to 14 (13.3%) and 56 (53.3%) during the first (2000-2009) and second (2010-2019) decades, respectively. In addition, 32 (30.4%) articles were published between 2020 and 2023.

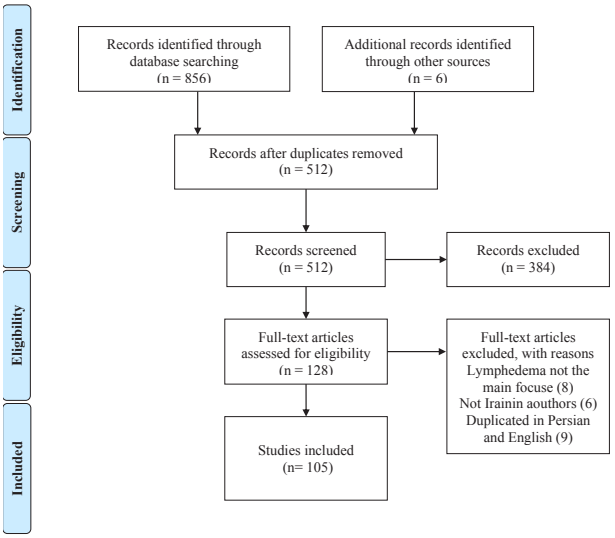


**Figure 1**: The PRISMA Flow Diagram

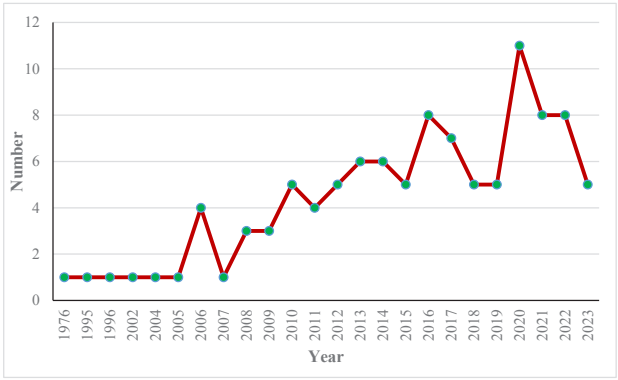


**Figure 2**: The increasing trend of lymphedema publications in Iran

### Characteristics of Lymphedema

Secondary lymphedema was studied in 79 (75.2%) articles, and primary lymphedema was studied in 17 (16.2%) articles. Moreover, both primary and secondary lymphedema were studied in 9 (8.6%) articles. The anatomical site of lymphedema was the upper and lower limb, and mixed in 71 (67.6%), 23 (21.9%), and 7 (6.6%) articles, respectively. The site of lymphedema was genitalia, abdomen, and eyelid in 4 (3.8%) articles. BCRL was the type of lymphedema in 68 (64.8%) articles. Congenital, Praecox, and Tarda were the lymphedema types in

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11 (10.4%) studies. The type of lymphedema was mixed in 9 (8.7%) articles; other types, such as filariasis, were investigated in 17 (16.2%) articles.

### Study Design and Level of Evidence

Of the 105 articles included in the scoping review, 49 (46.6%) were intervention-based studies. The design of 19 (18.1%) and 30 (28.6%) studies were RCTs and other types of interventional studies, respectively. In addition, cross-sectional, case-control, and, cohort designs were employed in 12 (11.4%), 1 (1%), and 4 (3.8%) studies, respectively. Moreover, 8 (7.3%) articles were review studies. Four review articles and one meta-analysis were included in this study. Twenty-five (23.8%) articles included case reports, case series, and family studies, and 6 (5.7%) studies had statistical modelling or data mining design. The LoE of 1a and 1b was reported for 2 (1.9%) and 18 (17.1%) articles, respectively. In 20 (19%), 7 (6.6%), and, 5 (4.8%) articles, the LOE was 2b, 2c, and 3a, respectively. Moreover, 46 (43.8%) articles had LOE4, while for 7 (7.6%) articles had LoE5.

**Table 1:** Main Topics Based on Different Characteristics of Included Articles[a]

| | Therapy, No. | Prevention, No. | Diagnosis, No. | Complication, No. | Total, No.(%) |
|---|---|---|---|---|---|
| **Year** | | | | | |
| **Up to 2000** | 1 | 0 | 2 | 0 | 3(2.9) |
| **2000-2009** | 6 | 0 | 7 | 1 | 14(13.3) |
| **2010-2019** | 32 | 6 | 13 | 5 | 56(53.3) |
| **2020-2023** | 15 | 9 | 6 | 2 | 32(30.5) |
| **Type** | | | | | |
| **Primary** | 7 | 0 | 10 | 0 | 17(16.2) |
| **Secondary** | 42 | 13 | 16 | 8 | 79(75.2) |
| **Both** | 5 | 2 | 2 | 0 | 9(8.6) |
| **Anatomy** | | | | | |
| **Upper** | 39 | 10 | 14 | 8 | 71(67.6) |
| **Lower** | 10 | 2 | 11 | 0 | 23(21.9) |
| **Other** | 5 | 3 | 3 | 0 | 11(10.5) |
| **Etiology** | | | | | |
| **BCRL** | 40 | 10 | 10 | 8 | 68(64.8) |
| **Other** | 14 | 5 | 18 | 0 | 37(35.2) |
| **Design** | | | | | |
| **RCT** | 16 | 2 | 0 | 1 | 19(18.1) |
| **Another b** | 28 | 1 | 1 | 0 | 30(28.6) |
| **Descriptive c** | 1 | 7 | 3 | 6 | 17(16.2) |
| **Case study** | 5 | 2 | 17 | 1 | 25(23.8) |
| **Review** | 4 | 3 | 1 | 0 | 8(7.6) |
| **Statistical** | 0 | 0 | 6 | 0 | 6(5.7) |
| **LoE** | | | | | |
| **1a** | 2 | 0 | 0 | 0 | 2(1.9) |
| **1b** | 14 | 2 | 1 | 1 | 18(17.1) |
| **2b** | 17 | 3 | 0 | 0 | 20(19) |
| **2c** | 0 | 3 | 3 | 1 | 7(6.7) |
| **3a** | 1 | 3 | 1 | 0 | 5(4.8) |
| **4** | 19 | 3 | 19 | 5 | 46(43.8) |
| **5** | 1 | 1 | 4 | 1 | 7(6.7) |
| **Total, No.(%)** | 54(51.4) | 15(14.3) | 28(26.7) | 8 (7.6) | 105(100) |

[a] Abbreviations: BCRL, breast cancer-related lymphedema; LoE, level of evidence; RCT, randomized controlled trial
[b] Other interventional studies, including non-randomized controlled trials and pilot interventions
[c] Descriptive studies, including cohort, case-control, and, cross-sectional

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### Topics

The main topics were as follows: treatment: 54 (51.6%), prevention: 15 (14.2%), diagnosis: 28 (26.6%), and complications: 8 (7.6%). It is worth noting that surgery, prediction, and QoL were the topics of 9, 4, and 2 articles, respectively. Epidemiology was addressed in three articles, and only one study was about lymphoscintigraphy. Table 1 demonstrates the number of main topics based on different characteristics, such as year of publication, lymphedema types, and study design types.

### Authors

Overall, 272 author names were determined; of whom, seven were not Iranian and were mostly affiliated with UK institutions. The most active Iranian scholar in the lymphedema field was S. Haghighat with 25 (23.8%) publications. Other Iranian researchers included A. Montazeri Z. Sheikhi, Z. Zakeri, and H. Bagheri, with 8 (7.6%) and 6 (5.7%) publications, respectively. The top three productive authors are presented in Table 2.

### Journals

Included articles were published in 79 journals 16 (20.2%) published in Persian. The "Iranian Journal of Breast Diseases" had the most published articles on lymphedema with 12 (11.4%) articles. In the next ranking, the journals "Scientific Journal of Rehabilitation Medicine", "Journal of Modern Rehabilitation", and, "Lymphology" were of more interest to Iranian researchers with 3 (2.8%) published articles in each journal. Table 2 demonstrates these journals and the rest of the top three rankings. Six (7.5%) journals were specifically about breast diseases, while five (6.3%) and three (3.7%) journals were mainly related to the fields of dermatology and rehabilitation, respectively. Additionally, six (7.5%) journals were in the field of lymphology and vascular medicine, as "Lymphology" and "Lymphatic Research and Biology" were the only two lymphedema subspecialty journals found in this scoping review. Altogether, 22 (27.8%) journals were focused on surgery, oncology, and QoL.

### Affiliations and Institutes

There were 432 institutional affiliations, and Tehran University of Medical Sciences with 76 (17.6%) affiliations achieved the first place. The other top two universities were Shahid Beheshti University of Medical Sciences, Shiraz University of Medical Sciences with 67 (15.5%) and 65 (15%) affiliations respectively as provided in Table 2. Among research centers and research institutes, 60 (13.8%) were related to the Academic Center for Education, Culture, and Research (ACECR). Moreover, 20 (4.6%) affiliations were from other countries, and 11 and 5 affiliations were from UK and USA, respectively. Among all affiliations, 61 (14%), 36 (8.3%), and 31 (7.1%) were related to surgery, rehabilitation, and nursing fields, respectively.

## DISCUSSION

This study reviewed the existing research output

**Table 2:** Top Three Productive Authors, Journals, and, Institutes in Lymphedema Research in Iran

| | Value, No.(%) |
|---|---|
| **Author, %** | |
| **Haghighat, Shahpar** | 26(23.8) |
| **Montazeri, Ali** | 9(7.6) |
| **Sheikhi, Zahra; Zakeri, Zeinab; Bagheri, Hossein** | 7(5.7) |
| **Journal, %** | |
| **Iranian Journal of Breast Diseases** | 12(11.4) |
| **Scientific Journal of Rehabilitation Medicine; Journal of Modern Rehabilitation; Lymphology** | 3(2.8) |
| **Journal of Research in Medical Sciences; Indian Journal of Surgery; Iranian Red Crescent Medical Journal; Nutrition and Cancer; Iranian Journal of Obstetrics Gynecology and Infertility; Biomedicines; Payesh; Multidisciplinary Cancer Investigation; Iranian Journal of Dermatology** | 2(1.9) |
| **Institutes, No. (%)** | |
| **Tehran University of Medical Sciences** | 76(17.6) |
| **Shahid Beheshti University of Medical Sciences** | 67(15.5) |
| **Shiraz University of Medical Sciences** | 65(15) |

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of lymphedema in Iran. Altogether, 105 articles were found to have focused on lymphedema. It should be noticed that lymphedema research is ignored globally and only in the last three decades, significant progress has been made [6, 11]. Looking into the trend of publication shows that the number of articles published between 2010 and 2019 is four times more than that of the previous decade. This increasing trend is still notable as 30.4% of included articles were just published during the last four years of 2020 to 2023; therefore, more research in this field is expected in the future. BCRL was the most studied type of lymphedema which is reasonable since BCRL is the most well-known type of lymphedema in Iran. However, other cancer-related lymphedema types were under-researched. Although 67.6% of articles were about upper limb lymphedema, the lower limb, which mostly is the anatomical site of lymphedema in gynecological cancer survivors, was studied in 22% of articles. Genital, head, and neck lymphedema were very limited among the included articles. These types of lymphedemas are now gaining more attention; therefore, more emphasis needs to be placed by Iranian researchers in these fields [12, 13]. Almost half of the included articles were interventional studies, and 18.1% were RCTs. It demonstrates the valuable efforts of researchers and the great potential of producing evidence for lymphedema management. Although the majority of these RCTs were focused on physical activity and CDT, which are the standard care of lymphedema, surgical intervention, cell therapy, and using complementary and alternative medicine such as low-level lasers are now the interest of many lymphedema researchers worldwide [14-17]. RCTs are valuable evidence in EBM, and the quality of RCT matters, but this study did not primarily aim to assess the quality of RCTs. Systematic review and meta-analysis are essential to generate evidence-based guidelines, which were not included in this study. There are several major guidelines for lymphedema management as the guideline by the International Society of Lymphology or the recent American joint societies' expert opinion on lymphedema [7, 18, 19]. These guidelines have been translated and adapted by researchers in other countries, and this scoping review strongly endorses Iranian researchers to standardize lymphedema management based on the EBM with suitable guidelines.

Nearly half of the included articles had the LoE of 1 and 2, which is promising, but the importance of descriptive studies should not be underestimated. For example, the absence of cohort studies is one of the main gaps in epidemiological studies of lymphedema in Iran. Well-established cohort studies have shown the incidence of BCRL and its risk factors among breast cancer survivors. It is also necessary to investigate subclinical lymphedema and find possibilities for early intervention [20, 21]. Moreover, no study investigated the financial burden of BCRL, research budgets, and the number and distribution of professionals in clinical management. The actual needs of patients with lymphedema were also missing. These data are necessary for researchers and policymakers to have a proper understanding of the management gap of lymphedema in Iran and to make decisions such as insurance coverage of lymphedema-related expenses [22, 23]. More than half of included studies were about therapy and management, while the diagnosis was the second most studied topic. Some interesting topics, such as surgery, prediction, and QoL, were present in the articles. Microsurgery is one of the latest improvements in lymphedema treatment, missing in the Iranian research output. Surgical interventions are mainly divided into physiologic and non-physiologic methods, which are now a part of education for some specialties, such as vascular surgery and plastic surgery [24]. Microsurgery, as the cutting edge of lymphedema treatment, requires trained professionals, equipment, and investments [25]. Another topic that interestingly was favored by Iranian researchers was the prediction or diagnosis of lymphedema based on AI or data mining and other statistical modeling. AI will play a vital role in the future of medicine, and its applications have been widely studied in cancer survivorship [26, 27]. A recent review concluded that AI could be helpful in a wide range of domains, including microsurgery for cancer-related lymphedema treatment and epidemiological interventions for filariasis eradication [28]. Articles reporting the AI application in lymphedema management shows the capacities of lymphedema research in Iran and forming national and international collaborations, which could lead to the weighty cooperation of Iranian researchers in this field.

One of the hot topics of lymphedema is lymph

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angiogenesis and biomedical research [6]. Such studies are essential to shed light on lymphedema pathophysiology and propose possible treatments [29]. Despite some limited genetic studies of BCRL, there was no other biomedical study among the research output of this scoping review. Unfortunately, no study used an animal model of lymphedema, which is the main cause of neglect in lymphedema biomedical research. Animal models of lymphedema have a vital role in the research of pathophysiology and surgical interventions for lymphedema [30]. As mentioned earlier, the majority of interventional studies were conducted by clinicians; therefore, it is essential to form collaborations between clinical researchers and biomedical investigators, especially those active in laboratory and animal model studies. The most active researcher was S. Haghighat affiliated with ACECR, and Tehran University of Medical Sciences was the most active medical center in this scoping review. The Breast Cancer Research Center of Motamed Cancer Institute (MCI), affiliated with ACECR, was established in 1996 to investigate breast cancer and its management, from early screening to survivorship support. The Quality-of-Life Department and the Lymphedema Clinic at this institute have been responsible for BCRL research and management since 2010. Moreover, this clinic is a referral center in Tehran and provides clinical research and management for other types of lymphedemas, such as primary lymphedema [31]. Other centers have been established in different provinces ever since, and there may be a link between the establishment of these centers and the increase in lymphedema publication. Although the main discipline of research output was related to surgical oncology, other disciplines, such as rehabilitation medicine, dermatology, vascular surgery, and nursing, were also present. One of the most interesting findings of this scoping review was the collaboration of researchers in rehabilitation medicine based on their affiliations and their interest in publishing articles in rehabilitation journals. The multidisciplinary engagement of professionals in lymphedema management is supported by the literature [32, 33]. Based on this scoping review, there is a potential for forming this collaboration among professionals of different specialties to improve lymphedema care delivery in Iran.

## CONCLUSION

This scoping review demonstrated the increasing trend of lymphedema publication research in Iran. The majority of articles reported the treatment of BCRL and QoL of breast cancer survivors with lymphedema. While a significant number of included articles were interventional studies, data on epidemiology and the financial burden of lymphedema are missing. Moreover, studies on animal models of lymphedema and biomedical research have been neglected. Finally, the next steps in lymphedema research should be directed at producing clinical guidelines and emphasizing EBM.

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Not applicable.

## CONFLICT OF INTEREST

All authors declare that no competing financial interests exist.

## ETHICS APPROVAL

Not applicable.

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