Published in final edited form as:

J Cancer Surviv. 2015 June ; 9(2): 161–171. doi:10.1007/s11764-014-0393-z.

An Algorithm to Identify the Development of Lymphedema After Breast Cancer Treatment

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Abstract

Purpose—Large, population-based studies are needed to better understand lymphedema, a major source of morbidity among breast cancer survivors. One challenge is identifying lymphedema in a consistent fashion. We sought to develop and validate an algorithm using Medicare claims to identify lymphedema after breast cancer surgery.

Methods—From a population-based cohort of 2,597 elderly (65+) women who underwent incident breast cancer surgery in 2003 and completed annual telephone surveys through 2008, two algorithms were developed using Medicare claims from half of the cohort and validated in the remaining half. A lymphedema-positive case was defined by patient report.

Results—A simple two ICD-9 code algorithm had 69% sensitivity, 96% specificity, positive predictive value >75% if prevalence of lymphedema is >16%, negative predictive value >90%, and area under receiver operating characteristic curve (AUC) of 0.82 (95% CI: 0.80 – 0.85). A more sophisticated, multi-step algorithm utilizing diagnostic and treatment codes, logistic regression methods, and a reclassification step performed similarly to the two-code algorithm.

Conclusions—Given the similar performance of the two validated algorithms, the ease of implementing the simple algorithm and the fact that the simple algorithm does not include treatment codes, we recommend that this two-code algorithm be validated in and applied to other population-based breast cancer cohorts.

Implications for Cancer Survivors—This validated lymphedema algorithm will facilitate the conduct of large, population-based studies in key areas (incidence rates, risk factors, prevention

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Conflict of Interest

All authors (Tina Yen, Purushuttom Laud, Rodney Sparapani, Jianing Li and Ann Nattinger) declare that they have no conflicts of interest.

Integrity of Research and Reporting

This study was approved by the Medical College of Wisconsin's institutional review board. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

measures, treatment and cost/economic analyses) that are critical to advancing our understanding and management of this challenging and debilitating chronic disease.

Keywords

lymphedema; algorithm; breast cancer; Medicare; survivorship

Introduction

Conducting high quality studies on large administrative datasets that address the quality of medical care often require applying validated claims-based algorithms to identify disease processes, treatment patterns, treatment complications and outcomes. While developing such algorithms is not straightforward and validating algorithms can be equally challenging, efforts to develop and validate claims-based algorithms have been successful [1–5]. With respects to cancer care, few validated claims-based algorithms to identify incident cancers exist in the current literature, including three (one from our group) which have been published to identify incident breast cancer [6–10]. Validated claims-based algorithms exist that identify recurrent disease and second primary cancers [11–15]. However, only a few validated algorithms have been published that address complications of cancer treatment [16, 17].

Despite advances in our understanding of breast cancer and its treatments, lymphedema (arm/hand swelling) remains one of the most feared complications of breast cancer treatment, is a major source of treatment-related morbidity, and is one of the most difficult diseases to study. This chronic condition can result in significant physical discomfort and disability, cosmetic deformity and psychological distress that all adversely affect activities of daily living and quality of life and is associated with significant medical costs [18–23]. Women are at risk of developing lymphedema over their lifetime and the time frame from treatment to development of lymphedema is highly variable [24].

The incidence of lymphedema in individual studies ranges from 0 to 94% [25–27]. This wide variation is due to the fact that the majority of studies are relatively small, single-institutional, retrospective reports with marked study heterogeneity with respect to differences in study design, patient populations and breast cancer treatments, diagnostic methods and criteria used to define lymphedema (subjective versus objective methods) [28], and timing and duration of follow-up assessments. Sentinel lymph node biopsy (SLNB), which involves the removal of only a few lymph nodes in eligible women, is associated with lower but still substantial rates of lymphedema than a full axillary node dissection (ALND); a recent systemic review and meta-analysis of studies from 2000–2012 reports a pooled estimated lymphedema incidence rate of 17% – 21% [24].

Given the general limitations of prior studies, larger population-based studies of lymphedema are needed to increase and expand our understanding of this complex and disabling chronic disease. However, a major challenge to population-based studies is identifying patients with lymphedema in a consistent fashion. To our knowledge, three prior studies have utilized a claims-based approach to defining lymphedema [29, 23, 30] [Table

1]. These three studies each used diagnostic codes with or without different treatment codes to define lymphedema but none have validated their approach.

As the number of cancer survivors continues to grow, the importance of increasing our awareness and understanding of the many short- and long-term consequences of cancer and its treatment has become increasingly emphasized [31]. We therefore sought to develop and validate an algorithm utilizing Medicare claims to identify women who develop lymphedema after breast cancer treatment in a population-based cohort of older breast cancer survivors.

Methods

Data sources

The study sample was derived from a population-based cohort of elderly breast cancer survivors who participated in a National Cancer Institute-sponsored survey study examining breast cancer care outcomes, which has been previously described [32, 33]. In brief, women residing in four geographically diverse states (California, Florida, Illinois, and New York) were identified from Medicare claims as having had an incident breast cancer surgery between the ages of 65 and 89 years in 2003, using our validated claims-based algorithm [6]. As shown in Figure 1, potential participants (n=8,742) were contacted by mail in September 2005; 5,659 were excluded either due to study ineligibility (n=2,995) or non-participation (n=2,664). Baseline (wave 1) and three subsequent structured telephone interviews were conducted by an experienced survey center. Survey waves 2, 3 and 4 were completed at a median duration of 40 (interquartile range: 6 [36–42 months]), 49 (interquartile range: 5 [46–51 months]) and 60 months (interquartile range: 4 [58–62 months]) after surgery, respectively. A total of 3,083 women confirmed their diagnosis of an incident breast cancer and completed the initial survey, with a participation rate of 70% among those eligible for the study; participation rates remained over 90% for the three follow-up surveys [32]. A multiple regression model predicting survey participation was performed comparing the 3,083 survey participants to the 2,664 non-participants [32]. Older subjects (75+ years) and those residing in NY were less likely to participate but participation did not differ based on socioeconomic status, race/ethnicity, comorbidity or type of breast surgery.

Tumor characteristics and stage information was provided by the four state cancer registries [34]. Medicare claims information was collected from inpatient, outpatient and carrier Standard Analytical Files through 2008. Three coding manuals (ICD-9 CM International Classification of Diseases, Current Procedural Terminology, and HCPCS Health Care Financing Administration Common Procedure Coding System) were searched to identify diagnostic, procedural, treatment and durable medical equipment codes that could potentially indicate lymphedema [35–37].

Lymphedema definition, case construction, creation of training and validation cohorts

Self-report of lymphedema was ascertained at approximately 3, 4 and 5 years of follow-up (at survey waves 2, 3 and 4). Of the initial 3,083 participants who completed wave 1, 5%–10% of women were either no longer eligible to participate or lost to follow-up due to

inability to contact or refusal at each subsequent wave: 295 at wave 2, 136 at wave 3, and 180 at wave 4 [32].

For participants who responded to more than one wave of the survey, we had the opportunity to test the validity of the algorithm with respect to lymphedema onset over multiple time intervals. Taking as the unit of analysis a time interval between surgery and a survey wave, each woman could have between 1 and 3 observations included in the analysis. Of the 2,597 women who had complete survey and claims information through at least survey wave 2, 1,981 (76%) completed waves 3 and 4 and had claims information through wave 4. These 2,597 women who had complete survey and claims information through at least survey wave 2 generated a total of 6,754 observations from waves 2–4 (Figure 1). These observations were randomly sampled and half were placed in the training cohort and half in the validation cohort. Therefore, a patient with more than one observation could have observations in one or both cohorts. There were a total of 3,356 observations (2,077 patients) included in the training cohort and 3,398 observations (2,119 patients) in the validation cohort.

For each of these observations, a case determination was made. A lymphedema-positive case was defined as a “yes” response to the lymphedema survey question: “Since undergoing breast cancer surgery (or last survey), has a doctor ever told you that you have lymphedema or arm edema?” This question was adapted from previously published work [38]. Once a woman responded “yes”, she was not re-asked the lymphedema question at subsequent waves and was deemed a lymphedema-positive case for all subsequent observations. If an observation was not deemed a lymphedema case (i.e., the woman responded “no” to the question), she was asked the lymphedema question at the next survey wave. Case determinations were made for each observation period and included in the algorithm construction training cohort or validation cohort if claims information was available for the observation period.

Lymphedema algorithm performance measures

Algorithm performance was assessed by determining sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the receiver operating characteristic curve (AUC). Self-reported lymphedema was the gold standard. Sensitivity (true positive rate) measures the proportion of self-reported lymphedema cases that were correctly identified to be lymphedema-positive by the algorithm. Specificity (true negative rate) measures the proportion of self-reported non-lymphedema cases that were correctly identified to be lymphedema-negative by the algorithm. The ideal algorithm would have 100% sensitivity (predict all cases from the self-reported lymphedema group as having lymphedema) and 100% specificity (not predict any cases from the non-lymphedema group as having lymphedema).

The PPV and NPV represent the probability that the algorithm gives the correct result. The PPV measures the proportion of algorithm-positive lymphedema cases that were self-reported lymphedema cases; the NPV measures the proportion of algorithm-negative cases that were self-reported non-lymphedema cases. The PPV is dependent on the prevalence of disease [39]. If the prevalence of lymphedema is very low, the PPV will not approach 100%

even if both the sensitivity and specificity are high. As lymphedema prevalence rates increase, the PPV increases and the NPV decreases.

The accuracy of the algorithm was measured by the AUC, which is determined by plotting the true positive rate (sensitivity) along the y-axis by the false positive rate (1-specificity) along the x-axis. An AUC of 1.0 represents a perfect test while an AUC of 0.5 represents a worthless test.

Simple lymphedema algorithm

Since the two lymphedema diagnosis codes (ICD-9 457.0, 457.1) were consistently used in all three published studies that have utilized a claims-based approach to defining lymphedema [23, 29, 30] [Table 1], we first developed a simple 2-code algorithm, which required only identifying either ICD-9 457.0 or 457.1 codes at any time point after surgery. Having an algorithm based on diagnosis codes only and excluding lymphedema treatment codes enhances the ability to use this algorithm to study lymphedema treatment outcomes. This simple 2-diagnosis code algorithm in the training cohort yielded 71% sensitivity and 95% specificity (Table 3).

Multi-step lymphedema algorithm

Next, we sought to determine whether a more sophisticated algorithm could be developed with improved performance compared to the simple two-code algorithm. For this algorithm development process, we included the evaluation of treatment codes to determine if they would enhance algorithm performance, particularly sensitivity.

Library of potential lymphedema codes—We began by conducting an exhaustive search for diagnostic, procedural, treatment and durable medical equipment codes that could potentially indicate lymphedema (Table 2). This search, led by a practicing breast surgeon and researcher (TY), was conducted by all research team members. An initial screen of the number of claims for each code that was present per patient since surgery was performed in the training cohort. The prevalence of these codes was examined separately in women reporting lymphedema and those that did not for differences which would aid in identifying codes potentially reflective of lymphedema. All HCPCS codes and three ICD-9 codes (459.1, 782.8, 782.9) were either never or very rarely identified and were therefore not further assessed. All other codes were further explored.

The four most clinically likely diagnostic codes for lymphedema are in bold (ICD-9 457.0, 457.1, 729.81 and 782.3). The presence of any of these four codes since surgery had a sensitivity of 80% with a specificity of 68%. Individually, the most sensitive code was 457.1 (other lymphedema, including acquired [chronic] and secondary) with a sensitivity of 60% and specificity of 96% (Table 2). The prevalence of either 457.0 (postmastectomy lymphedema syndrome) or 457.1, the two lymphedema-specific diagnosis codes, was 9.5%; the sensitivity and specificity were 71% and 95%, respectively.

The three codes in italics (ICD-9 457.2, 682.3, 682.4) were deemed “sequelae” codes as these diagnoses (lymphangitis, diffuse cellulitis, acute abscess, acute lymphangitis) are more likely to occur in patients with lymphedema than those without lymphedema. These codes

would have been considered in the algorithm to rule out lymphedema cases; however, given the very low prevalence and sensitivity of these codes (presence of any one of these 3 codes had 12% sensitivity and 97% specificity), these codes were not considered good candidates and were not further explored.

The three underlined codes (ICD-9 459.2, 459.3, 611.0) were deemed “non-specific” codes as lymphedema could result as a sequelae of these diagnoses (vein compression, idiopathic chronic venous hypertension, inflammatory disease of the breast), although unlikely. These codes would have been considered in the algorithm if they enhanced the algorithm performance; however, due to the very low prevalence and sensitivity of these codes (presence of any one of these 3 codes had 17% sensitivity and 92% specificity), they were also not considered good candidates and were not further explored.

All 7 procedural/treatment (CPT) codes related to lymphedema were further evaluated. As shown in Table 2, the most prevalent codes were for physical therapy (CPT 97001, which are relatively non-specific and could be unrelated to lymphedema) and manual therapy techniques (CPT 97140), which are more specific for lymphedema. Of these 7 codes, sensitivity (75%) and specificity (73%) were highest for the manual therapy techniques code (CPT 97140), which includes manual lymphatic drainage therapy, a treatment that is specific for lymphedema.

Medicare coverage for the HCPCS codes that were evaluated is summarized in Table 2. Since all A, E and L-codes (compression bandages, compression stockings, pneumatic devices) have either C (carrier judgment), D (special coverage instructions apply) or M (non-covered) Medicare coverage status [40, 41] is not surprising that these codes were either not found or rarely identified due to variable or no Medicare reimbursement. As expected, no single claim with any S code, which includes all gradient pressure aids as well as S8950 (complex lymphedema therapy, the most specific therapy for lymphedema), was found as S codes are all I (not payable by Medicare) coverage status codes [40].

Development of 3-step lymphedema algorithm—Lymphedema algorithm construction subsequently focused on the 4 ICD codes (457.0, 457.1, 729.81 and 782.3) and the 7 CPT treatment codes and discovering what combinations of available billing codes were indicative of lymphedema. This process involved a careful and deliberate model search on the test data that was not automated and was refined based on clinical insight. An extensive number of logistic regression models were evaluated to predict self-reported lymphedema using variables constructed from these 11 codes. These constructed variables included: 1) presence/absence of code; 2) if present, the number of times the code was identified at various time intervals (15, 30, 90, 120 and 180 days) after each code was identified; 3) for the 4 diagnosis codes, whether a CPT code was identified at the same time as the ICD-9 code; 4) the presence of any of the 10 discussed ICD-9 codes or seven procedural/treatment codes prior to surgery; 5) the presence of any arm/shoulder/hand ICD-9 codes 710 – 996 prior to surgery; 6) evaluation of any codes present in the false-negative (code negative but survey positive) group that could potentially be used to increase algorithm sensitivity. These analyses revealed that the combination of diagnosis and treatment codes with the highest sensitivity included 6 codes: ICD 457.0, 457.1, 729.81,

CPT 97016, 97124 or 97140. Using the presence of any of these 6 codes for screening, the sensitivity was 84% but specificity was only 61% for detecting lymphedema. We therefore sought to develop a multi-step algorithm that would improve specificity without compromising sensitivity significantly.

The first phase of algorithm development involved screening for the presence of any of the above 6 diagnostic and treatment codes within a timeframe of one year prior to surgery to the most recent available claims. A patient with any of the 6 codes present moved on to the second step of the algorithm, which involved applying a logistic regression model, to remove cases of edema which existed prior to incident breast cancer surgery. A model predicting an incident lymphedema case was developed using the presence of these 6 codes (individually and in combinations) as predictor variables. Stepwise regression was used to determine the final logistic model which included the presence of ICD 457.0, 457.1, and/or 729.81 codes since surgery. The third step of the algorithm required reclassifying to algorithm-negative the lymphedema algorithm-positive cases (n=14 for the training cohort) that had ICD-9 codes 782.3 (edema) or 729 (other disorders of soft tissue) one year prior to surgery. In the training cohort, this three-step algorithm yielded an AUC of 0.83, sensitivity of 71%, specificity of 95% and PPV of >75% if the prevalence of lymphedema is 16% or higher (Table 3). The NPV of this algorithm is excellent at >90% for a wide range of lymphedema prevalence rates.

Algorithm Face Validity—To provide face validity of the lymphedema algorithm, risk factors for lymphedema among the 1,148 women in this algorithm cohort who had documented nodal status and wave 3 information were assessed with a multiple logistic regression model and compared with the previously published results in the same breast cancer survey cohort where lymphedema was defined by self-report [33]. The independent variables entered into the model included: hypothesized risk factors (number of lymph nodes removed, surgeon case volume), variables for which univariate associations were significant at the 0.05 level (tumor size, type of breast cancer [DCIS or invasive], lymph node status, type of breast surgery, receipt of chemotherapy), and factors that have been observed as predictors of lymphedema by other studies (patient age, radiation therapy, hormonal therapy).

All data analyses were conducted using SAS statistical software (Version 9.3, SAS Institute; Cary, NC).

Results

In the total cohort of 2,597 patients, the mean age of the women at the time of surgery was 72.0 (SD 5.4) years and 92% were white. Of the women with available pathologic tumor staging information, the majority had early stage disease: 96% had tumors less than 5 cm in size and 78% were lymph node-negative. Two-thirds (66%) underwent breast-conserving surgery; 34% underwent mastectomy. No axillary surgery was performed in 18%, while 26% underwent SLNB only and 56% underwent ALND. Two-thirds of the cohort received radiation therapy, 20% chemotherapy, and 70% hormonal therapy. There were no differences in patient, tumor or treatment characteristics between the training and validation

cohort groups. In the training cohort, 7.2% of observations were lymphedema-positive cases. In the validation cohort, 7.8% of observations were lymphedema-positive cases. These proportions were lower than expected, but are likely explained by the strict definition of lymphedema (patient's recall of being told by her doctor that she had lymphedema since undergoing breast cancer surgery) required for this study.

Algorithm validation

When applied to the training cohort, the simple 2-code algorithm had excellent specificity (95%) and moderate sensitivity (71%). When this simple algorithm was applied to the validation cohort, the results were similar: AUC 0.82 (95% CI: 0.80 – 0.85), sensitivity 69%, specificity 96%, PPV > 75% if prevalence of lymphedema is >16% and NPV >90% (Figure 2, solid lines; Table 3).

The multi-step algorithm in the training cohort yielded similar results to the simple algorithm (Table 3). Moreover, this multi-step algorithm in the validation cohort yielded similar sensitivity and specificity results and AUC (0.83; 95% CI: 0.80 – 0.86) compared to the simple algorithm (Table 3). Similar to the simple algorithm, the PPV of this multistep algorithm is >75% if the prevalence rate of lymphedema is at least 16% and the NPV of this simplified algorithm is > 90% for a wide range of lymphedema prevalence rates (Figure 2, dashed lines).

To provide further face validity of the simple lymphedema algorithm, using a multiple logistic regression model, we assessed risk factors for lymphedema (defined by the 2-code algorithm) among the 1,148 women in this algorithm cohort who had documented nodal status and wave 3 information and compared these results to those previously published in the same breast cancer survey cohort where lymphedema was defined by self-report [33]. As shown in Table 4, in the algorithm cohort of 1,148 women, the results of the multiple logistic regression model with the outcome of lymphedema defined by the 2-code claims algorithm are similar to those results with lymphedema defined by self-report, which are similar to previously published results [33].

Discussion

In this study, we have developed and validated a simple 2-code algorithm and a more complex 3-step algorithm for the use of Medicare claims data to identify women who develop lymphedema after breast cancer treatment in a population-based cohort of older breast cancer survivors. The more complicated, multi-step algorithm performs similarly to the much simpler 2-code algorithm, which involves only the identification of either lymphedema ICD-9 code 457.0 or 457.1 at any time point after incident breast cancer surgery.

This simple algorithm has an overall sensitivity of 69% and specificity of 96%, using a gold standard of a patient reporting that her doctor told her she had lymphedema or arm edema since undergoing breast cancer surgery. The positive predictive value of this algorithm varies across different lymphedema prevalence rates (Figure 2) but is greater than 75% when the incidence of lymphedema is greater than 16%. The negative predictive value of this

algorithm is greater than 90% across a wide range of lymphedema incidence rates. Given the similar performance of both algorithms, and the ease of implementing the simplified algorithm, we recommend using the simpler two ICD-9 code algorithm. Another reason to favor using the simple algorithm is that it does not include lymphedema treatment codes, thereby enhancing the ability to most effectively study lymphedema treatment and its outcomes in cohorts identified by this algorithm as having lymphedema. The ability to systematically study lymphedema treatment, in particular, in large, population-based cohorts is critical since lymphedema is a life-long, chronic disease with significant treatment costs, which are often out-of-pocket expenses [23]. Overall, there is a lack of high-quality studies evaluating access to and utilization of lymphedema treatment, as well as comparative effectiveness and cost-effectiveness of various lymphedema treatment modalities [42–44].

The algorithm development process illustrates several issues with respect to the use of Medicare claims to identify incident lymphedema cases. First, our gold standard for lymphedema was strictly defined by a patient's recall of being told by her doctor that she had lymphedema or arm edema since undergoing breast cancer surgery. Review of medical records for documentation of lymphedema was not performed. In addition, by using this strict definition, we acknowledge that our algorithm may not capture women who have mild symptoms of lymphedema and/or do not report their symptoms to their physician. Our algorithm focuses on women with likely more severe, clinically important cases of lymphedema. Second, despite exhaustive attempts to maximize the algorithm sensitivity, we were unable to achieve a sensitivity greater than 70%, which may be partially due to undercoding of lymphedema claims. Therefore, milder cases of lymphedema are likely not captured by this algorithm and incidence rates of lymphedema determined by this algorithm would need to be inflated by approximately 30% to more closely represent true incidence rates.

In an attempt to maximize the positive predictive value of the algorithm, we accepted this moderate sensitivity of 70%. There are limitations to using this algorithm if the prevalence of lymphedema is low [39]. However, based on the recently published meta-analysis of studies from 2000–2012, lymphedema rates are greater than 15% at a certain time point postoperatively even in this era of SLNB [24]. At these incidence rates (Figure 2), the PPV of the algorithm is 75% or higher. Finally, optimal development of the multi-step algorithm may have been affected by the lack of Medicare coverage for essentially all of the HCPCS durable medical equipment codes that were evaluated. Of the 28 codes examined, only 2 were identified with a near-zero prevalence (Table 2); therefore, no HCPCS codes could be evaluated for inclusion during algorithm development. However, as previously discussed, since the simple algorithm does not include codes related to lymphedema treatment, this simple algorithm allows studies focusing on various aspects of lymphedema treatment to be performed.

Despite these limitations, to our knowledge, this is the first claims-based, validated algorithm that identifies incident cases of lymphedema after breast cancer surgery. Face validity of this algorithm is demonstrated in Table 4, which shows that algorithm-identified cases of lymphedema, compared to self-reported cases of lymphedema, are similar with respects to predictors of lymphedema. To assess its generalizability, the algorithm should be

further validated in other large, population-based breast cancer cohorts, including younger women and more contemporary cohorts. Results must be interpreted with the knowledge of the algorithm's performance.

Potential uses of this algorithm include subsequent studies of lymphedema in large administrative databases to further refine studies in several key areas, including changes in incidence rates, risk factors, and prevention measures. Furthermore, as already mentioned, since this algorithm does not include lymphedema treatment codes, studies on treatment options and cost/economic analyses of the burden and treatment of lymphedema options could be explored. By identifying patients with clinically apparent lymphedema after breast cancer treatment by a standard, claims-based definition, this validated algorithm will facilitate the conduct of large, population-based studies of lymphedema in a uniform fashion. The results of these studies will be critical to advancing our understanding and management of this challenging and debilitating chronic disease that is feared by all breast cancer survivors.

Acknowledgments

This research was supported by a career development award and supplement to Dr. Yen from the National Cancer Institute (K07CA125586, K07CA125586-03S1) and two research grants from the National Cancer Institute to Dr. Nattinger (R01CA81379, R01CA127648). The content does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

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Figure 1.

Study diagram. Between 2005 through 2006, a cohort of 8,742 women aged 65 years or older were initially identified as potentially eligible, based on Medicare claims, for a breast cancer study. A total of 5,659 were excluded, either due to ineligibility (n=2,995) or non-participation (n=2,664). A total of 3,083 women completed the baseline/initial survey wave and participation rates remained over 90% for the three follow-up survey waves. The cohort for this study comprises the 2,597 women who completed at least Wave 2 of the survey and had available claims information, generating a total of 6,754 observations for waves 2–4. These observations were randomly sampled and half were placed in the training cohort (3,356 observations; 2,077 patients) and half in the validation cohort (3,398 observations; 2,119 patients).

Figure 2.

Performance of two algorithms. This figure displays the positive and negative predictive value (PPV and NPV) curves in the validation cohort for the multi-step (dashed lines) and simple, 2-code (solid lines) lymphedema algorithms. The x-axis represents the prevalence of lymphedema; the y-axis represents the predictive value. The blue lines represent the PPV curves; the black lines represent the NPV curves.

Table 1

Claims-based definitions of lymphedema in the literature

Study Year	Data source	Codes used to identify lymphedema claims
Shih YC. 2009 [23]	MedStat MarketScan Health and Productivity Management database	ICD-9 457.0 and 457.1
Kwan ML. 2010 [30]	Kaiser Permanente Northern California electronic medical records	ICD-9 457.0 and 457.1 CPT 97140 and 97139 Durable medical equipment (DME) orders associated with breast cancer-related lymphedema
Reiner AS. 2011[29]	Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database	ICD-9 457.0 and 457.1 Any claims for treatment prescribed for secondary lymphedema (36 CPT and HCPCS codes; see Table 1 of study)

Table 2

Diagnostic, procedural and durable medical equipment codes potentially indicating lymphedema in the training cohort

Code	Outcome variable definition	Medicare coverage ^d	Prev (%)	SN (%)	SP (%)
Diagnostic Codes (ICD-9) - 2008					
457.0	Postmastectomy lymphedema syndrome		3.8	34	98
457.1	Other lymphedema, including acquired (chronic) and secondary		7.9	60	96
457.2	<i>Lymphangitis (chronic, subacute, NOS)</i>		0.2	<1	99
459.1	Post-phlebotic syndrome (chronic venous HTN due to DVT)		0.2	0	99
<u>459.2</u>	<u>Compression of vein, includes vena cava syndrome</u>		0.8	3	99
<u>459.3</u>	<u>Chronic venous HTN (idiopathic)</u>		0.1	0	99
<u>611.0</u>	<u>Inflammatory disease of the breast, includes mastitis</u>		7.3	14	93
682.3	<i>Diffuse cellulitis, acute abscess, acute lymphangitis (upper arm and forearm, axilla, shoulder)</i>		3.2	11	97
682.4	<i>Diffuse cellulitis, acute abscess, acute lymphangitis (hand, wrist)</i>		1.3	2	99
729.81	Swelling of limb (arm, hand)		15.7	35	86
782.3	Edema (anasarca, dropsy, localized edema NOS)		21.9	26	78
782.8	Changes in skin texture (induration/thickening)		0.6	1.2	99
782.9	Other symptoms involving skin and integumentary tissues		0.6	0.8	99
Procedural, Treatment and Durable Medical Equipment Codes					
CPT					
Physical Medicine and Rehabilitation Codes - 2008					
97001	Physical therapy evaluation		42.0	66	60
97002	Physical therapy re-evaluation		7.4	15	93
97003	Occupational therapy evaluation		9.1	34	93
97004	Occupational therapy re-evaluation		0.7	4	99
97016	Vasopneumatic devices		1.0	6	99
97124	Massage, including effleurage, petrissage and/or tapotement		5.7	10	95
97140	Manual therapy techniques, including manual lymphatic drainage		30.6	75	73
HCPCS					
2008					
A6448	Light compression bandage, elastic (width < 3 inches); start 1/1/04	C	NF		
A6449	Light compression bandage, elastic (width < 3 and >= 5 inches); start 1/1/04	C	<0.1	0	100
A6450	Light compression bandage, elastic (width >=5 inches); start 1/1/04	C	NF		

Code	Outcome variable definition	Medicare coverage ^a	Prev (%)	SN (%)	SP (%)
A6451	Moderate compression bandage, elastic; start 1/1/04	C	NF		
A6452	High compression bandage, elastic; start 1/1/04	C	0	0	100
A6542	Gradient compression stocking, custom made; start 1/1/06 (DELETED January 1, 2010)	M	NF		
A6543	Gradient compression stocking, lymphedema; start 1/1/06 (DELETED January 1, 2010)	M	NF		
A6549	Gradient compression stocking, not otherwise specified; start 1/1/06 (Code changed 1/1/2010)	M	NF		
E0651	Pneumatic compressor; segmental home model without calibrated gradient pressure; start 1/1/88	D	NF		
E0652	Pneumatic compressor; segmental home model with calibrated gradient pressure; start 1/1/88	D	NF		
E0655	Pneumatic appliance; half arm; start 1/1/86	D	NF		
E0665	Pneumatic appliance; full arm; start 1/1/86	D	NF		
E0668	Segmental pneumatic appliance for use with pneumatic compressor; full arm; start 1/1/88	D	NF		
E0672	Pressure pneumatic appliance; full arm; start 1/1/95	D	NF		
E0676	Intermittent limb compression device (includes all accessories), NOS; start 1/1/07	D	NF		
L8010	Mastectomy sleeve; start 1/1/86	D	0.1	0.8	100
L8210	Gradient compression stocking, custom made; start 1/1/86 (DELETED January 1, 2006)	M	NF		
L8220	Gradient compression stocking, lymphedema; start 1/1/86 (DELETED January 1, 2006)	M	0	0	100
L8239	Gradient compression stocking, NOS; start 1/1/98 (DELETED January 1, 2006)	C	NF		
S8420	Gradient pressure aid (sleeve and glove combination), custom made; start 1/1/02	I	NF		
S8421	Gradient pressure aid (sleeve and glove combination), ready made; start 1/1/02	I	NF		
S8422	Gradient pressure sleeve, custom, medium; start 1/1/02	I	NF		
S8423	Gradient pressure sleeve, custom, heavy; start 1/1/02	I	NF		
S8424	Gradient pressure aid (sleeve), ready made; start 1/1/02	I	NF		
S8427	Gradient pressure aid (glove), ready made; start 1/1/02	I	NF		
S8428	Gradient pressure aid (gauntlet), ready made; start 1/1/02	I	NF		
S8431	Compression bandage, roll; start 1/1/02	I	NF		
S8950	Complex lymphedema therapy; start 1/1/00	I	NF		

Abbreviations: NF, code not found; NOS, not otherwise specified; Prev, prevalence; SN, sensitivity; SP, specificity HCPCS codes list start and, if applicable, stop dates.

^a Medicare coverage status for HCPCS codes[34, 35][34, 35][34, 35][34, 35]^{34,35}; C, carrier judgment; D, special coverage instructions apply; I, not payable by Medicare (no grace period); M, non-covered by Medicare

Table 3
Comparison of sensitivity, specificity and AUC of two lymphedema algorithms in training and validation cohorts

	2-code algorithm (ICD 457.0 or 457.1)			Multi-step algorithm		
	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
Training cohort	71.2% (65.5% – 76.9%)	95.3% (94.6% – 96.1%)	0.83 (0.80 – 0.86)	71.2% (65.5% – 76.9%)	95.8% (95.0% – 96.5%)	0.83 (0.81 – 0.86)
Validation cohort	69.4% (63.9% – 75.0%)	95.7% (95.0% – 96.4%)	0.82 (0.80 – 0.85)	69.4% (63.9% – 75.0%)	96.0% (95.3% – 96.7%)	0.83 (0.80 – 0.86)

Abbreviations: CI, confidence interval; AUC area under receiver operating characteristic curve

Table 4

Comparison of predictors of lymphedema when defined as self-report versus the simple 2-code algorithm

Variable	Category (n)	Lymphedema defined by self-report ^a				Lymphedema defined by two-code algorithm ^a			
		OR	95% CI	P Values		OR	95% CI	P Values	
No. lymph nodes examined	None (182)	1.00		<0.0001		1.00		<0.0001	
	1 – 5 (506)	1.51	0.61 – 3.75			1.92	0.68 – 5.48		
	6 – 10 (201)	3.96	1.54 – 10.20			5.01	1.68 – 14.97		
	11 – 15 (151)	3.76	1.39 – 10.12			6.74	2.17 – 20.94		
	16 (108)	7.92	2.92 – 21.49			10.87	3.47 – 34.11		
Lymph node metastasis	No (946)	1.00		0.0055		1.00		0.11	
	Yes (202)	2.00	1.23 – 3.27			1.59	0.90 – 2.80		
Type of breast cancer	Invasive (886)	1.00		0.26		1.00		0.79	
	DCIS (182)	0.70	0.30 – 1.59			1.20	0.48 – 2.94		
	Unknown (80)	0.55	0.25 – 1.21			0.80	0.35 – 1.85		
Tumor size (mm)	0 – 20 (838)	1.00		0.92		1.00		0.28	
	21 – 50 (195)	1.10	0.69 – 1.76			0.91	0.52 – 1.59		
	> 50 (45)	1.27	0.55 – 2.92			1.16	0.46 – 2.92		
	Unknown (70)	1.18	0.51 – 2.72			2.17	0.94 – 5.00		
Type of breast surgery	BCS (752)	1.00		0.26		1.00		0.44	
	Mastectomy (396)	1.40	0.78 – 2.53			1.30	0.67 – 2.53		
Receipt of radiation therapy	No (383)	1.00		0.70		1.00		0.17	
	Yes (765)	1.12	0.63 – 1.99			1.58	0.82 – 3.03		

Variable	Category (n)	Lymphedema defined by self-report ^a				Lymphedema defined by two-code algorithm ^a			
		OR	95% CI	P Values		OR	95% CI	P Values	
Receipt of chemotherapy	No (940)	1.00				1.00			
	Yes (208)	0.73	0.43 – 1.24	0.24		1.05	0.58 – 1.91	0.86	
Receipt of hormonal therapy	No (352)	1.00				1.00			
	Yes (796)	0.88	0.58 – 1.32	0.53		0.83	0.52 – 1.32	0.42	
Patient age (years)	65 – 74 (747)	1.00				1.00			
	75 – 84 (363)	0.71	0.47 – 1.06	0.21		0.88	0.55 – 1.39		
	85 – 89 (38)	0.68	0.22 – 2.04			0.87	0.25 – 3.06	0.84	
Annual surgeon case volume of Medicare operations	< 6 (304)	1.00				1.00			
	6 – 12 (350)	0.91	0.58 – 1.44	0.91		1.03	0.60 – 1.77		
	> 12 (444)	0.92	0.59 – 1.43			1.24	0.74 – 2.08		
	Unknown (50)	0.72	0.27 – 1.89			0.68	0.22 – 2.17	0.65	

Abbreviations: ALND, axillary lymph node dissection; BCS, breast-conserving surgery; CI, confidence interval; DCIS, ductal carcinoma in situ; OR, odds ratio; SLNB, sentinel lymph node biopsy

^aThe self-reported prevalence of lymphedema was 14%; the simplified algorithm prevalence rate was slightly lower at 10%.