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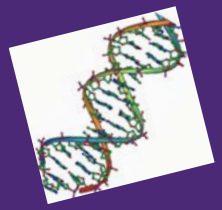
LATENT CLASS ANALYSIS OF LYMPHEDEMA SYMPTOMS AND PHENOTYPIC CHARACTERIZATION

Mei R. Fu, PhD, RN, FAAN
Associate Professor with Tenure



Research Team

Mei R. Fu, PhD, RN, FAAN [a]; Bradley E Aouizerat, MS, PhD;[b] Gary Yu, Dr.PH[a], Yvette Conley, PhD, FAAN;[c] Deborah Axelrod, MD, FACS [d,e]; Amber A. Guth, MD, FACS [d,e]; Karen Hiotis, MD;[d,e] Joan Scagliola, MSN, RN[e]; Jean-Pierre Gagner, MD, PhD[f]; Janet H. Van Cleave, PhD, RN, AOCNP;[a] David Zagzag, MD., PhD[f]

From: [a]Rory Meyers College of Nursing, New York University

[b]Bluestone Center for Clinical Research, Department of Oral and Maxillofacial Surgery, College of Dentistry, New York University

[c]School of Nursing, University of Pittsburgh, Pittsburgh, PA

[d]Department of Surgery, New York University School of Medicine

[5]NYU Clinical Cancer Center

[e]Pathology and Neurosurgery, Division of Neuropathology, Microvascular and Molecular Neuro-Oncology Laboratory, NYU Langone Medical Center

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Learning Objectives

- The learner will be able to obtain knowledge about the complex cancer-related symptoms and phenotypic characterization.

- The learner will be able to obtain knowledge about latent class analysis for identifying symptom classes.

What is LYMPHEDEMA ?

- **Accumulation of lymph fluid in the interstitial spaces of the affected limb and areas**
- **Abnormality of or injuries to the lymphatic system**

"With breast cancer, you go in for your treatment, once cancer is under control you are kind of done with it. With lymphedema, you will never be done with it because you are having this big arm, pain, burning, heaviness, and soreness every day. It's something that you have to live with for the rest of your life."

Mr. S, 7 years of lymphedema

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Fu, R.M. (2014). Breast cancer-related lymphedema: Symptoms, diagnosis, risk reduction, and management. *World Journal of Clinical Oncology*, 10;5(3):241-7. doi: 10.5306/wjco.v5.i3.241. PMID: 25114841

Lymphedema Symptoms

Cancer Related Symptoms:

- ***Subjective phenomenon***
- ***Indicates abnormal changes in body functioning or side effects from cancer treatment.***

Fu, M.R. & Rosedale, M. (2009). Breast cancer survivors' experience of lymphedema related symptoms. *Journal of Pain and Symptom Management*, *38*(6), 849-859. PMID: 19819668

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Breast Cancer &Lymphedema Symptom Experience Index

The following questions are about your experiences with movement on your affected body side today or in the past three month. The word "affected" means the same body side(s) on which you received breast surgery or radiation.

On which body side was your cancer treated?
☐Right ☐Left ☐Both

Do you have limited movement of your affected___?	**How Severe?**				
	No 0	A little 1	Somewhat 2	Quite a bit 3	Very Severe 4
1. shoulder					
2. elbow					
3. wrist					
4. fingers					

The following questions are about symptoms in your affected arm, hand, breast, axilla (under arm), or chest today or in the past three month.

	How Severe?				
Have you had ___?	No 0	A little 1	Somewhat 2	Quite a bit 3	Very Severe 4
5. swelling					
6. breast swelling					
7. chest wall swelling					
8. firmness					
9. tightness					
10. heaviness					
11. toughness or thickness of skin					
12. stiffness					
13. tenderness					
14. hotness/increased temperature					
15. redness					
16. blistering					
17. pain					
18. numbness					
19. burning					
20. stabbing					
21. tingling					
22. arm or hand fatigue					
23. arm or hand weakness					
24. pocket of fluid develop					

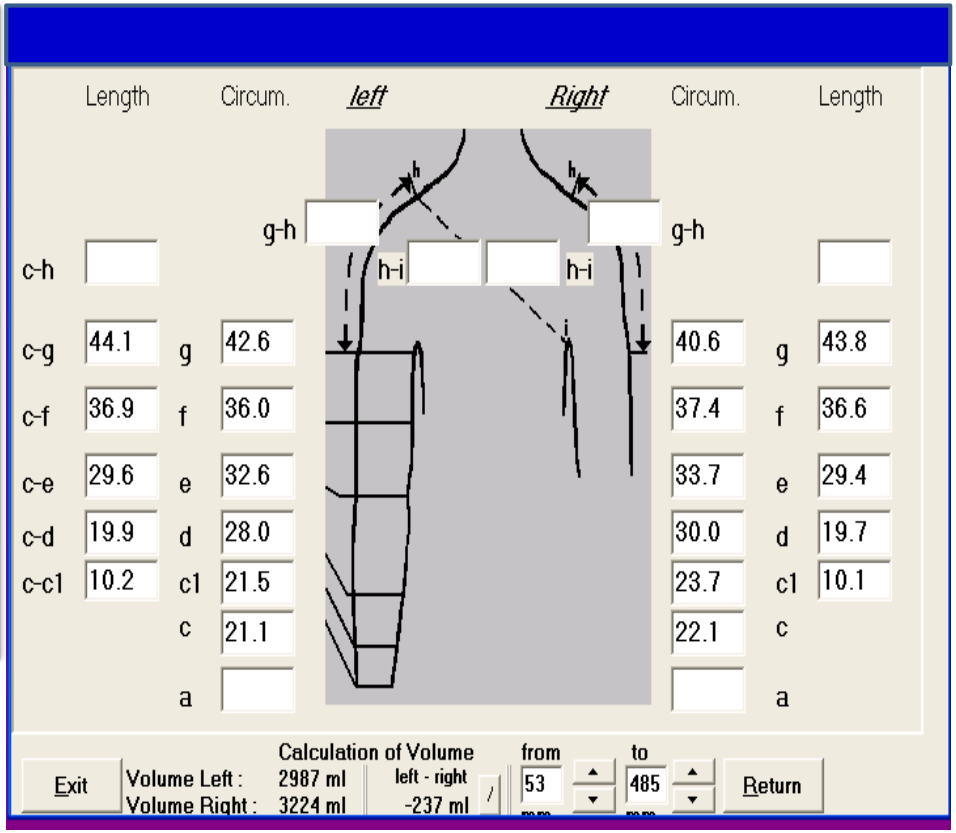
Purpose of the Study

To determine whether latent class analysis (LCA) would aid in the identification of lymphedema symptom patterns and associations with phenotypic characterization of demographics and clinical factors, physiological outcomes of limb volume and lymph fluid level, and patient-centered outcomes of daily function, social, and affective wellbeing.

Methods

- A prospective, descriptive and repeated-measure design
- 140 women at pre-surgery and followed at 4-8 weeks and 12 months post-surgery
- Lymphedema symptoms and patient-centered outcomes of daily function, social, and affective wellbeing were evaluated using a reliable and valid instrument: *The Lymphedema and Breast Cancer Symptom Experience Index (BCLE-SEI)*

Limb Volume
Infra-Red Perometer Measurement



Fu, M.R., Axelrod, D., Guth, A., Cartwright- Alcarese, F.,Qiu, Z., Goldberg, J., Kim, J., Scagliola, J., Kleinman, R., Haber, J., & (2014). Proactive approach to lymphedema risk reduction: a prospective study. *Annals of Surgical Oncology*, *21*(11), 3481-3498. Online First. DOI: 10.1245/s10434-014-3761-z

Lymph Fluid Level
BIOIMPEDANCE ANALYSIS

The Imp XCA, a FDA approved device, uses a single frequency below 30 kHz to measure impedance and resistance of extracellular fluid.

Fu, M.R., Cleland, C.M., Guth, A.A., Kayal, M., Haber, J., Cartwright- Alcarese, F., Kleinman, R., Kang, Y., Scagliola, J., & Axelrod, D. (2013). L-Dex Ratio in Detecting Breast Cancer-Related Lymphedema: Reliability, Sensitivity, and Specificity. *Lymphology*, *46*(2)85-96.

Data Analysis

- ✓ Latent class analysis (LCA) was used to identify classes of lymphedema symptoms
- ✓ Logistic regressions were used to explore the association of latent class of lymphedema symptoms with categorical demographic and clinical variables.
- ✓ ANOVAs and post-hoc pairwise comparison test with a Bonferroni correction for multiple comparisons at the 5% alpha level

Latent class analysis model: Prevalence and lymphedema symptom counts within each class at 12-month post-surgery				
Symptoms	**Average N=140**	**Low Symptom Class n=55 (39%)**	**Moderate Symptom Class n=62 (44%)**	**Severe Symptom Class n=23 (16%)**
Limited Limb Mobility [a]				
Limited Shoulder Movement	30%	6%	38%	60%
Limited Elbow Movement	6%	0%	6%	17%
Limited Wrist Movement	7%	2%	2%	34%
Limited Arm Movement	28%	0%	33%	75%
Arm Firmness	16%	0%	17%	48%
Arm Tightness	44%	12%	58%	75%
Toughness or thickness of skin	10%	2%	5%	43%
Arm Stiffness	35%	4%	44%	76%
Arm Hotness	8%	0%	0%	47%
Fluid Accumulation [a]				
Limited Fingers	7%	2%	3%	30%
Hand Swelling	16%	5%	10%	54%
Arm Swelling	23%	2%	19%	77%
Breast Swelling	30%	12%	38%	49%
Chest Wall Swelling	16%	2%	17%	42%
Numbness	43%	29%	44%	72%
Burning	10%	2%	7%	33%
Arm Heaviness	34%	0%	44%	80%
Pain/Discomfort [a]				
Tenderness	38%	2%	47%	92%
Blister	2%	0%	0%	9%
Pain, aching, or soreness	44%	12%	51%	96%
Stabbing	10%	0%	6%	38%
Tingling	38%	28%	36%	66%
Fatigue	22%	0%	27%	56%
Arm Weakness	29%	4%	32%	77%
Seroma, pocket of fluid	10%	0%	7%	40%
Redness	4%	0%	3%	17%
Symptom Count	5.460	1.162	5.948	14.013

Association between the Symptom Classes at 12-Month Follow-Up and L-Dex				
Median (IQR)	Low Risk	Moderate Risk	High Risk	P-value
L-DEX Pre-Surgery	-1.10 (-3.50 - 3.00)	0.35 (-3.00 – 3.20)	-0.50* (-4.20 – 2.30)	0.639
L-DEX Post-Surgery	-0.40 (-3.50 – 1.80)	1.15 (-2.20 – 5.70)	4.70* (0.60 – 7.80)	0.003; A < C
L-DEX Follow-Up	-1.00 (-4.80 – 1.90)	0.15 (-2.90 – 3.20)	4.40* (-0.40 -17.40)	0.001; A, B < C
A (Low), B (Moderate), C (Severe) symptom class pairwise differences between the three classes with a Bonferroni correction at the 5% alpha level. *p < 0.05 - Repeated measures ANOVA over the three time points				

Association between the Symptom Classes at 12-Month Post-Surgery and Lymph Volume (LV) % Change				
Median (IQR)	Low Risk	Moderate Risk	High Risk	P-value
LV Pre-Surgery	-1% (-3% –2%)	0% (-2% – 2%)	-1%*** (-5% – 2%)	0.162
LV Post-Surgery	0% (-3% – 3%)	1% (-2% – 4%)	3%*** (-2% –7%)	0.064
LV Follow-Up	-1% (-3% – 3%)	1% (-2% – 5%)	6%*** (-1% – 9%)	0.001; A < C
A (Low), B (Moderate), C (Severe) symptom class pairwise differences between the three classes with a Bonferroni correction at the 5% alpha level. *p < 0.05, ** p < 0.01, *** p < 0.001 – Repeated measures ANOVA over the three time points				

Association between Symptom Distress Subscales and the Symptom Classes at 12-Month Post-Surgery

Median (IQR) Symptom Distress	Low Symptom Class	Moderate Symptom Class	Severe Symptom Class	P-value	
Impaired Daily Living	0.00 (0.00 – 0.00)	0.00 (0.00 – 2.00)	8.00 (2.00 – 13.00)	0.0001; A < B < C	
Social Distress	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	1.00 (0.00 - 3.00)	0.0001; A, B < C	
Emotional Distress	0.00 (0.00 – 0.00	1.00 (0.00 – 4.00)	11.00 (4.00 – 12.00)	0.0001; A < B < C	
Impaired Self-Perception	0.00 (0.00 – 0.00)	1.00 (0.00 – 1.00)	2.00 (1.00 – 2.00)	0.0001; A < B < C	
Sleep Disturbance	0.00 (0.00 – 0.00)	0.00 (0.00 – 1.00)	2.00 (0.00 – 3.00)	0.0001; A < B < C	
Impaired Sexuality	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	1.00 (0.00 – 2.00)	0.0001; A, B < C	
Work Outside Home	0.00 (0.00 – 0.00)	0.00 (0.00 – 1.00)	1.50 (0.00 – 2.00)	0.0001; A < B < C	
Days Absent from Work	0.00 (0.00 – 0.00)	0.00 (0.00 – 16.00)	3.50 (0.00 – 21.00)	0.0001; A < B, C	

A (Low), B (Moderate), C (Severe) symptom class pairwise differences between the three classes with a Bonferroni correction at the 5% alpha level.

Conclusions

- T Latent class analysis is able to identify three distinct lymphedema symptom classes with lower, moderate and severe symptom class.
- Identification of symptom classes is a priori for the prediction of clinically elevated high-risk populations for physiologic outcomes of limb volume and lymph fluid level as well as patient-centered outcomes of daily function, social and affective wellbeing.