Latent Class/Profile Analysis on Symptom Clusters in Pediatric Studies

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Abstract

Studying symptoms in child patients is important. "Symptom cluster" usually refers to either a group of symptoms that occur simultaneously or a group of individual patients sharing similar symptoms. This presentation discusses how to use latent profile analysis (LPA) to classify patients into different latent profile/groups with respect to a set of symptom measures of interest. Four PROMIS symptoms measures (depression, anxiety, pain, and fatigue) in child patients with cancer were used for demonstration. Distinctive latent profiles/groups of patients that were unknown a priori were identified. Patients are similar within profile, but differ cross profiles with respect to the levels of the PROMIS symptom measures. Change in latent profile membership over time was further examined using latent transition analysis (LTA).

Introduction

- Patients with cancer, particularly those undergoing chemotherapy, experience multiple co-occurring, interrelated symptoms.

- It is important to study both individual symptoms and symptom clusters.

- The terminology of symptom clusters has different meanings:

  -- a group of symptoms that are associated with simultaneous occurrence → "**variable centered**" approach.

  -- a group of individual patients sharing similar symptoms → "**person centered**" approach.

Variable-centered approaches

- Symptom clusters are clinically determined before empirical studies based on co-occurrence of related symptoms.

- When symptom clusters are not pre-determined, data-reduction methods can be used to reduce a large number of observed variables (items) to a small number of underlying latent variables.

  -- Exploratory factor analysis (EFA)

  -- Principal component analysis (PCA)

  -- Confirmatory factor analysis (CFA)

Person-centered approaches

Clustering individual patients, instead of symptoms, into distinctive groups with similar patterns of symptoms.

- Traditional clustering approaches

  -- Use ad hoc dissimilarity measures, such as Euclidean distance, for clustering
  -- No model fit test
  -- Require standardization of the observed variables before modeling

- Mixture modeling
  -- Latent class analysis (LCA) (categorical measures)
  -- Latent profile analysis (LPA) (continuous measures)
  -- Latent transition analysis (LTA) (longitudinal data)
  -- Growth mixture modeling (GMM) (longitudinal data)

Advantages of mixture modeling

- Rather than ad hoc measures, such as Euclidean distance, latent classes/profiles are identified in mixture modeling based on posterior membership probabilities.

- The optimal number of classes/profiles are determined based on formal statistical procedures (e.g., model fit statistical tests), thus the choice of the cluster criterion is less arbitrary.

- Can be readily extended to longitudinal data analysis forming a latent transition analysis (LTA)

- All different types of observed variables, such as continuous, dichotomous, ordered categorical (ordinal), unordered categorical (nominal), censored, counts, or combinations of these variable can be used for mixture modeling.

Demonstration of LPA Application

- To investigate the symptom patterns in children undergoing cancer chemotherapy and change of the patterns over time using the Patient Reported Outcomes Measurement Information System (PROMIS) measures.

- Four PROMIS symptom measures (anxiety, depression, pain, and fatigue)

  -- Each of the first three scales has 8 items, while fatigue has 10 items
  -- IRT scores were generated for each scale and used for further analysis.

- A total of 98 patients 8-to-18 years undergoing cancer chemotherapy recruited from two settings (Children's National Health System in Washington, D.C., and the Center for Cancer and Blood Disorders of Northern Virginia).

- PROMIS assessments at 3 time points: T_1 - the start of a cycle of chemotherapy; T_2 - mid-way through the cycle; and T_3 - after blood cell count recovery following the cycle of chemotherapy.

Statistical Analysis

- LPA was conducted to explore potential latent classes/profiles of patients with respect to the four symptom measures at T_1, T_2, and T_3, respectively.

- LPA was extended to the longitudinal data, forming a LTA model to identify latent profiles of patients simultaneously for each time point; and assess whether and how the latent profile status change over time.

- The latent profile membership and the latent transitions estimated from the final LTA model were saved as categorical outcome measures for further analysis.

- External validity of the LPA solution was assessed by testing the association between the latent profile membership and the PROMIS function measures (i.e., mobility, upper extremity, and peer relationship).

- A baseline single-item legacy fatigue measure was used to predict the transitions of profile status over time, controlling for covariates.

Results

- Two latent profiles were identified at each time point (see Figure 1).

    -- Profile 1: "Less Severe Symptoms" profile

    -- Profile 2: "Severe Symptoms" profile

    -- For both Profiles 1 and 2, the mean values of the symptom scores at T_2 were not significantly different from those at T_1.

    -- The mean values of the symptom scores in each profile at T_3 were statistically different from those at T_1.
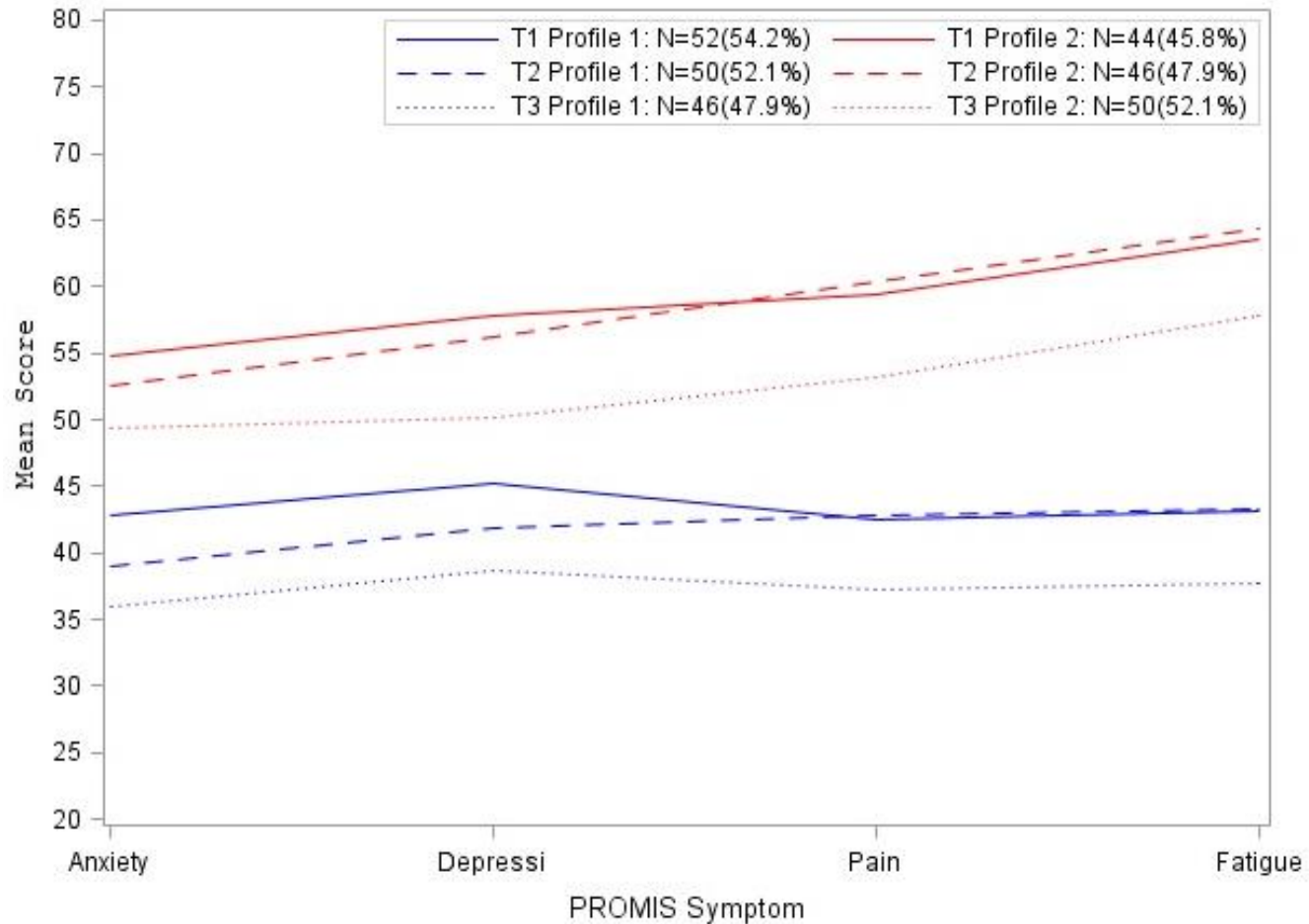
Figure 1. Latent Profiles of PROMIS Symptom Measures by Time.
Note. Higher scores indicate more of the measured symptom being experienced

Prevalence of the patients with severe symptoms over time

- The percentage of patients in Profile 2 at different time points:

  T_1: 44.8%
  T_2: 47.9%
  T_3: 52.1%

- To make comparisons meaningful, latent profiles were estimated from the restricted LTA model where equality restrictions were imposed on the levels and variations of symptom measures in each profile over time.

- If we classify patients into profiles based on the same standard, the percentage of patients in Profile 2 (: "Severe Symptoms" profile) become (see Figure 2):

  T_1: 44.8%
  T_2: 46.9%
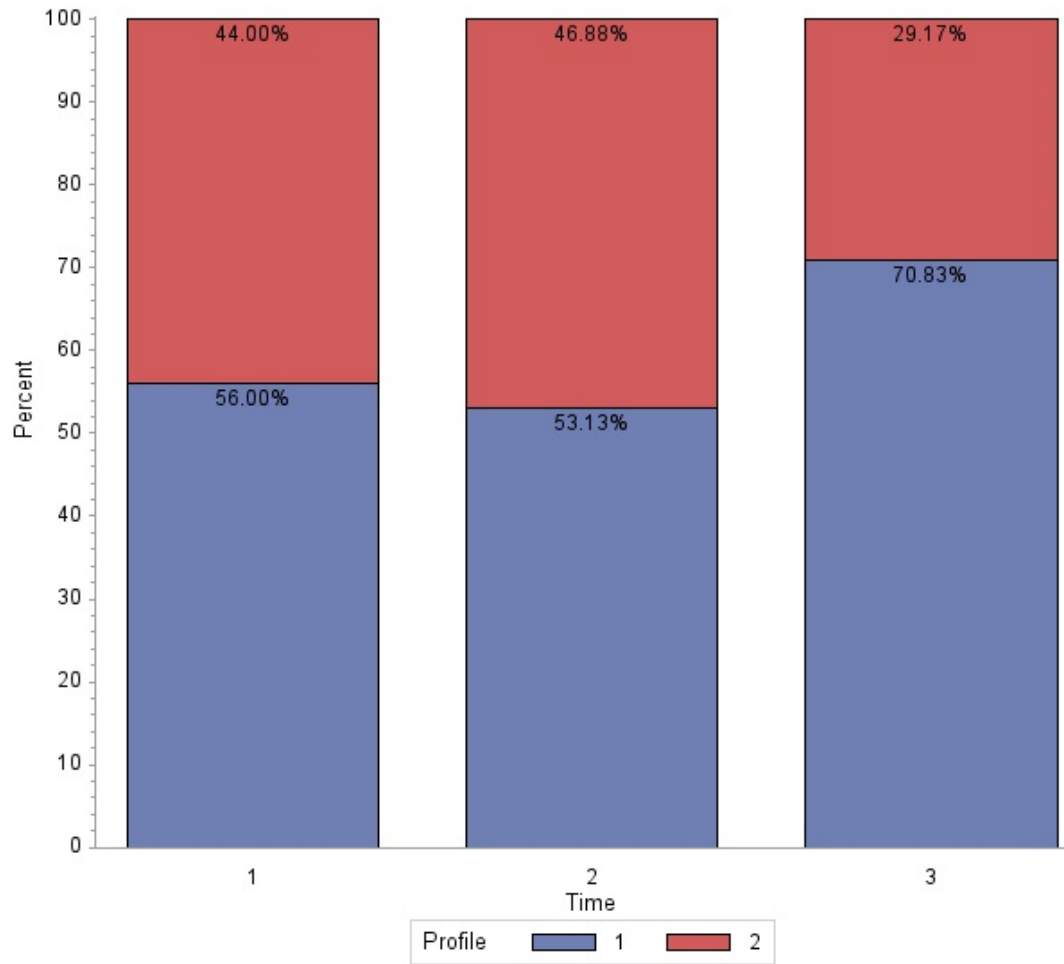 T_3: 29.17%

Figure 2. Latent profiles by time estimated from the restricted LTA model

External validity of the estimated latent symptom profiles

- Test associations between the PROMIS function measures (mobility, upper extremity, peer relationship) and the latent profile membership.

  -- All the function scores were significantly lower on average among patients in Profile 2 than in Profile 1 at all the time points (Lower function scores indicate worse health status) (see Table 1).

Table 1. Associations between the PROMIS function measures and the latent profile membership by time point[#]

Score	Profile 1 Mean (SD)	Profile 2 Mean (SD)	P-value
Time 1 (N=96)	(N=52)	(N=44)	
Peer Relationships	52.40 (10.16)	45.34 (10.16)	0.001
Upper Extremity	49.79 (8.41)	42.76 (8.42)	<0.001
Mobility	44.76 (8.21)	37.42 (8.42)	<0.001
Time 2 (N=84)	(N=47)	(N=37)	
Peer Relationships	51.36 (9.93)	44.84 (8.71)	0.002
Upper Extremity	48.16 (9.47)	40.43 (10.20)	<0.001
Mobility	43.26 (8.58)	35.74 (8.97)	<0.001
Time 3 (N=86)	(N=66)	(N=20)	
Peer Relationships	45.91 (9.92)	35.56 (6.57)	<0.001
Upper Extremity	49.65 (9.38)	40.57 (8.87)	<0.001
Mobility	45.91 (9.92)	35.56 (6.57)	<0.001

Note.
[#]: Latent profile size varies due to missing values in the function measures.

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Selected findings from Latent transition analysis

- Given two latent profiles detected at each time point, there is a total of eight possible latent transitions from $T_1 \rightarrow T_2 \rightarrow T_3$.

- The most likely transition patterns in the sample were L-L [44 (45.8%)] and H-H [24 (25.0%)].

- Patients with a score of the baseline single-item legacy fatigue measure ≥3 were significantly less likely (OR=0.05, 95% C.I.: 0.01, 0.19) to experience the L-L transition, but much more likely to experience H-H transition (OR=9.25, 95% C.I.: 2.49, 34.38), controlling for socio-demographics.

Discussion

- This is the first longitudinal study to examine symptom clusters in children undergoing cancer chemotherapy using mixture modeling.

- Children with cancer can be classified into two latent profiles with respect to the PROMIS symptom measures: less severe vs. severe symptom profiles.

- Close to half of the patients (44.8%) were classified into the Severe Symptom Profile at the start of a cycle of therapy, and the profile prevalence remained stable (46.9%) mid-way through the cycle, indicating that heath did not get worse after therapy.

- The prevalence of Profile 2 significantly declined (29.17%) T_3 (after blood cell count recovery following the cycle of chemotherapy), indicating an improvement of health status after therapy, and the improvement occurred basically after T_2.

- The function scores (e.g., mobility, upper extremity, and peer relationship) were significantly lower on average in the "Severe Symptoms" profile (i.e., Profile 2) at each specific time, indicating good external validity for the latent profiles.

- Patient's profile status changed over time. From T_1 to T_3, the most likely transition patterns in the sample were L-L [44 (45.8%)] and H-H [24 (25.0%)].

- The baseline single-item legacy fatigue measure can be used as a "biomarker" to predict symptom change/transition over time: Patients with a score of ≥ 3 at baseline were less likely to experience the L-L transition, but much more likely to experience H-H transition.

- LTA is a useful technique not only for symptom studies but also for many other outcome measures that can be continuous, categorical, dichotomous, censored, counts, or combinations of these variable.

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