Latent Class Analysis for Asthma Patient Outcome Measures

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Abstract
Asthma Disease Activity Score, a newly derived composite score, has been developed to capture multiple aspects of asthma outcome measures. A disease severity indicated by this composite score is used to predict future asthma attack. However, composite measures are not without the usual assumptions and associated limitations. Latent class analysis (LCA) is a multivariate approach to classify individuals based on their responses to a set of observable categorical variables into a set of mutually exclusive latent classes. Unlike other statistical methods, LCA makes no assumptions about distributions of the indicators. Thus, it serves an alternative way to assess asthma disease severity based on multiple asthma outcome measures. This paper will apply the LCA method to patient outcome measures and compare the composite score method with the latent class model through an examination of data from clinical trials.

Key Words: Latent Class Analysis, Asthma Disease Activity Scores, Asthma Attack, Multivariate Analysis, Patient Outcome Measures

1. Introduction

Patient outcome measures have been commonly used in the asthma clinical trials to capture aspects of disease severity from patients. Single measures such as FEV1 and the daytime symptom score are the common endpoints used in the asthma trials. The composite measures including the Asthma Control Test (ACT) score and newly derived Asthma Disease Activity Score (ADAS) are capturing the multiple aspects of asthma disease severity. The composite measures get more attention in recent years as they provide more reliable prediction in the occurrence of asthma attack.

The ADAS scores were derived based on a sequential statistical analysis of clinical trial data, beginning with factor analysis or principal component analysis, development of classification rules to characterize high and low disease activity, and discriminant analysis to develop a continuous measure of disease activity. The multi-normal distributions among all outcome measures have to be assumed in constructing such composite scores.

The Latent Class Model (LCM) has been applied in the clinical trials to assess the degree of temperament, depression, and disease severity which cannot be directly observed but inferred from the observed measures. It is a statistical method used to identify a set of discrete, mutually exclusive latent classes of individuals based on their responses to a set of observed categorical variables. The latent class model has the advantages of making no assumptions about the distributions of the categorical observed variables.

The purpose of this paper is to apply the Latent Class Analysis (LCA) [1, 2] as an alternative approach to the newly derived ADAS composite score to assess asthma disease severity. The classifications of the asthma disease severity from the two methods are compared in terms of discriminant validity and prediction of asthma attack. In this paper, we used the LCA procedure in SAS developed by and downloadable from the Methodology Center at Penn State University [3].

2. Latent Class Model

Two sets of parameters are estimated in the traditional latent class model: the latent class membership probabilities (γ, gamma) and item-response probabilities conditional on latent class membership (ρ, rho). The ρ parameters express the correspondence between the observed items and the latent classes. Suppose a latent class model with *C* classes is to be estimated based on a dataset including *m* categorical items, a covariate *x*, and a grouping variable g_i. Let $Y_i = (Y_{i1}, \ldots, Y_{iM})$ represent the vector of individual *i*'s responses to the M items where $Y_{im} = 1, 2, \ldots, r_m$. Let $c_i = 1, 2, \ldots, C$ be the latent class membership of individual *i* and let *I(y=k)* be the indicator function that equals 1 if response *y* equals *k* and 0 otherwise. Suppose also that g_i represents the value of individual *i*'s group membership, x_i represents the value of the covariate for individual *i*, and its value can relate to the probability of membership in each latent class, γ. Then the latent class model can be expressed as:

$$P(Y = y|x_i, g) = \sum_{c=1}^{C} \gamma_{c|g}(x_i) \prod_{m=1}^{M} \prod_{k=1}^{r_m} \rho_{mk|cg}^{I(y_{im}=k)} \qquad (1)$$

Where $\gamma_{c|g}(x_i) = P(C_i = c|x_i, G_i = g)$ is a standard baseline category multinomial logistic model [4]. For example, with one covariate x, the γ parameters are expressed as:

$$\gamma_{c|g}(x_i) = P(C_i = c|x_i, G_i = g) = \frac{\exp(\beta_{0c|g} + x_i\beta_{1c|g})}{1 + \sum_{j=1}^{C-1} \exp(\beta_{0j|g} + x_i\beta_{1j|g})} \qquad (2)$$

For c= 1, …, C-1 with class C as the reference class in the logistic regression. This enables estimation of the log-odds that an individual falls in latent class c relative to reference class C. For example, if Class 2 is the reference class, the log-odds of membership in Class 1 relative to Class 2 for an individual in Group 1 with value x_i on the covariate is:

$$\log\left(\frac{\gamma_{1|1}(x_i)}{\gamma_{2|1}(x_i)}\right) = \beta_{01|1} + \beta_{11|1}x_i \qquad (3)$$

The exponentiated β parameter corresponding to the covariate is an odds ratio, reflecting the increase in odds of class membership (relative to reference class C) corresponding to a one unit increase in the covariate. Note that the multiple covariates can be included simultaneously.

Because class membership probabilities are modeled as functions of the covariates in Equation (2), and individuals vary with respect to their covariates, there is a vector of estimated class membership probabilities corresponding to each individual (or group of

individuals with the same responses to the covariates). The prevalence of each latent class is calculated as the average across participant-specific class membership probabilities.

The parameters are estimated by maximum likelihood using an EM expectation-maximization procedure from PROC LCA in the SAS 9.2 system. Missing data on the latent class indicators are handled in this procedure, with data assumed to be missing at random (MAR). With missing items, the model given by Equation (1) is modified so that the product over m=1, …, M is replaced by a product over items observed for that individual. A test of the null hypothesis that data are missing completely at random appears in the output.

3. Method

There are several patient outcome measures in one asthma trial, including daily diary symptoms of wheezing, breathing, and coughing scores, number of awakenings at night, daily rescue medication usage, Asthma Control Questionnaire (ACQ) score, Asthma Quality of Life Questionnaires (AQLQ), FEV1, Daily Peak Flow, *etc*. We adopted the ADAS study method [5] to determine which outcome measures distinguished different levels of disease activity optimally. This study led us to select the following outcome measures as the components of the ADAS score:

- Daily number of awakenings at night (Nighttime awakenings)
- Daily rescue medication use (Rescue β- agonist puffs/day)
- Asthma Quality of Life Questionnaires (AQLQ Symptom Domain)
- Percent Predicted FEV1 (FEV1% predicted)

The ADAS was then calculated as follows from these four variables based on a regression model:

ADAS = 5.7497 + 0.1611 * (Rescue β- agonist puffs/day) - 0.0307 * (FEV1% predicted) -0.2951 * (AQLQ Symptom Domain) + 0.0858 * (Nighttime awakenings)

The content validity, internal consistency, longitudinal and predictive validity of this composite ADAS had been demonstrated in a number of clinical trials.

We used these four variables selected from the ADAS study and applied Latent Class Model (LCM) to classify each patient into a number of latent groups. Based on the above clinical data, classifications of asthma patients are compared in terms of discriminant validity and prediction of asthma attack by means of ADAS and LCM methods. Discriminant validity is the degree of treatment effects among asthma responders or non-responders. Asthma attack is defined as any of asthma related hospitalization or emergency room visit or clinical deterioration judged by the investigators.

The dataset used for the analyses was from one Phase-III Asthma Adults Clinical Trial with 781 randomized medium ICS dependent asthmatics in a 26- week treatment period. Four treatments (MFF 200/10mcg BID, MF 200 mcg BID, F 10 mcg BID, and Placebo) were carried out at multiple global sites. The trial had demonstrated treatment effects in the primary and other secondary endpoints.

Since LCM uses categorical indicators as item responses, converting continuous measures into categorical data is necessary. The categorization of four variables based on clinical judgment and the number of subjects is summarized in Table 1. The optimal LCM is determined by fitting data to models of two classes, three classes, or more classes [6]. The fit indices for model selection, including likelihood-ratio G^2 statistics, Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC), are shown in Table 2, in which the 2-Class and 3-Class LCMs show similar fit. Therefore, the 3-Class LCM was chosen to match with the ADAS classification.

4. Results and Discussion

The LCA results from the SAS procedure, PROC LCA, for the Asthma Clinical trial were shown in Tables 3 and 4, in which latent class memberships and item response probabilities were provided. Based on these item response probabilities, the asthma responders were classified to three groups: good responders, moderate responders, and non-responders. Tables 5 and 6 showed that the percentages of these three types of responders in each treatment group by both ADAS and LCA approaches in Weeks 12 and 26 respectively. The LCA approach has the majority of moderate responders while the ADAS approach results in more non-responders than the other groups. In fact, the result from the LCA approach matched with the actual clinical evaluation.

From the perspective of discriminant validity, both approaches have similar proportions of good responders. Based on the graphs in Tables 5 and 6, the numbers of moderate responders and non-responders in the ADAS approach are very similar and thus both curves are almost on top of each other, whereas in the LCA approach, evidence of good separation of these three responder groups can be found in both tables. For the good responder group in the LCA approach, the line showed a downward trend in the treatment effect, indicating that the order of treatment effect is MFF, MF, F and placebo groups and thus the MFF treatment has the best dose response than other treatment groups. On the other hand, the line with the non-responders in the LCA approach demonstrated an increasing trend, implying that more non-responders are in the placebo as compared to other treatment groups (F, MF, and MFF). On the contrary, the treatment effect in each responder group is not obvious in the ADAS approach. Therefore, the LCA approach has better discriminant validity than the ADAS approach at both Week 12 and Week 26.

The prediction of asthma attack is another important concern in asthma clinical trial. The capibility of predicting future asthma attack from patients' outcome measures becomes another indicator of good classification of certain responder groups. Given the status of the responders at Week 4, occurrences of asthma attack events were assessed at two time points: after Week 4, between Weeks 4 and 12 (see Table 7). Given the responder status at Week 12, this assessment of asthma attack events occuring after Week 12 was provided in Table 8.

In the LCA approach, the non-responder group had the highest asthma attack event rates at all two time points (14.89% and 14.89%,). Meanwhile, the good responder group had the lowest event rates occurring after Week 4 and between Weeks 4-12. Given the responder status at Week 12, the event rates after Week 12 are similar between the good responder group and the moderate responder group. The non-responders remain to have the highest event rate in comparison to other responder groups.

On the other hand, in the ADAS approach, the non-responders had the highest event rate after Week 4 (8.5%) and between Weeks 4 and 12 (6.6%), but they did not show any obvious linear trend like the one found in the LCA approach. At the time point after Week 12, not much difference was found in the event rates among all three responder groups. As a result, the LCA approach has a better classification compared to the ADAS approach in terms of predictivity validity.

5. Conclusion

In conclusion, the results of responder classification based on Latent Class Model are better than the ADAS composite approach in terms of discriminant validity among treatment groups and prediction of asthma attack events. The LCA approach calculates fit indexes to provide numerical basis to select optimally the number of classes for classification whereas the ADAS approach offers only heuristic grouping. Furthermore, the Latent Class Model does not need the assumption of normal distribution. For the highly skewed dataset, it provides a better solution than the ADAS composite score approach. Thus, LCM is a good and valid alternative to the ADAS composite score.

Reference

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[3] Stephanie Lanza, Linda Collins, David Lemmon, and Joseph Schafer, "PRCO LCA: A SAS procedure for Latent Class Analysis," *Structural Equation Modeling*, 14 (4): 671-694, 2007.
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Table 1. Descriptive statistics of data after grouping.

Variable in Model	Code	Label	Week 4	Week 12
			N (%)	N(%)
# of Awakening	<=1	1	601 (76.95)	680 (87.07)
	>1, < 4	2	104 (13.32)	50 (6.40)
	>=4	3	76 (9.73)	51 (6.53)
# of Puffs/day	<=1	1	570 (72.98)	651 (83.35)
	>1, < 4	2	137 (17.54)	94 (12.04)
	>=4	3	74 (9.48)	36 (4.61)
AQLQ- Symptom Domain	>=4	1	691 (88.48)	576 (73.75)
	> 1.9, < 4	2	47 (6.02)	38 (4.87)
	<=1.9	3	43 (5.51)	167 (21.38)
% Predicted FEV1	>= 80	1	234 (29.96)	195 (24.97)
	>=60, <80	2	418 (53.52)	362 (46.35)
	<60	3	129 (16.52)	224 (28.68)

Variable in Model	Code	Label	Week 4	Week 12
			N (%)	N (%)
# of Awakening- Change	-2	1	28 (3.59)	21 (3.97)
	-1	2	95 (12.16)	81 (10.37)
	0	3	578 (74.01)	626 (80.15)
	1	4	62 (7.94)	32 (4.10)
	2	5	18 (2.3)	11 (1.41)
# of Puffs/day- Change	-2	1	23 (2.94)	22 (2.82)
	-1	2	139 (17.8)	130 (16.65)
	0	3	538 (68.89)	582 (74.52)
	1	4	69 (8.83)	42 (5.38)
	2	5	12 (1.54)	5 (0.64)
AQLQ- Symptom Domain – Change	-2	1	2 (0.26)	3 (0.38)
	-1	2	44 (5.63)	31 (3.97)
	0	3	702 (89.88)	717 (91.81)
	1	4	22 (2.82)	17 (2.18)
	2	5	11 (1.41)	13 (1.66)
% Predicted FEV1 - Level Change	-2	1	1 (0.13)	0 (0.00)
	-1	2	141 (18.05)	112 (14.34)
	0	3	511 (65.43)	567 (72.60)
	1	4	125 (16.01)	101 (12.93)
	2	5	3 (0.38)	1 (0.13)

Table 2. Fit Index of LCM

Change from baseline at		#Class	G square	DF	AIC	BIC	CAIC	ABIC
5 levels per response	Week 4	2	243.12	591.00	309.12	462.92	495.92	358.13
	Week 4	**3**	**169.83**	**574.00**	**269.83**	**502.86**	**552.86**	**344.09**
	Week 12	2	196.83	591.00	262.83	416.63	449.63	311.84
	Week 12	**3**	**130.24**	**574.00**	**230.24**	**463.27**	**513.27**	**304.49**

Table 3. Latent Class Proportion & Item Response Probability for 3-Class at Week 4

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Response change at WK4

Class:                       1          2          3
                        0.1374     0.8014     0.0612

Rho estimates (item response probabilities):
  Response category  1:
Class:                       1          2          3
  awake          :       0.2476     0.0002     0.0007
  pff            :       0.1644     0.0038     0.0034
  qol            :       0.0000     0.0000     0.0226
  fev            :       0.0000     0.0017     0.0000

  Response category  2:
Class:                       1          2          3
  awake          :       0.2759     0.1132     0.0015
  pff            :       0.4766     0.1494     0.0027
  qol            :       0.1624     0.0369     0.1074
  fev            :       0.3549     0.1735     0.0138

  Response category  3:
Class:                       1          2          3
  awake          :       0.3493     0.8221     0.3787
  pff            :       0.3285     0.7834     0.0981
  qol            :       0.8120     0.9400     0.7397
  fev            :       0.5571     0.6768     0.4381

  Response category  4:
Class:                       1          2          3
  awake          :       0.0584     0.0645     0.3696
  pff            :       0.0304     0.0634     0.6317
  qol            :       0.0256     0.0231     0.1304
  fev            :       0.0880     0.1446     0.5480

  Response category  5:
Class:                       1          2          3
  awake          :       0.0688     0.0000     0.2494
  pff            :       0.0001     0.0000     0.2642
  qol            :       0.0000     0.0000     0.0000
  fev            :       0.0000     0.0034     0.0000
```

Table 4. Latent Class Proportion & Item Response Probability for 3-Class at Week 12

Class:	1	2	3
	0.2695	0.0408	0.6897

Rho estimates (item response probabilities):

Response category 1:

Class:	1	2	3
awake :	0.1422	0.0315	0.0001
pff :	0.1039	0.0005	0.0002
qol :	0.0000	0.0000	0.0056
fev :	0.0000	0.0000	0.0000

Response category 2:

Class:	1	2	3
awake :	0.2254	0.0717	0.0580
pff :	0.5444	0.0081	0.0281
qol :	0.0776	0.0371	0.0250
fev :	0.2706	0.0454	0.0995

Response category 3:

Class:	1	2	3
awake :	0.6071	0.2870	0.9083
pff :	0.3502	0.1133	0.9375
qol :	0.8333	0.8667	0.9543
fev :	0.5942	0.5217	0.7898

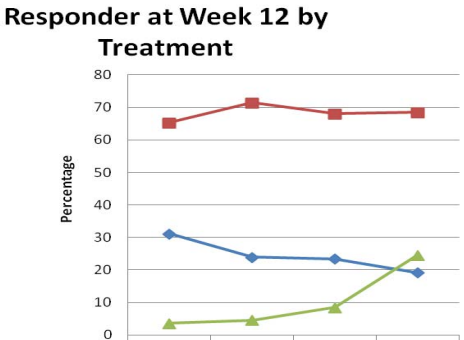
Response category 4:

Class:	1	2	3
awake :	0.0137	0.4470	0.0274
pff :	0.0014	0.8301	0.0279
qol :	0.0508	0.0003	0.0117
fev :	0.1352	0.4329	0.1089

Response category 5:

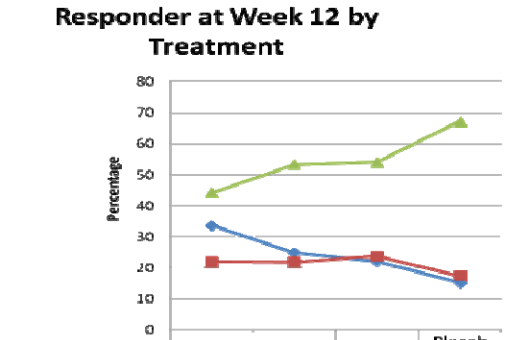
Class:	1	2	3
awake :	0.0117	0.1628	0.0061
pff :	0.0000	0.0480	0.0064
qol :	0.0382	0.0958	0.0035
fev :	0.0000	0.0000	0.0019

Table 5: Discriminant Validity at Week 12



	MFF	MF	F	Placebo
Good Responder	31.14	24	23.4	19.18
Moderate Reponder	65.27	71.43	68.09	68.49
No Responder	3.59	4.57	8.51	24.64

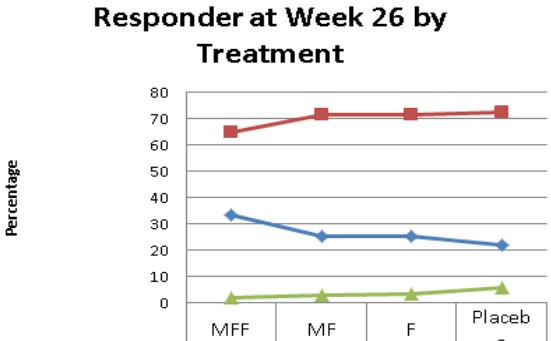
(a) LCA Approach



	MFF	MF	F	Placebo
Good Responder	33.7	24.9	22.2	15.3
Moderate Reponder	22.1	21.9	23.7	17.5
No Responder	44.2	53.3	54.1	67.2

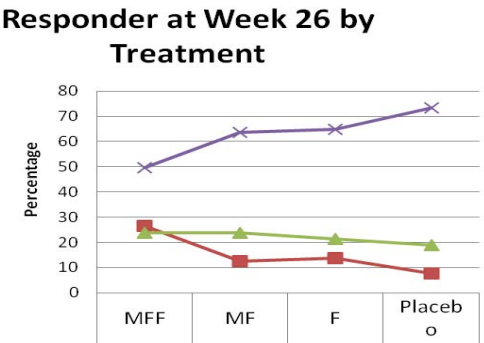
(b) ADAS Approach

Table 6. Discriminant Validity at Week 26



	MFF	MF	F	Placebo
Good Responder	33.55	25.48	25.41	22.13
Moderate Reponder	64.52	71.34	71.31	72.13
No Responder	1.94	3.18	3.28	5.74

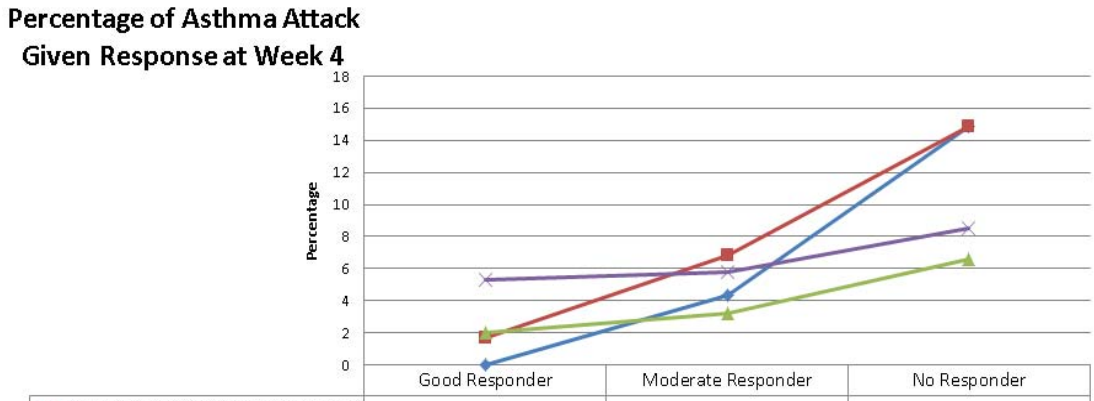
(a) LCA Approach



	MFF	MF	F	Placebo
Good Responder	26.5	12.6	13.7	7.8
Moderate Reponder	23.8	23.8	21.4	19
No Responder	49.7	63.6	65	73.3

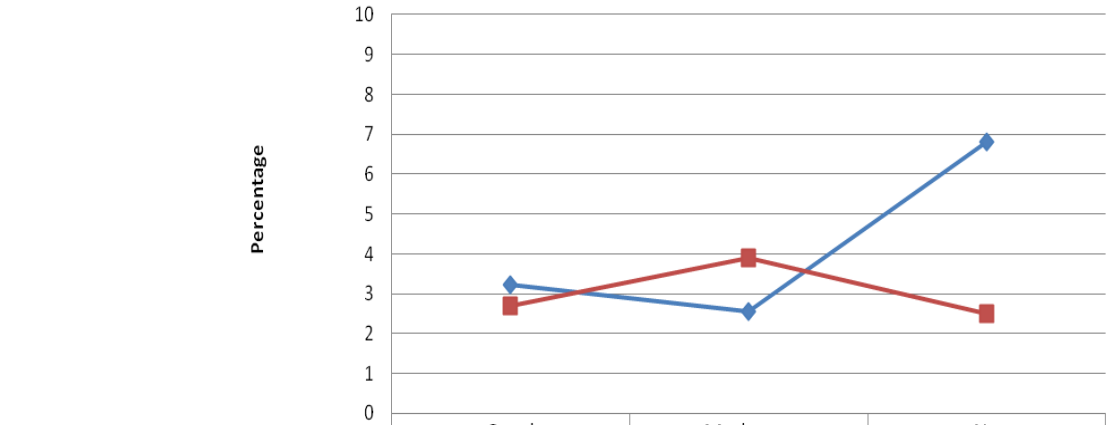
(b) ADAS Approach

Table 7. The Percentage of Asthma Attack at Different Time Points Given Response at Week 4



	Good Responder	Moderate Responder	No Responder
Asthma Attack between Weeks 4-12 (LCA)	0	4.35	14.89
Asthma Attack > Week 4 (LCA)	1.72	6.83	14.89
Asthma Attack between Weeks 4-12 (ADAS)	2	3.2	6.6
Asthma Attack > Week 4 (ADAS)	5.3	5.8	8.5

Table 8. The Percentage of Asthma Attack at Different Time Points Given Response at Week 12



	Good Responder	Moderate Responder	No Responder
Asthma Attack > Week 12 (LCA)	3.23	2.56	6.82
Asthma Attack > Week 12 (DAS)	2.7	3.9	2.5