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A study on interaction effect among risk factors of delirium using multifactor dimensionality reduction method

Jong Hyeong Lee[1] · Yong Won Lee[2] · Yoon Seok Lee[3] · Jea Young Lee[4]

[124]Department of Statistics, Yeungnam University
[3]Champoom Hanwoo Research Institution

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Abstract

Delirium is a neuropsychiatric disorder accompanying symptoms of hallucination, drowsiness, and tremors. It has high occurrence rates among elders, heart disease patients, and burn patients. It is a medical emergency associated with increased morbidity and mortality rates. That's why early detection and prevention of delirium are significantly important. And This mental illness like delirium occurred by complex interaction between risk factors. In this paper, we identify risk factors and interactions between these factors for delirium using multi-factor dimensionality reduction (MDR) method.

Keywords: Delirium, multifactor dimensionality reduction, risk factors.

1. Introduction

Studies about human diseases has been continuously conducted in medical and biological research (Lee *et al.*, 2010a). Especially in recent times, due to increasing proportion of mental disorders such as depression, associated studies are actively pursued. Among them, delirium is a neuropsychiatric syndrome that accompanies a wide range of symptoms such as cognitive impairment, hyperactivity, hallucinations, nervousness and tremors (Brown *et al.*, 2002). It's a sudden occurrence of physical and mental confusion and a drastic alternation of brain function. These symptoms are temporary phenomenons that they usually disappear following elimination of delirium. However, since hyperactivity in a confusion state might appear as a symptom of diseases associated with life that it requires close examination. Commonly about 20 percent of hospitalized patients experience delirium and delirium rate

[1] Master student, Department of Statistics, Yeungnam University, Kyungsan, Kyeongbuk 712-749, Korea.
[2] Doctor of philosophy, Department of Statistics, Yeungnam University, Kyungsan, Kyeongbuk 712-749, Korea.
[3] Research director, Champoom Hanwoo Research Institution, Chilgok, Kyeongbuk 718-910, Korea.
[4] Corresponding author: Professor, Department of Statistics, Yeungnam University, Kyungsan, Kyeongbuk 712-749, Korea. E-mail: jlee@yu.ac.kr

especially among elderly patients are reported to exceed 60 percent (Inouye, 1994; Cole *et al.*, 1993; Inouye *et al.*, 1999).

Patients in intensive care unit (ICU) are more likely to have delirium by complicating disease and drug use (Granberg *et al.*, 1996). Usually it occurs in 2 to 3 days after hospitalization and lasts about a month (Yu *et al.*, 2008). Most of patients cannot recall their memories in this confusion state and they are uncooperative toward treatment which makes it difficult to proceed treatment. Also, death rate of delirium patients is higher than normal patients and they are usually hospitalized for longer. In this context, early detection and prevention must be considered very importantly.

Many studies associated with risk factors of delirium have been reported in foreign countries. "Delirium in an intensive care unit; a study of risk factors." (Dubois *et al.*, 2001) and "Delirium in the intensive care unit: a review" (Arend *et al.*, 2009) are typical examples. However, in korea, not only there are insufficient numbers of studies about Delirium, but also there are inadequate reports about incidences while only vague awareness of Delirium exist. Thus, we want to examine the risk factor and interaction effect among risk factors based on data of researches conducted to patients in korea.

We have used statistical methods to identify factors associated with disease in medical research (Choi *et al.*, 2009). For example, Logistic regression method was applied to categorical data in many study (Kang *et al.*, 2011). Currently, multifactor dimensionality reduction (MDR) method is mainly used to identify interaction effect in the area of Genetics (Lee *et al.*, 2010b). The MDR method is different from the traditional statistic technique like general linear model that it uses non-parametric method. The MDR method is non-parametric (i.e., no hypothesis about the value of a statistical parameter is made), model-free (i.e., it assumes no particular inheritance model), and is directly applicable to case-control and discordant-sib-pair studies.

The purpose of this study was to investigate interaction effect related to delirium occurrence through executing MDR method on 31 risk factors on and to prevent delirium using MDR method. First of all, in chapter 2, we introduce MDR method which is used to identify interaction effect among risk factors. In chapter 3, we apply MDR method to real data to establish major factor and interaction effect. Finally in chapter 4, we suggest conclusion based on the result of our experiment and furthermore, we discuss about necessity and direction of further research.

2. Multifactor dimensionality reduction

The MDR method have been suggested by Ritchie in 2001 (Ritchie *et al.*, 2001). It is non-parametric and model-free. And it is directly applicable to case-control and discordant-sib-pair studies. we can show that MDR has reasonable power to identify interactions among two or more loci in relatively small samples. Therefore, MDR is often used to demonstrate interaction effect among risk factor. The steps in this study are listed below.

Step 1. Case-Control(1:1) data balanced.

Step 2. The data are divided into a training set (e.g. 9/10 of the data) and an independent testing set (e.g. 1/10 of the data) as part of cross-validation.

Step 3. Set the initial value of n - SNP combinations.

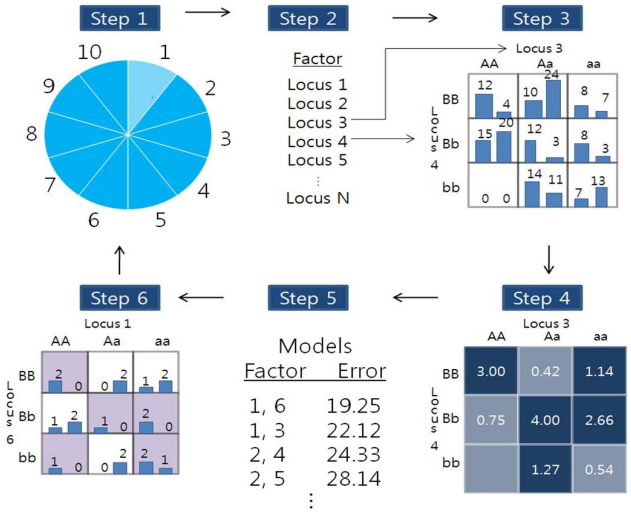

Figure 2.1 procedure of MDR method형

Step 4. A set of n genetic and/or environmental factors are selected. The n factors and their possible multi-factor classes are represented in n-dimensional space; for example, for two loci with three genotypes each, there are nine possible two-locus-genotype combinations.

Step 5. Then, the ratio for the number of cases to the number of controls is calculated within each multifactor class. Each multifactor class in n-dimensional space is then labeled as "high risk" if the computed ratio equals or exceeds 1, or as "low risk" if the computed ratio value doesn't exceed 1; thus reducing the n-dimensional space to one dimension with two levels ("low risk" and "high risk").

Step 6. Among all of the two factor combinations, a single model that has the fewest misclassified individuals is selected. This two-locus model will have the minimum classification error among the two locus models. ME is classification error occurred during training set. Prediction error (PE) is classification error occurred during testing set.

$$ME = \{(Total_{high} - Case_{high}) + Case_{low}\}/N$$

$Total_{high}$ is total number of high-risk, $Case_{high}$ is number of case groups in high-risk, $Case_{low}$ is number of case groups in Low-risk. In order to evaluate the predictive ability of the model, PE is estimated using 10-fold cross-validation

Step 7. Using different random number seeds, this entire procedure is performed ten times to reduce the chance of observing spurious results due to chance divisions of the data.

Step 8. The result is a set of models, one for each model size is considered.

From this set, the model with the combination of loci and/or discrete environmental factors that maximizes the cross-validation consistency and minimizes the prediction error is selected.

Cross-validation consistency measures number of times an MDR model is identified in each possible 9/10 of the subjects (Chung *et al.*, 2005). Therefore, best-combination carry high CVC value and low average value of ME and PE.

3. Application of MDR method

3.1. Materials

This study is based on 414 patients with delirium who were treated at Medical Center in emergency room and conducted on seniors aged over 70 for 24 months during Jan, 2008 - Dec, 2009. The Patient's information considering age, sex, medical history, etc were observed based on medical record. Delirium was diagnosed according to DSM-Ⅳ (Diagnostic and Statistical Manual of Mental Disorders; Kwak *et al.*, 2011). 42 Patients of all patients were diagnosed with delirium. In this paper, we used 31 risk factors of delirium reported by Emma Arend in 2009 while we eliminated the age factor. All factors are divided as binary type according to the standard. Below are 31 risk factors reported by Emma Arend (Arend *et al.*, 2009).

Table 3.1 31 Risk factors that may cause delirium

Predisposing factor	Precipitating	
	Acute illness	Pharmacology
Dementia	Infection	Anaesthetics
Nursing home	Hypoxia	analgesics
Alcohol abuse	Metabolic abnormality	Antibiotics
Smoking	Electrolyte imbalance	anticholiergic
Visual impairment	Malnutrition	antihistamine
Hearing loss	Hemodynamic instability	Antihypertensives
Bun/Cre	CNS disorder	bronchodilator
Stroke/epilepsy	(Central Nervous System)	cardiacdrug
Congestive heart	Head trauma	diuretic
failure	Seizure	Sedative
Depression	Vascular problem	Steroid

The risk factors were classified into three main groups of Predisposing, Acute illness, and Pharmacology according to its characteristic. All factors adds up to thirty-one factors : Predisposing (ten factors - Dementia, transfer from nursing home, Bun/Cre, etc), Acute illness (ten factors - Hypoxia, metabolic abnormality, Electrolyte imbalance, etc), Pharmacology (eleven factors -Anaesthetics, analgesics, Antibiotics, etc).

3.2. Chi-square test of a single factor

We used chi-squared test to establish statistical significance between each factor and delirium. Table 3.2 is the result of chi-square test on thirty-one risk factors and it displays factors which statistical significance appeared. According to the table, fourteen factors are significant such as metabolic abnormality, Stroke/epilepsy, Bun/Cre, Hemodynamic instability, Electrolyte imbalance, Analgesics, Sedative, Diuretic, Malnutrition, Cardiac-drug, Bronchodilator, Hypoxia, Antibiotics and Transfer from Nursing home.

Table 3.2 Results of chi-square test

Risk Factors	p-value
Metabolic abnormality	<0.001
Stroke/epilepsy	<0.001
Bun/Cre	<0.001
Hemodynamic instability	<0.001
Electrolyte imbalance	<0.001
Analgesics	0.007
Sedative	0.002
Diuretic	0.002
Malnutrition	0.002
Cardiac-drug	0.030
Bronchodilator	0.005
Hypoxia	0.007
Antibiotics	0.024
Transfer from Nursing home	0.049

⁎ All p-value < 0.05

3.3. Results of MDR application

Table 3.3 displays outcome of MDR method application to thirty-one risk-factors of delirium research data. In this table, the results are organized in descending order according to accuracy of test set based on MDR method.

Table 3.3 MDR results for a single factor

factors	ME	PE	Odds Ratio	95% C.I
Metabolic abnormality	0.291	0.290	8.17	4.14-16.11
Antibiotics	0.405	0.475	2.25	1.10-4.60
Electolyte imbalance	0.356	0.478	3.54	1.84-6.79
Bronchodilator	0.389	0.479	2.46	1.29-4.68
Stroke_epilepsy	0.371	0.482	4.97	2.39-10.34
Diuretic	0.399	0.485	2.94	1.46-5.95
Emodynamic instability	0.376	0.491	4.67	2.25-9.66
Hypoxia	0.393	0.493	2.38	1.26-4.54

⁎ All p-value < 0.001

Metabolic abnormality has ME of 0.291 and a PE of 0.290, antibiotics has ME of 0.405 and a PE of 0.475. Electrolyte has relatively low ME value of 0.356 compared to value of antibiotics, but it has relatively higher PE value of 0,478 compared to electrolyte imbalance. Odds ratio (OR) is 8.17 in case of metabolic and the value appears to be 4.14 times larger at minimum and 16.11 times larger at maximum with 95% confidence level when it does not have metabolic abnormality. For when MDR is conducted on Stroke_epilepsy, ME is 0.371 and PE is 0.482 that values are relatively higher, but it is confirmed that it has higher odds ratio of 4.97 than other risk-factors. Also hemodynamic instability has OR of 4.67 that it has third largest values.

Table 3.4 displays MDR result of interaction effect between two-risk factors. PE are ranked in ascending order. Interaction effect of metabolic abnormality and hemodynamic instability has lowest PE of 0.242 and ME of 0.242. Also, their odds ratio (10.536) is appeared to be the highest. It means, the possibility of a people having etabolic abnormality and hemodynamic instability developing delirium is 10 times higher than that of those who didn't. combination of stroke_epilepsy and metabolic abnormality has a ME of 0.228, PE of 0.261 and odds ratio of 11.543 (Table 3.2).

Table 3.4 MDR results for two-combinations

combinations	ME	PE	OR	95% C.I
Metabolic abnormality Hemodynamic instability	0.242	0.242	10.536	5.197-21.362
Stroke_epilepsy Metabolic abnormality	0.228	0.267	11.543	5.541-24.046
Stroke_epilepsy Hemodynamic instability	0.268	0.280	8.194	4.133-16.244
Metabolic abnormality Cardiac drug	0.265	0.304	7.789	3.910-15.519
Malnutrition Congestive	0.301	0.305	3.769	1.959-7.252
Stroke_epilepsy Electolyte imbalance	0.261	0.319	7.665	3.712-15.828
Bun/Cre Metabolic abnormality	0.269	0.326	9.471	4.777-18.776
Metabolic abnormality Depression	0.274	0.358	8.789	4.448-17.366
Metabolic abnormality Analgesics	0.284	0.361	6.544	3.339-12.824
Metabolic abnormality Bronchodilator	0.279	0.370	6.963	3.134-15.467

⁎ All p-value < 0.001

Table 3.5 MDR results for interaction among three risk factors

SNP Combinations	ME	PE	OR	95% C.I
Stroke_epilepsy Metabolic abnormality Hemodynamic instability	0.188	0.202	19.364	7.898-47.472
Metabolic abnormality Malnutrition Congetive	0.216	0.242	6.889	3.342-14.201
Stroke_epilepsy Metabolic abnormality Analgesics	0.219	0.271	12.049	5.391-26.928
Malnutrition Diuretic Congetive	0.244	0.283	5.381	2.661-10.882
Stroke_epilepsy Metabolic abnormality Depression	0.211	0.285	12.886	6.061-27.399
Stroke_epilepsy Metabolic abnormality Bun/Cre	0.213	0.295	12.886	6.061-27.399
Stroke_epilepsy Metabolic Cardiacdrug	0.210	0.302	13.980	3.031-32.500

Among three risk factors, combination of stroke_epilepsy, metabolic abnormality and hemodynamic instability have smallest ME of 0.188, PE of 0.202 and largest odds ratio of 19.634 (Table 3.5). We know that combinations of stroke_epilepsy and metabolic abnormality have large odds ratio over than ten as shown in Table 3.5.

In summary, metabolic abnormality has small PE and ME in MDR result for single ef-

fect. And PE of stroke_epilepsy are fifth smallest in result for single effect. Also for the combination of metabolic abnormality and stroke_epilepsy, it has small ME and PE in two factors interaction while carrying high odds ratio that it is considered to be major risk-factor. Simultaneously in case of interaction effect between three risk factors including metabolic abnormality and stroke_epilepsy also display small ME, PE value while carrying high odds ratio. Consequently, we judge metabolic abnormality and stroke_epilepsy, which are included in every combinations, as major risk-factor of delirium.

Table 3.6 Frequency of delirium occurrence according to the major risk factor

Interaction		Delirium		Total	χ^2 (p-value)
		0	1		
Metabolic &stroke_epilepsy	0	299	11	310	58.907 (<0.001)
	1	73	31	104	
Total		372	42	414	

Table3.6 shown above displays frequency of delirium occurrence according to interaction effect between metabolic abnormal and stroke_epilepsy which are judged as major risk-factors (Table 3.6). Looking at the table, only 11 out of 310 patients (3.5%) who do not carry two risk factors has delirium, but 31 out of 104 patients (29.8%) who have valid risk factors has delirium. Thus, interaction effect between metabolic abnormality and stroke_epilepsy proved to give more significant effect on delirium occurrence (χ^2 =58.907, p<0.001).

4. Conclusions

Delirium mainly occurs in toxicopathy, metabolic disease, systemic infection, nervous system infection, strokes, anesthesia and so on. These abnormalities of brain function are matters of life that it requires especially careful management.

We applied MDR method to the Delirium data having 31 factors reported by Emma Arend to identify interaction effect among risk factors while eliminating one risk. We applied MDR method to 31 risk factors out of 32 risk factors, which we eliminated risk-factor of age, reported by Emma Arend in order to investigate interaction effect among risk-factors which effect occurrence of delirium (Arend *et al.*, 2009).

We have used MDR Method, which are non-parametric and model-free, to identify interaction effect associated with human diseases and traits. MDR has reasonable power of test to identify interactions among factors. In this study, we apply MDR method to 414 delirium data which are observed during Jan, 2008 - Dec, 2009 to demonstrate interaction effect among risk factors of delirium. As the result, metabolic abnormality has smallest ME and PE in single effect. Antibiotics was second, followed by electolyte, bronchodilator and stroke_epilepsy. For MDR result for interaction between two risk-factors, interaction of metabolic abnormality and stroke_epilepsy has smallest ME of 0.228 and PE of 0.267. It has the highest odds ratio of 11.543 for two combinations. For interaction effect among three risk factors, five-combinations, which include metabolic abnormality and stroke_epilepsy, out of 7 high ranks were included while Odds ratios for all five-combinations displayed ratio over 10. Therefore, We identified Interaction of metabolic abnormality and stroke_epilepsy as a major interaction associated with delirium.

In summary, among candidates of risk-factors for delirium which appears among elderly

patients, metabolic abnormality and stroke_epilepsy are identified as a major risk factors in this study. Thus, risk of delirium is higher among patients who carry complex symptoms of metabolic abnormality and stroke_epilepsy that patients with these symptoms must pay close attention.

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