Potential biomarkers for predicting of depression in diabetes mellitus

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Abstract

Background

To identify the potential biomarkers for predicting depression in diabetes mellitus using the support vector machine technique to analyze routine biochemical tests and vital signs between two groups: subjects with both diabetes mellitus and depression, and subjects with diabetes mellitus alone.

Methods

Electronic medical records upon admission and biochemical tests and vital signs of 135 patients with both diabetes mellitus and depression and 178 patients with diabetes mellitus alone were identified for this retrospective study. After the covariate regression analysis on age and sex, the two groups were classified by the recursive feature elimination-based support vector machine and the biomarkers were also identified by 10-fold cross validation. Specifically, the training data, evaluation data, and testing data were split for ranking the parameters, determine the optimal parameters, and assess classification performance.

Results

The experimental results identified 12 predictive biomarkers with classification accuracy of 74%. The 12 biomarkers are hydroxybutyrate, magnesium, hydroxybutyrate dehydrogenase, creatine kinase, total protein, high-density lipoprotein cholesterol, cholesterol, absolute value of the lymphocyte, blood urea nitrogen, chlorine, platelet count, and glutamyltranspeptidase. Receiver operating characteristic curve analysis was also used with area under the curve being 0.79.

Conclusions

Some biochemical parameters may be potential biomarkers to predict depression among the subjects with diabetes mellitus.

Background

Diabetes mellitus is a chronic illness affecting about 347 million people worldwide in 2017, and this number is expected to increase more than half by 2035 [1, 2]. The disease will also lead to emotional distress other than physical symptoms and impose psychosocial impacts on life quality, which complicates its management.

Depression and diabetes mellitus are common comorbid conditions [3]. A meta-analysis reported that patients with diabetes mellitus more than doubled the odds of developing depression [3]. Another study described that depression was highly prevalent, affecting approximately 26% of the patients with diabetes mellitus [4]. In addition, depression was found to be associated with a greater number of complications of diabetes mellitus [5]. Furthermore, depression itself is a disabiling disease and imposes...
a significant impact on life quality by undermining physical health [6] and impairing cognitive functions [7]. Therefore, it is not surprising that diabetes mellitus comorbidity with depression is associated with higher morbidity and mortality rates, decreased compliance with treatment, poorer functionality, poor glycemic control, and more expenditure on use to health services [7–12]. A prospective study involving more than 4,000 patients having diabetes mellitus with comorbidity of depression reported a higher risk of developing macrovascular complications, even when variables such as the type of treatment and the existed history of complications before the study were controlled [13]. This highlights the severity of diabetes mellitus in comorbidity with depression and the need to treat both conditions concurrently.

Comorbid depression in diabetes mellitus might be considered not as the result of mental problem only, but more important, as an early sign of a multi-systemic disorder. Thus, medical monitoring is an important component of case assessment. The diagnosis of depression mainly depends on doctors’ clinical experience and scale. The lack of objective indicators, the strong subjective consciousness of doctors and patients, and the avoidance or denial in some symptoms due to patients’ insufficient understanding of the disease interfere with the accuracy of scale score; and this may affect the correct diagnosis of the disease [14–16]. Therefore, it is particularly important to identify objective indicators of depression diagnosis and establish scientific diagnostic methods. Nonetheless, very few approaches have been proposed to facilitate early prediction of depression in patients having diabetes mellitus because objective indicators of laboratory examinations are rare.

Recently, machine learning algorithms have been widely used in the medical sciences. It was reported that machine learning algorithms in combination with smartphone-based data will be a new approach to classify affective states accurately in bipolar disorder [17]. In addition, machine learning methods may be used to predict treatment effect of electroconvulsive therapy (ECT) [18], cognitive behavioral therapy (CBT) [19], and clozapine [20]; or to help diagnostic clarification [21]. According to KIM et al., comprehensive machine-learning methods that adopt supervised classification and appropriate feature selection methods that have interaction with the classifier show particular advantages in predicting complicated disorders with multi-facet etiology such as depression [22]. Support Vector Machine (SVM) is a method of machine learning and is of great significance in accurately identifying depression among patients with diabetes mellitus in clinical practice. This method provides insights for understanding the underlying pathological mechanisms of depression.

Previous studies have reported a high accuracy of over 80% in differentiating patients with depression from healthy controls, using machine learning methods to analyze heart rate variability (HRV) and/or protein markers [22, 23]. Nevertheless, the existing extraction procedures of parameters are usually complex. For example, Danni Kuang et al. [23] need to examine the 64 features of HRV in the Ewing test including the different states—resting, valsalva, deep breathing, and standing states. By contrast, our study was much simpler in that only easy-to-obtain routine biochemical tests and vital signs of patients were needed. By SVM, the best executing classification system can be set up with a small number of parameters that are selected from a variety of biochemical tests and vital signs.
To address this need, we proposed using SVM to identify potential prediction biomarkers for depression in patients with diabetes mellitus.

**Methods**

**Data Acquisition**

Biochemical tests and vital signs were obtained from electronic medical records of admissions in West China Hospital of Sichuan University between January 1, 2011 and October 31, 2016. A total of 313 patients were divided into two groups: 135 with both diabetes mellitus and depression (comorbidity group), and 178 with diabetes mellitus alone (DM group). Specifically, the DM group was diagnosed using the ICD-10 categories E10.x - E14.x, and the depression in comorbidity group was diagnosed using the ICD-10 categories F32.x and F33.x. To avoid confounding, patients with other diseases or of non-Han ethnicities were excluded. Each department had different biochemical parameters checked as appropriate, and we analyzed the same biochemical parameters for both groups (Table 2). Written informed consent had been obtained from all patients, and the Institutional Ethics Committee of Sichuan University approved this study.
## Table 2
The 52 biochemical tests and 5 vital signs.

|   | 52 biochemical tests and 5 vital signs                          |
|---|----------------------------------------------------------------|
| 1 | red blood count (RBC)                                          |
| 2 | hemoglobin (HGB)                                                |
| 3 | mean cell hemoglobin concentration (MCHC)                       |
| 4 | platelet count (PLT)                                            |
| 5 | white blood cell count (WBC)                                    |
| 6 | percentage of neutrophils                                      |
| 7 | percentage of lymphocytes                                      |
| 8 | percentage of monocytes                                         |
| 9 | eosinophil percentage                                           |
|10 | basophil percentage                                             |
|11 | absolute value of neutrophils                                   |
|12 | absolute value of the lymphocyte                                |
|13 | absolute value of the monocytes                                 |
| 1 | body temperature                                                |
| 2 | acidophi absolute value                                         |
| 3 | creatine kinase (CK)                                            |
| 4 | lactic dehydrogenase (LDH)                                      |
| 5 | total bilirubin                                                 |
| 6 | direct bilirubin                                                |
| 7 | bilirubin indirect                                              |
| 8 | hydroxybutyrate dehydrogenase                                   |
| 9 | triglyceride                                                    |
|10 | cholesterol                                                    |
|11 | calcium                                                         |
|12 | magnesium                                                       |
|13 | phosphorus                                                      |
| 1 | respiration                                                     |
| 2 | high-density lipoprotein cholesterol (HDL-C)                    |
| 3 | low-density lipoprotein cholesterol (LDL-C)                     |
| 4 | albumin (A)                                                     |
| 5 | total protein                                                   |
| 6 | A/G                                                             |
| 7 | creatinine                                                      |
| 8 | aspartate aminotransferase (AST)                                |
| 9 | alanine aminotransferase (ALT)                                  |
|10 | AST/ALT                                                         |
|11 | serum cyscatin-c                                                |
|12 | uric acid                                                       |
|13 | hydroxybutyric acid                                            |
|14 | bilirubin indirect                                              |
|15 | A/G                                                             |
|16 | albumin (A)                                                     |
|17 | total protein                                                   |
|18 | sodium                                                          |
|19 | potassium                                                       |
|20 | • anion gap                                                     |
|21 | • serum cyscatin-c                                              |
|22 | • hydroxybutyric acid                                          |
|23 | • triglyceride                                                  |
|24 | • cholesterol                                                  |
|25 | • calcium                                                       |
|26 | • magnesium                                                     |
|27 | • alanine aminotransferase (ALT)                                |
|28 | • AST/ALT                                                       |
|29 | • serum cyscatin-c                                              |
|30 | • hydroxybutyric acid                                          |
|31 | • triglyceride                                                  |
|32 | • cholesterol                                                  |
|33 | • calcium                                                       |
|34 | • magnesium                                                     |
|35 | • alanine aminotransferase (ALT)                                |
|36 | • AST/ALT                                                       |
|37 | • serum cyscatin-c                                              |
|38 | • hydroxybutyric acid                                          |
|39 | • triglyceride                                                  |
|40 | • cholesterol                                                  |
|41 | • calcium                                                       |
|42 | • magnesium                                                     |
|43 | • alanine aminotransferase (ALT)                                |
|44 | • AST/ALT                                                       |
|45 | • serum cyscatin-c                                              |
|46 | • hydroxybutyric acid                                          |
|47 | • triglyceride                                                  |
|48 | • cholesterol                                                  |
|49 | • calcium                                                       |
|50 | • magnesium                                                     |
|51 | • alanine aminotransferase (ALT)                                |
|52 | • AST/ALT                                                       |

|   | 1 body temperature                                               |
|---|----------------------------------------------------------------|
| 2 | respiration                                                     |
| 3 | diastolic blood pressure                                        |

| 1 | body temperature                                                |
|---|----------------------------------------------------------------|
| 2 | respiration                                                     |
| 3 | diastolic blood pressure                                        |
Data Processing

To detect whether biochemical tests and vital signs can function as markers for predicting depression in diabetes mellitus, a RFE-SVM algorithm was adopted to identify the markers and assess the classification performance (Fig. 1).

Before applying the machine learning method to identify predictive markers, covariate regression analysis was performed because age and sex both differed significantly between the DM group and the comorbidity group ($P < 0.05$) (Table 1). After covariate regression analysis, the experimental data were split into training data, evaluation data, and testing data with the proportion of 1/2, 1/4, 1/4 to obtain feature ranking, determine the optimal features, and assess the classification performance. Specifically, the implementation of the machine learning can be summarized as follows:

| Demographic of 313 patients having both diabetes mellitus and depression and having diabetes mellitus alone. |
|---------------------------------------------------------------|
| **Table 1**                                                   |
| **DM group** (n = 178) | **Comorbidity group** (n = 135) | **Statistics** | **$P$** |
| Sex | Male (n = 114) | Male (n = 42) | 27.97 | < 0.001 |
| Age | 54.59 ± 9.64 | 57.26 ± 8.14 | -2.68 | 0.01    |

- Determine the feature ranking by recursive feature elimination-based SVM on the training data. The experiments were repeated 1,000 times with 10-fold cross validation.

- Train a SVM classification model on the training data using the liblinear toolbox, and determine the most predictive features using the evaluation data based on the feature ranking obtained above. The feature that ranked No. 1 was first used to train the model, and the performance was evaluated by the evaluation data. Then, the feature that ranked No. 2 was combined to train the model and to compare the performance with the previous one. If the performance of the latter classifier was worse than the former, the feature that ranked No. 2 would be removed. In this way, only the features that could increase the classification accuracy were remained, and finally we obtained 12 biomarkers (Fig. 2).

- Train the classification model on the training data with the selected 12 biomarkers, and assess the performance on the testing data by the measurements of accuracy, AUC, sensitivity, and specificity.

Statistical analysis
Statistical analysis was performed using SPSS 20.0. We conducted the test of normality of variances using K-S method and applied log operation to conform to the normal distribution. Two-sample t test and chi-squared test were used for comparison between groups. Statistical significance was set at $P < 0.05$ for both tests.

**Results**

In this retrospective study, medical records upon admission of 313 patients were analyzed. Demographic characteristics of the DM group ($n = 178$) and the comorbidity group ($n = 135$) were summarized (Table 1). The two groups differed significantly in age and sex with in comorbidity group had older patients and more women (Table 1).

The two groups differed significantly in the 12 biomarkers of hydroxybutyrate, magnesium, creatine kinase, total protein, high-density lipoprotein cholesterol, cholesterol, absolute value of the lymphocyte, blood urea nitrogen, chlorine, platelet count, glutamyltranspeptidase, and hydroxybutyrate dehydrogenase, with $P < 0.05$ (except Hydroxybutyrate Dehydrogenase) (Table 3). The performance of classification of both groups reached 75% for sensitivity, 72% for specificity, 74% for accuracy, and 0.79 for AUC based on ROC analysis (Fig. 3).
Table 3
Biomarkers of experimental results of 313 patients having both diabetes mellitus and depression and having diabetes mellitus alone.

| DM group (n = 178) | Comorbidity group (n = 135) | Statistics | P          |
|-------------------|-----------------------------|------------|------------|
| Hydroxybutyrate   | 0.27 ± 0.59                 | 0.17 ± 0.22| 0.12       | < 0.001    |
| Magnesium         | 0.84 ± 0.11                 | 0.88 ± 0.11| 0.06       | 0.04       |
| Hydroxybutyrate Dehydrogenase | 129.49 ± 28.92 | 126.50 ± 42.39 | -1.74 | 0.08*      |
| Creatine Kinase   | 80.75 ± 37.69               | 80.94 ± 108.09 | -3.00 | 0.003*     |
| Total Protein     | 69.22 ± 6.32                | 66.47 ± 4.46| 0.06       | 0.04       |
| High-density Lipoprotein Cholesterol | 1.25 ± 0.32 | 1.40 ± 0.37 | -2.74 | 0.006*     |
| Cholesterol       | 4.22 ± 0.79                 | 4.70 ± 0.94| 0.06       | 0.04       |
| Absolute Value of the Lymphocyte | 1.68 ± 0.52 | 1.67 ± 0.57 | 0.07 | 0.01       |
| Blood Urea Nitrogen | 5.98 ± 1.82               | 5.19 ± 1.97| -3.72      | < 0.001*   |
| Chlorine          | 105.12 ± 3.40               | 104.99 ± 4.10| 0.07 | 0.003      |
| Platelet Count    | 150.01 ± 57.76              | 174.28 ± 58.86| 0.11 | < 0.001    |
| Glutamyltranspeptidase | 36.59 ± 57.55 | 26.81 ± 20.28 | 0.12 | < 0.001    |

Note: * the results by log operation

Discussion
In this retrospective study, we found 12 important depression biomarkers using SVM. These biomarkers are hydroxybutyrate, magnesium, hydroxybutyrate dehydrogenase, creatine kinase, total protein, high-density lipoprotein cholesterol, cholesterol, absolute value of the lymphocyte, blood urea nitrogen, chlorine, platelet count, and glutamyltranspeptidase, which differentiate depression in patients with diabetes mellitus at an overall classification accuracy of 74%. Twelve identified factors imply that modulation of the inflammatory, immune, energy metabolism, and lipid metabolism pathways were mainly involved in the pathophysiology process of depression in patients with diabetes mellitus.

We found three biomarkers involved in inflammatory and immune pathway including magnesium, absolute value of the lymphocyte, and glutamyltranspeptidase. Depression often coexists with diabetes, metabolic disorders and other diseases, and is linked to inflammatory and oxidative stress [24]. The research found there is a link between depression and insulin resistance [25]. Diabetes can cause a rise in blood sugar and insulin levels and has an effect on inflammation that may contribute to depression. Recent studies have shown that oxidative stress may enhance induction of HO-1 expression, which may
result in insulin resistance and insufficiency [26, 27]. It is clear that increased oxidative stress may lead to insulin resistance and impose an impact on insulin secretion in patients having depressive disorder [27]. One study demonstrated that reducing inflammation through non-drug treatments such as psychological interventions, physical exercises, and meditation can play a role in preventing depression [28]. Magnesium has received great concern over its potential role in the pathophysiology of depression [29–31]. Lymphocytes are produced by lymphoid organs and constitute an important component of immune response. Previous studies indicated a decrease in lymphocyte counts among depressive patients [32], which was in agreement with our findings. One explanation is that inflammatory or chronic stress-induced cellular immunosuppression would cause elevated neutrophils and leukocytes and a relatively reduced lymphocyte counts [32–34]. Glutathione (GSH) is an important substance that protects cells from oxidative stress, and its synthesis requires the participation of Glutamyltranspeptidase [35, 36]. In addition, some researchers reported Glutamyltranspeptidase deficiency in human resulted specific symptoms such as abnormal behavior, mental retardation, and absence seizure [37, 38]. Emerging evidence showed that antidepressant treatments decrease inflammatory and improve mitochondrial dysfunction in patients with depression [39, 40].

We also found five biomarkers potentially related to energy metabolism. These biomarkers are hydroxybutyrate, hydroxybutyrate dehydrogenase, creatine kinase, total protein, and blood urea nitrogen. Hydroxybutyrate is a product of ketone body metabolism pathway. A previous study reported that synthesis and degradation of ketone bodies influenced immensely the pathophysiologic process of depression [41]. Hydroxybutyrate might be helpful for screening depression and predicting its progress [41]. Creatine kinase (CK) activity was reported to increase in the prefrontal cortex, hippocampus, and striatum of rats, and CK levels were increased in the serum of a patient with depression after antidepressant treatment [42, 43]. The normal role of CK is to catalyze the reversible transfer of the phosphoryl group from phosphocreatine to adenosine diphosphate (ADP), and through this process ATP used as energy by cells is generated [44]. The final product of protein metabolism is urea [45]. Hu et al. found that 10% of 260 hemodialysis patients had a diagnosis of depression using the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. They also found that patients with lower monthly income, shorter duration of hemodialysis, and lower levels of blood urea nitrogen were more likely to have a diagnosis of depression. They considered that depression symptoms were usually associated with poor appetite and poor nutrition in hemodialysis patients with depression [46]. We observed lower concentrations of total protein in patients with both diabetes mellitus and depression compared to patients with diabetes mellitus alone, the result is consistent with the research by Peng et al. [27]. The above results suggested that blood biochemical parameters, including urea nitrogen, lactate dehydrogenase, alanine transaminase, uric acid, and total protein, were significantly different between depression patients and healthy controls, and that multiple biochemical parameters in combination may improve the diagnostic effectiveness of depression and the comprehensive management for depressive patients.

Additionally, we found some other biomarkers that may be related to lipid metabolism, such as cholesterol and high-density lipoprotein cholesterol. One of the characteristics of depression is loss of
appetite. Previous studies suggested that LDL-c increase is mostly determined by the severe loss of body fat [47, 48]. Higher level of cholesterol was observed in patients with depression than in controls [27]. In the same way, increased levels of cholesterol were found to be associated with comorbidity of diabetes mellitus and depression in our study.

Changes of creatine kinase, cholesterol, total protein, and high-density lipoprotein cholesterol etc. in blood are not specific to depression and may be present in other psychiatric disorders such as eating disorders [47], schizophrenia [49, 50], and / or bipolar disorder [51, 52]. Researchers suggested that a single biomarker often lacks in sensitivity and specificity [27] and thus may not well distinguish depression from other diseases. Monitoring changes in multiple factor levels will provide a more comprehensive and accurate assessment, which can help us better understand the disease status and characteristics of specific diseases. Although the model of multiple biomarkers is more conducive for the diagnosis of diseases, it is usually used in the diagnosis of cancer instead of nervous system diseases [53, 54]. Our study is advantageous in that laboratory biochemical indexes are routine examinations in clinical settings, which could be obtained with minimal invasiveness, maximal convenience, and low cost, thus having a great potential for wider clinical access and more efficient population screening. Due to the inconsistency of biochemical test results between the two groups, different test items were deleted. The lack of biochemical tests as variables in SVM learning affected accuracy, which is one limitation of the present study. Second, the parameters chosen retrospectively instead of consecutively were inadequate and included only those that were clinically applicable. This may have caused an enrollment bias and an erroneous classification by the algorithm. This is one of the major methodological limitations of the present study, which should be remedied in future investigations using a prospective and consecutive design.

Conclusions

(1) SVM can facilitate clinical diagnosis of depression in patients with diabetes mellitus using commonly available laboratory parameters. (2) Twelve potential biomarkers were identified for depression diagnosis in patients with diabetes mellitus.

Abbreviations

ECT: Electroconvulsive therapy; CBT: Cognitive behavioral therapy; SVM: Support Vector Machine; HRV: Heart rate variability; DM: Diabetes mellitus; CK: Creatine kinase; ADP: Adenosine diphosphate; ATP: Adenosine Triphosphate.

Declarations

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**Authors’ contributions**

Author XL designed the study and completed the original draft of the manuscript. Data analysis was performed by authors XL and QZ. Authors RZ and MY managed and extracted data. WD, QW, WJ, and TL managed the literature analyses. Corresponding author XH revised the draft of the manuscript. All authors contributed to and have approved the final manuscript.

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**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

Ethical approval was obtained from the Institutional Ethics Committee of Sichuan University. Written informed consent was obtained from each participant.

**Consent for publication**

Not applicable.

**Competing interests**

We declared that there was no conflict of interests in this study.

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References

1. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabetic medicine: a journal of the British Diabetic Association. 1998;15(7):539–53.

2. Markle-Reid M, Ploeg J, Fraser KD, Fisher KA, Bartholomew A, Griffith LE, Miklavcic J, Gafni A, Thabane L, Upshur R. Community Program Improves Quality of Life and Self-Management in Older Adults with Diabetes Mellitus and Comorbidity. Journal of the American Geriatrics Society 2017.

3. Tareen RS, Tareen K. Psychosocial aspects of diabetes management: dilemma of diabetes distress. Translational pediatrics. 2017;6(4):383–96.

4. Egede LE, Ellis C. Diabetes and depression: global perspectives. Diabetes Res Clin Pract. 2010;87(3):302–12.

5. de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ: Association of depression and diabetes complications: a meta-analysis. Psychosomatic medicine 2001, 63(4):619–630.

6. Cooney GM, Dwan K, Greig CA, Lawlor DA, Rimer J, Waugh FR, McMurdo M, Mead GE. Exercise for depression. The Cochrane database of systematic reviews 2013(9):Cd004366.

7. Hammar A, Ardal G. Cognitive functioning in major depression—a summary. Front Hum Neurosci. 2009;3:26.

8. Jayakody K, Gunadasa S, Hosker C. Exercise for anxiety disorders: systematic review. Br J Sports Med. 2014;48(3):187–96.

9. Angevaren M, Aufdemkampe G, Verhaar HJ, Aleman A, Vanhees L. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. The Cochrane database of systematic reviews 2008(3):Cd005381.

10. Lustman PJ, Clouse RE. Depression in diabetic patients: the relationship between mood and glycemic control. J Diabetes Complicat. 2005;19(2):113–22.

11. Schram MT, Baan CA, Pouwer F. Depression and quality of life in patients with diabetes: a systematic review from the European depression in diabetes (EDID) research consortium. Curr Diabetes Rev. 2009;5(2):112–9.

12. Lin EH, Heckbert SR, Rutter CM, Katon WJ, Ciechanowski P, Ludman EJ, Oliver M, Young BA, McCulloch DK, Von Korff M. Depression and increased mortality in diabetes: unexpected causes of death. Ann Fam Med. 2009;7(5):414–21.

13. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia. 2006;49(5):837–45.

14. Cummins N, Scherer S, Krajewski J, Schnieder S, Epps J, Quatieri TF. A review of depression and suicide risk assessment using speech analysis. Speech Commun. 2015;71(C):10–49.

15. Balsters MJH, Krahmer EJ, Swerts MGJ, Vingerhoets AJJM. Verbal and Nonverbal Correlates for Depression: A Review. Current Psychiatry Reviews. 2012;8(3):-. 
16. Pinto JV, Passos IC, Gomes F, Reckziegel R, Kapczinski F, Mwangi B, Kauer-Sant'Anna M. Peripheral biomarker signatures of bipolar disorder and schizophrenia: A machine learning approach. Schizophr Res. 2017;188:182–4.

17. Faurholt-Jepsen M, Busk J, Frost M, Vinberg M, Christensen EM, Winther O, Bardram JE, Kessing LV. Voice analysis as an objective state marker in bipolar disorder. Translational psychiatry. 2016;6:e856.

18. van Waarde JA, Scholte HS, van Oudheusden LJ, Verwey B, Denys D, van Wingen GA. A functional MRI marker may predict the outcome of electroconvulsive therapy in severe and treatment-resistant depression. Molecular psychiatry. 2015;20(5):609–14.

19. Hahn T, Kircher T, Straube B, Wittchen HU, Konrad C, Strohle A, Wittmann A, Pfleiderer B, Reif A, Arolt V, et al. Predicting treatment response to cognitive behavioral therapy in panic disorder with agoraphobia by integrating local neural information. JAMA psychiatry. 2015;72(1):68–74.

20. Khodayari-Rostamabad A, Hasey GM, Maccrimmon DJ, Reilly JP, de Bruin H. A pilot study to determine whether machine learning methodologies using pre-treatment electroencephalography can predict the symptomatic response to clozapine therapy. Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology. 2010;121(12):1998–2006.

21. Khodayari-Rostamabad A, Reilly JP, Hasey G, Debruin H, MacRimmon D: Diagnosis of psychiatric disorders using EEG data and employing a statistical decision model. Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Annual Conference 2010, 2010:4006–4009.

22. Kim EY, Lee MY, Kim SH, Ha K, Kim KP, Ahn YM. Diagnosis of major depressive disorder by combining multimodal information from heart rate dynamics and serum proteomics using machine-learning algorithm. Prog Neuro-psychopharmacol Biol Psychiatry. 2017;76:65–71.

23. Kuang D, Yang R, Chen X, Lao G, Wu F, Huang X, Lv R, Zhang L, Song C, Ou S. Depression recognition according to heart rate variability using Bayesian Networks. J Psychiatr Res. 2017;95:282–7.

24. Hendrickx H, McEwen BS, Ouderaa F. Metabolism, mood and cognition in aging: the importance of lifestyle and dietary intervention. Neurobiol Aging. 2005;26(Suppl 1):1–5.

25. Qiuhua S, Bergquist-Beringer S, Sousa VD. Major depressive disorder and insulin resistance in nondiabetic young adults in the United States: the National Health and Nutrition Examination Survey, 1999–2002. Biol Res Nurs. 2011;13(2):175–81.

26. Keane KN, Cruzat VF, Carlessi R, de Bittencourt PIH, Newsholme P. Molecular Events Linking Oxidative Stress and Inflammation to Insulin Resistance andβ-Cell Dysfunction. Oxidative Med Cell Longev. 2015;2015:1–15.

27. Peng YF, Xiang Y, Wei YS. The significance of routine biochemical markers in patients with major depressive disorder. Scientific reports. 2016;6:34402.

28. Irwin MR, Piber D. Insomnia and inflammation: a two hit model of depression risk and prevention. World psychiatry: official journal of the World Psychiatric Association (WPA). 2018;17(3):359–61.

29. Linder J, Brismar K, Beck-Friis J, Saaf J, Wetterberg L. Calcium and magnesium concentrations in affective disorder: difference between plasma and serum in relation to symptoms. Acta psychiatraca
Scandinavica. 1989;80(6):527–37.

30. Cade JF. A SIGNIFICANT ELEVATION OF PLASMA MAGNESIUM LEVELS IN SCHIZOPHRENIA AND DEPRESSIVE STATES. The Medical journal of Australia. 1964;1:195–6.

31. Ryszewska-Pokrasniewicz B, Mach A, Skalski M, Januszko P, Wawrzyniak ZM, Poleszak E, Nowak G, Pilc A, Radziwon-Zaleska M: Effects of Magnesium Supplementation on Unipolar Depression: A Placebo-Controlled Study and Review of the Importance of Dosing and Magnesium Status in the Therapeutic Response. Nutrients 2018, 10(8).

32. Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, McCorkle R, Seligman DA, Schmidt K. The relationship of depression and stressors to immunological assays: a meta-analytic review. Brain Behav Immun. 2001;15(3):199–226.

33. Dantzer R, O’Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nature reviews Neuroscience. 2008;9(1):46–56.

34. Seidel A, Arolt V, Hunstiger M, Rink L, Behnisch A, Kirchner H. Cytokine production and serum proteins in depression. Scand J Immunol. 1995;41(6):534–8.

35. Griffith OW. Biologic and pharmacologic regulation of mammalian glutathione synthesis. Free Radic Biol Med. 1999;27(9–10):922–35.

36. Lieberman MW, Barrios R, Carter BZ, Habib GM, Lebovitz RM, Rajagopalan S, Sepulveda AR, Shi ZZ, Wan DF. Gamma-Glutamyl transpeptidase. What does the organization and expression of a multipromoter gene tell us about its functions? Am J Pathol. 1995;147(5):1175–85.

37. Hammond JW, Potter M, Wilcken B, Truscott R. Siblings with gamma-glutamyltransferase deficiency. J Inherit Metab Dis. 1995;18(1):82–3.

38. Iida M, Yasuhara T, Mochizuki H, Takakura H, Yanagisawa T, Kubo H. Two Japanese brothers with hereditary gamma-glutamyl transpeptidase deficiency. J Inherit Metab Dis. 2005;28(1):49–55.

39. Ortmann CF, Reus GZ, Ignacio ZM, Abelaira HM, Titus SE, de Carvalho P, Arent CO, Dos Santos MA, Matias BI, Martins MM, et al. Enriched Flavonoid Fraction from Cecropia pachystachya Trecul Leaves Exerts Antidepressant-like Behavior and Protects Brain Against Oxidative Stress in Rats Subjected to Chronic Mild Stress. Neurotox Res. 2016;29(4):469–83.

40. Lee SY, Lee SJ, Han C, Patkar AA, Masand PS, Pae CU. Oxidative/nitrosative stress and antidepressants: targets for novel antidepressants. Prog Neuro-psychopharmacol Biol Psychiatry. 2013;46:224–35.

41. Jia HM, Feng YF, Liu YT, Chang X, Chen L, Zhang HW, Ding G, Zou ZM. Integration of (1)H NMR and UPLC-Q-TOF/MS for a comprehensive urinary metabonomics study on a rat model of depression induced by chronic unpredictable mild stress. PloS one. 2013;8(5):e63624.

42. Agostinho FR, Scaini G, Ferreira GK, Jeremias IC, Reus GZ, Rezin GT, Castro AA, Zugno AI, Quevedo J, Streck EL. Effects of olanzapine, fluoxetine and olanzapine/fluoxetine on creatine kinase activity in rat brain. Brain research bulletin. 2009;80(6):337–40.
43. Ferreira GK, Cardoso MR, Jeremias IC, Goncalves CL, Freitas KV, Antonini R, Scaini G, Rezin GT, Quevedo J, Streck EL. Fluvoxamine alters the activity of energy metabolism enzymes in the brain. Braz J Psychiatry. 2014;36(3):220–6.

44. Bessman SP, Carpenter CL. The creatine-creatine phosphate energy shuttle. Annual review of biochemistry. 1985;54:831–62.

45. Koo HN, Lee JK, Hong SH, Kim HM. Herbkines increases physical stamina in mice. Biol Pharm Bull. 2004;27(1):117–9.

46. Lee S. Anorexia nervosa in Hong Kong: a Chinese perspective. Psychological medicine. 1991;21(3):703–11.

47. Nova E, Lopez-Vidriero I, Varela P, Casas J, Marcos A. Evolution of serum biochemical indicators in anorexia nervosa patients: a 1-year follow-up study. Journal of human nutrition dietetics: the official journal of the British Dietetic Association. 2008;21(1):23–30.

48. Weinbrenner T, Zuger M, Jacoby GE, Herpertz S, Liedtke R, Sudhop T, Gouni-Berthold I, Axelsson M, Berthold HK. Lipoprotein metabolism in patients with anorexia nervosa: a case-control study investigating the mechanisms leading to hypercholesterolaemia. Br J Nutr. 2004;91(6):959–69.

49. Skibinska M, Kapelski P, Rajewska-Rager A, Szczepankiewicz A, Naroza B, Duda J, Dmitrzak-Weglarz M, Twarowska-Hauser J, Pawlak J. Correlation of metabolic parameters, neurotrophin-3, and neurotrophin-4 serum levels in women with schizophrenia and first-onset depression. Nordic journal of psychiatry 2019:1–8.

50. Meng XD, Cao X, Li T, Li JP. Creatine kinase (CK) and its association with aggressive behavior in patients with schizophrenia. Schizophrenia research 2018.

51. Hu Q, Wang C, Liu F, He J, Wang F, Wang W, You P. High serum levels of FGF21 are decreased in bipolar mania patients during psychotropic medication treatment and are associated with increased metabolism disturbance. Psychiatry research. 2018;272:643–8.

52. Chen J, Chen H, Feng J, Zhang L, Li J, Li R, Wang S, Wilson I, Jones A, Tan Y, et al. Association between hyperuricemia and metabolic syndrome in patients suffering from bipolar disorder. BMC Psychiatry. 2018;18(1):390.

53. Zhu CS, Pinsky PF, Cramer DW, Ransohoff DF, Hartge P, Pfeiffer RM, Urban N, Mor G, Bast RC Jr, Moore LE, et al. A framework for evaluating biomarkers for early detection: validation of biomarker panels for ovarian cancer. Cancer prevention research (Philadelphia Pa). 2011;4(3):375–83.

54. Dunn BK, Jegalian K, Greenwald P. Biomarkers for early detection and as surrogate endpoints in cancer prevention trials: issues and opportunities. Recent results in cancer research Fortschritte der Krebsforschung Progres dans les recherches sur le cancer. 2011;188:21–47.

Figures
Figure 1
The flowchart of data processing.

Figure 2
The procedure of feature selection on the evaluation data.
Figure 3

ROC curve analysis with AUC value.