Alpha 1-antitrypsin as a Potential Biomarker for Diagnosing Major Depressive Disorder

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Research

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Abstract

Background: Despite decades of intensive research on major depressive disorder (MDD), the pathogenesis of MDD is still unclear and the objectively diagnostic method remains unavailable. Therefore, we conducted this study to assess whether alpha 1-antitrypsin (AAT) could be a potential biomarker for diagnosing MDD.

Methods: The levels of AAT, liver function-related indicators, renal function-related indicators, blood lipids-related indicators, high sensitivity C-reactive protein, homocysteine and transferrin were detected. The orthogonal partial least-squares discriminant analysis (OPLS-DA) was used to find the differential variables, Random Forest was used to identify the simplified biomarker panel, and receiver-operating characteristic (ROC) curve analysis was used to evaluate the diagnostic performance of the identified panel.

Results: The 86 MDD patients and 99 healthy controls (HCs) were recruited. In total, we found nine differential variables between MDD patients and HCs, and a potential biomarker panel consisting of AAT, albumin (ALB) and apolipoprotein A1 (APOA) was identified. This panel could effectively separate MDD patients from HCs in two independent samples sets. The level of AAT was significantly negatively correlated with HDRS score and improved after antidepressant treatment. Meanwhile, MDD patients with suicide idea or behavior had significantly lower AAT levels compared to MDD patients without suicide idea or behavior.

Conclusions: Our results suggested that AAT held the promise to become a potential biomarker for diagnosing MDD, and also might be a potential novel therapeutic target for MDD.

Introduction

Major depressive disorder (MDD) is a common mental disease with high morbidity, disability and recurrence rates in clinical practice. Due to the increasing social pressure, the incidence rate of MDD is increasing year by year, and its object is gradually inclined to adolescents [1]. Restricted by various factors such as differences in regional development and cultural concepts, MDD also has the characteristics of low diagnosis rate and poor treatment effect. It has even become the main cause of suicide, bringing huge economic burden to individual, families and society [2–4]. At present, the diagnosis of MDD mainly relies on the subjective identification of symptom clusters, which unfortunately results in a considerable error rate [5]. Thus, it is urgently needed to identify disease biomarkers for objectively diagnosing MDD.

Many theories have been developed to explain the pathogenesis of MDD, such as neurotransmission deficiency [6], oxidative stress and immune system dysfunction [7, 8] and gut microbiota alternation [9, 10]. Luscher et al. proposed the central and causal role of GABAergic deficits in the etiology of MDD [6]. Previous studies reported that the disturbances in leukocyte function and/or leukocyte number could be potential biomarkers of MDD [7, 8]. Our previous animal and human studies found that the disordered gut

microbiota might have a causal role in the development of MDD [9, 10]. These theories have made a great contribution to the prevention and treatment of MDD. But, none of these theories has been universally accepted. It means that some novel and comprehensive pathophysiologic mechanisms underlying the disorder are needed.

Alpha 1-antitrypsin (AAT) is a single-chain glycoprotein mainly synthesized by liver cells and a positive acute phase protein (APP). It is the most abundant serine protease inhibitor in human blood. AAT could inhibit the synthesis and release of inflammatory mediators, and also inhibit the release of many pro-inflammatory factors, such as cytokine interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α. Meanwhile, it could play an anti-apoptotic effect by eliminating cytotoxic substances, such as peroxides and free radicals. Our previous study found that AAT was decreased in serum of MDD patients [11]. Beiko et al. reported that anxiety and depression were common comorbidities in individuals with AAT deficiency [12]. Therefore, we conducted this study to further investigate the role of AAT in the onset and development of MDD, and explore whether or not AAT could be a potential biomarker for diagnosing MDD.

Material And Methods

Patient enrollment

The MDD and healthy controls (HCs) subjects were recruited from the First Affiliated Hospital of Chongqing Medical University between October 2019 and January 2020. The Ethical Committee of Chongqing Medical University reviewed and approved this study. MDD subjects were independently diagnosed by two experienced psychiatrists according to DSM-IV criteria. Hamilton Rating Scale for Depression (HDRS) was used to evaluate the disease severity and Beck Scale for Suicide Ideation (BSI) was performed to assess the suicidal ideation. The MDD candidates with one or more confounding factors were excluded: preexisting physical or other mental disorders, younger than 18 or older than 65, female in pregnancy, lactation or menstruation, and/or illicit drug use. Meanwhile, HCs subjects were recruited from the Medical Examination Center of the same hospital. The HCs candidates with one or more confounding factors were excluded: any current or previous lifetime history of mental disorders, systemic medical disorder, female in pregnancy, lactation or menstruation, and/or illicit drug use. Informed written consent was obtained from all the included subjects. The blood routine, liver functions and urine routine of the included subjects were without abnormal changing.

Samples collection and regrouping

Upon meeting all the above-mentioned inclusion and exclusion criteria, venipuncture was performed on site to collect the serum. The samples were transferred into the laboratory under low temperature and then stored at -80 °C until later analysis. Samples were collected at any time during regular business hours (9 am to 6 pm, Monday to Friday). We did not make any effect to restrict the timing for serum collection. Totally, serum samples from 99 HCs and 86 MDD patients were obtained. The detailed information of the included subjects was displayed in Table 1. These samples were randomly assigned

into training set (69 HCs and 60 MDD patients) and testing set (30 HCs and 26 MDD patients). The 33 of the included MDD patients were received antidepressant therapy for one month, and then their serum samples were collected again.

Table 1
Baseline data of MDD patients and healthy controls

Variables	MDD	HCs	P-value
Number	86	99	-
Age	34.52 (14.69)	36.41 (13.54)	0.36
Sex (F/M)	52/34	61/38	0.87
BMI (kg/m^2)	23.61 (2.39)	23.15 (2.24)	0.18
Married (Y/N)	46/40	57/42	0.58
Education (years)	11.93 (3.63)	11.62 (4.10)	0.60
Medication (Y/N)	47/39	0/99	< 0.00001
Smoke (Y/N)	20/66	31/68	0.22
Alcohol (Y/N)	18/68	24/75	0.59
Suicide idea (Y/N)	56/30	0/99	< 0.00001
Suicide behavior (Y/N)	27/59	0/99	< 0.00001
Family history (Y/N)	4/82	6/93	0.67
HDRS scores	30.44 (8.34)	1.38 (1.43)	< 0.00001
BSI scores	10.16 (4.26)	0.42 (0.83)	< 0.00001

Abbreviations: HCs, healthy controls; F, female; M, male; Y, yes; N, no; HDRS, Hamilton Depression Rating Scale; BMI, body mass index; MDD, major depressive disorder; BSI, Beck Scale for Suicide Ideation.

Biochemical indicator detecting

The detecting of serum biochemical indicators referred to the method described in our previous study [13]. Serum indicators of hepatic function (PALB, Prealbumin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBA, total bile acid; BILT, total bilirubin; BILD, direct bilirubin; ALP, alkaline phosphatase; GGT, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; 5-NT,5'-Nucleoticlase), renal function (Crea; Urea; UA, uric acid; CYSC, Cystatin C), lipids (TC, total Cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; APOA, apolipoprotein A1; APOB, apolipoprotein B; LPA, lipoprotein a), CRPHS (hypersensitive C-reactive protein), TRSF (transferrin) and HCY (homocysteine) were measured using commercially available enzymatic

colorimetric assays and an automated analyzer system (Cobas 8000 modular device Roche Diagnostics, Switzerland).

Statistical analysis

Student's t-test, chi-square test, Pearson correlation analysis or paired t-test was used when appropriate. The orthogonal partial least-squares discriminant analysis (OPLS-DA) was build using samples in training set, and the variables with variable importance in projection (VIP) > 1.0 (equivalent to a p-value of less than 0.05) were viewed as the important metabolites responsible for discriminating MDD patients from HCs subjects. Meanwhile, the Student's t-test and Benjamini and Hochberg False Discovery Rate method were conducted to assess whether these identified important variables were still significantly different between the two groups. The variables with adjusted p-value < 0.05 and VIP > 1.0 were identified as the differential variables between HCs and MDD patients. Finally, the Random Forest was used to obtain a simplified biomarker panel from these identified differential variables. The receiver-operating characteristic (ROC) curve analysis was further used to evaluate the diagnostic performance of the identified simplified biomarker panel.

Results

Discriminative model construction

The score plot of OPLS-DA model built with samples in training set showed that MDD patients and HCs subjects were clearly separated with little overlap (R2Y = 0.71, Q2Y = 0.60; Fig. 1A), representing the strong explanatory power of the data. The positive values of R2Y and Q2Y indicated the robust differences between these two groups. Meanwhile, this model could effectively predict the samples in testing set: the T-predicted scatter plot showed that 26 of the 30 HCs subjects and 22 of the 26 MDD patients were correctly predicted (Fig. 1B), indicating the good predictive ability of the model. In addition, the 399-iteration permutation tests also suggested that the model was valid and stable.

Differential variables in MDD patients

By analyzing the OPLS-DA loadings plot, a total of nine variables with VIP > 1.0 was identified: ALB, APOA, AAT, CHE, ALP, TRSF, HDLC, CYSC and BILT. The results of univariate statistical analysis showed that a total of 15 variables with adjusted p-value < 0.5 was identified: PALB, ALB, CYSC, APOA, GLB, AAT, ALP, CHE, TRSF, HDLC, BILD, BILT, 5-NT, and TG. Finally, nine differential variables responsible for the discrimination between MDD patients and HCs subjects were identified (VIP > 1.0 and adjusted p-value < 0.5). As compared to HCs subjects, MDD patients were characterized by significantly lower levels of ALB, APOA, AAT, CHE, ALP, TRSF, HDLC and BILT, along with significantly higher level of CYSC. The detailed information was described in Table 2.

Table 2
Differential variables responsible for subjects' classification

Variables	VIP	P-value[a]	Adjust P-value[b]	Fold change[c]
ALB	2.31	1.83E-18	5.31E-17	1.16
APOA	1.88	1.14E-13	1.65E-12	1.17
AAT	1.84	4.86E-12	4.69E-11	1.13
CHE	1.76	3.01E-12	2.18E-11	1.38
ALP	1.33	1.16E-08	6.70E-08	1.50
TRSF	1.32	7.73E-08	3.73E-07	1.15
CYSC	1.25	1.74E-07	7.21E-07	0.87
HDLC	1.24	5.9E-06	2.13E-05	1.14
BILT	1.13	2.55E-05	8.21E-05	1.39
[a]P-value was from Student T-test.				
[b]Adjust P-value was obtained using Benjamini and Hochberg False Discovery Rate.				
[c] >1.0 and < 1.0 indicated lower and higher level, respectively, in MDD patients.				

Simplified biomarker panel identification

The results of Random Forest showed that the most significant deviations between HCs subjects and MDD patients could be described by the following three variables: AAT, ALB and APOA. The simplified biomarker panel consisting of AAT, ALB and APOA could yield the highest predictive power for future diagnostic applications. The results of ROC analysis showed that this panel could yield an area under the curve (AUC) of 0.974 (95% confidence interval (CI) = 0.953–0.995) in training set (Fig. 2A). Moreover, this panel could yield an AUC of 0.878 (95% CI = 0.771–0.986) in an independent set (Fig. 2A). The diagnostic performance of simplified biomarker panel was similar to the OPLS-DA model built with all variables, suggesting the efficacy of this panel in MDD detection.

Correlations between demographic data and differential variables

Pearson correlation analysis was used to explore the potential correlations between demographic data and differential variables (Fig. 3). The results showed that AAT was significantly negatively correlated with HDRS (r= -0.404, p = 0.0001), BSI (r= -0.394, p = 0.0002), suicide idea (r= -0.359, p = 0.0007), and suicide behavior (r= -0.331, p = 0.0018). Both ALB and APOA were significantly negatively correlated with suicide behavior (r= -0.277, p = 0.0097; r= -0.259, p = 0.0159). The CYSC was significantly correlated with

age (positively, r = 0.351, p = 0.0009) and education (negatively, r= -0.268, p = 0.0144). The ALP was significantly negatively correlated with HDRS (r= -0.254, p = 0.0181) and BSI (r= -0.239, p = 0.0269). The CHE and TRSF were significantly negatively correlated with BSI (r= -0.274, p = 0.0106) and age (r= -0.301, p = 0.0052), respectively.

Supplementary analysis

There were 56 MDD patients with suicide idea and 30 MDD patients without suicide idea. As shown in Fig. 4A, compared to MDD patients without suicide idea, MDD patients with suicide idea had significantly higher HDRS scores (p = 0.00015) and BSI scores (p = 0.00003), and significantly lower AAT levels (p = 0.00068); the ALB level and APOA level were similar between these two groups. There were 27 MDD patients with suicide behavior and 59 MDD patients without suicide behavior. As shown in Fig. 4B, compared to MDD patients without suicide behavior, MDD patients with suicide behavior had significantly higher HDRS scores (p = 0.02500) and BSI scores (p = 2.51E-09), and significantly lower levels of AAT (p = 0.0018), ALB (p = 0.0097) and APOA (p = 0.0160).

To study the changes of these identified differential variables after treatment, the levels of the variables before and after treatment in 33 MDD patients receiving antidepressant therapy were collected. The paired t-test was used to analyze the experimental data. As shown in Fig. 5A, we found that eight of nine differential variables in MDD patients were improved after treatment. Moreover, compared to the levels before treatment, the levels of AAT, ALP, CHE, and APOA after treatment were significantly increased (p = 0.0001, p = 0.0081, p = 0.0054, p = 0.0201, respectively). Meanwhile, we found that both the HDRS scores (p = 1.17E-15) and BSI scores (p = 8.00E-05) were significantly decreased after treatment (Fig. 5B).

Discussion

Developing an objectively diagnostic method with high specificity and sensitivity for MDD has been proven to be a formidable and elusive task, although we and other researchers have completed many meaningful works [14–17]. In the present work, a potential biomarker panel consisting of AAT, ALB and APOA was identified. We examined the diagnostic performance of this panel in two independent sets: in training set, the application of this panel resulted in an AUC of 0.974 (sensitivity, 91.7%; specificity, 92.8%); in testing set, the AUC was 0.878 (sensitivity, 92.3%; specificity, 80.0%). Moreover, the levels of these potential biomarkers had been improved after treatment. These results demonstrated that this biomarker panel might be a “good” classifier of MDD patients and HCs, and our findings could be helpful for future developing an objectively diagnostic method for MDD.

AAT has a variety of anti-inflammatory and tissue protection properties [18]. It could play an anti-inflammatory effect by regulating various immune cells, such as neutrophil and lymphocytes [19]. Thus, AAT has an important role in many chronic diseases, such as liver cirrhosis and gastric cancer [18]. In recent years, the role of inflammation and oxidative stress in the pathogenesis of neuropsychiatric diseases has been recognized by many scholars [20, 21]. Previous study showed that many MDD

patients were accompanied by activation of the inflammatory response system (IRS), and then showed the compensatory immune regulatory response system (CIRS) activation [22]. As a positive acute phase response protein, AAT is an important component of CIRS. Therefore, there may be an important connection between AAT and MDD.

Some studies reported that the level of AAT was decreased in serum of MDD patients compared to non-depressed subjects [23, 24]. Another study found that the level of AAT was not significantly changed in plasma of depressed patients than in controls [25]. Using serum proteomics, we identified 74 differential proteins enriching in the acute phase response system, and AAT was found to be decreased in MDD patients than in HCs [11]. Meanwhile, Beiko et al. reported that anxiety and depression were common comorbidities in individuals with AAT deficiency [12]. In this study, we found that the AAT level in serum of MDD patients was the significantly decreased compared to HCs. This disparity may have resulted from differences in the demographic and clinical characteristics of the included MDD patients or HCs, sample sizes, and/or different races. However, the change of AAT level in MDD patients may be related to the phenomenon of oxidative stress during the onset of depression. MDD patients may consume large amounts of AAT for anti-inflammatory and immune regulation, then resulting in the decease of AAT level in serum.

There is a strong association between MDD and suicidal idea or behavior [26]. Here, we found that compared to MDD patients without suicidal idea or behavior, MDD patients with suicidal idea or behavior had the significantly lower average HDRS score. Our previous study found that suicidal behavior in MDD was associated with a more pronounced inflammatory phenotype [27]. In this study, we found that both suicidal idea and suicidal behavior were significantly negatively correlated with AAT, and suicidal behavior was also significantly negatively correlated with ALB and APOA. Moreover, the significantly lower average ALB and APOA levels were only found in MDD patients with suicidal behavior vs. MDD patients without suicidal behavior, not in MDD patients with suicidal idea vs. MDD patients without suicidal idea. These results might indicate that ALB and APOA were the two risk factors of MDD patients attempting suicide.

Several limitations of the present study should be taken into account when interpreting our findings. Firstly, the sample size was relatively small, future studies with large sample size are needed to validate and support our conclusions. Secondly, the present study was conducted with adult HCs and MDD patients; whether or not the results are appropriate for children, adolescents or an exclusive sample of elderly patients is unknown. Thirdly, the subjects were recruited in a city of China (Chongqing); whether similar results would have been obtained in MDD patients from other places, such as Africa, Europe and North America, cannot be determined from this study.

Conclusion

In conclusion, our results showed that a potential biomarker panel consisting of AAT, ALB and APOA could yield high sensitivity and specificity in differentiating MDD patients from HCs. This was confirmed

in two independent samples of MDD patients. The AAT was found to be significantly negatively correlated with HDRS score and was significantly improved after treatment, suggesting that it held the promise to become a potential biomarker for diagnosing MDD and also might a potential novel therapeutic target for MDD. Further research is needed to confirm the diagnostic performance of this panel in different populations.

Abbreviations

MDD, major depressive disorder; AAT, alpha 1-antitrypsin; OPLS-DA, orthogonal partial least-squares discriminant analysis; ROC, receiver-operating characteristic; HCs, healthy controls; APP, acute phase protein; IL, cytokine interleukin; TNF, tumor necrosis factor; HDRS, Hamilton Rating Scale for Depression; BSI, Beck Scale for Suicide Ideation; PALB, Prealbumin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBA, total bile acid; BILT, total bilirubin; BILD, direct bilirubin; ALP, alkaline phosphatase; GGT, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; 5-NT, 5'-Nucleoticlase; Crea; Urea; UA, uric acid; CYSC, Cystatin C; TC, total Cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; APOA, apolipoprotein A1; APOB, apolipoprotein B; LPA, lipoprotein a; CRPHS, hypersensitive C-reactive protein; TRSF, transferring; HCY, homocysteine; AUC, area under the curve.

Declarations

Author's contribution

Jian-jun Chen developed the study concept. All authors contributed to the study design. Testing and data collection were performed by Shun-jie Bai, Kunxia Chen and Huili Bai. Shun-jie Bai, Jing Xie and Jian-jun Chen performed the data analysis and interpretation under the supervision of Huili Bai. Shun-jie Bai drafted the paper, and Jian-jun Chen and Jing Xie provided critical revisions. All authors approved the final version of the paper for submission.

Acknowledgements

None.

Ethics approval and consent to participate

This study was approved by the Ethical Committee of Chongqing Medical University. The included subjects provided the written informed consents before sample collection. Data collection and processing were performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and material

All datasets generated during and analyzed during this study will be made available after garnering institutional approval and enacting appropriate data sharing agreements.

Competing interests

The authors declare no financial or other conflicts of interest.

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Authors' contributions

Jian-jun Chen designed and guided the manuscript. Shun-jie Bai, Jing Xie, Kunxia Chen, Huili Bai, Jian-jun Chen contributed to collection and assembly of data, data analysis and interpretation. Shun-jie Bai wrote and edited the manuscript. Jian-jun Chen reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Figures

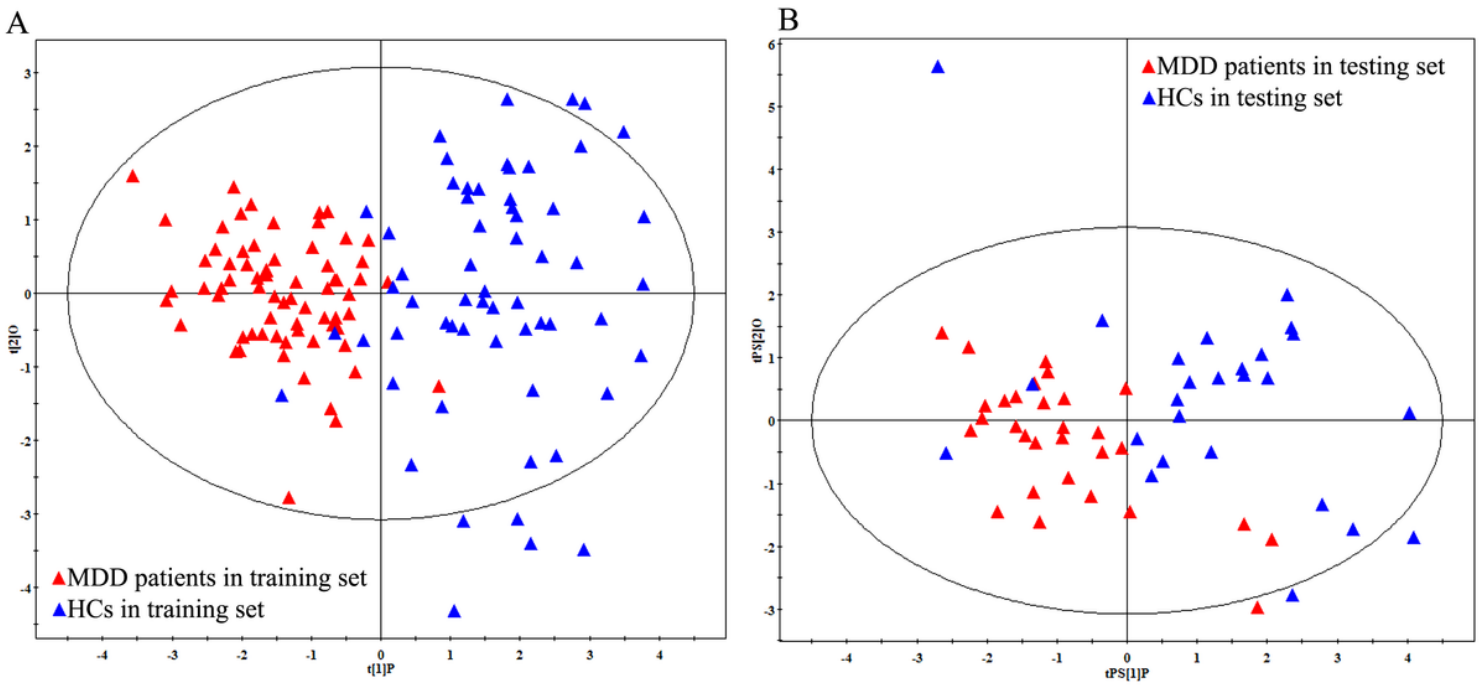

Figure 1

OPLS-DA model built with all variables. A) an obvious discrimination between MDD patients (blue triangle) and HCs (red triangle) in training set was observed. B) T-predicted scatter plot showed that MDD patients (blue triangle) and HCs (red triangle) in testing set could be effectively predicted.

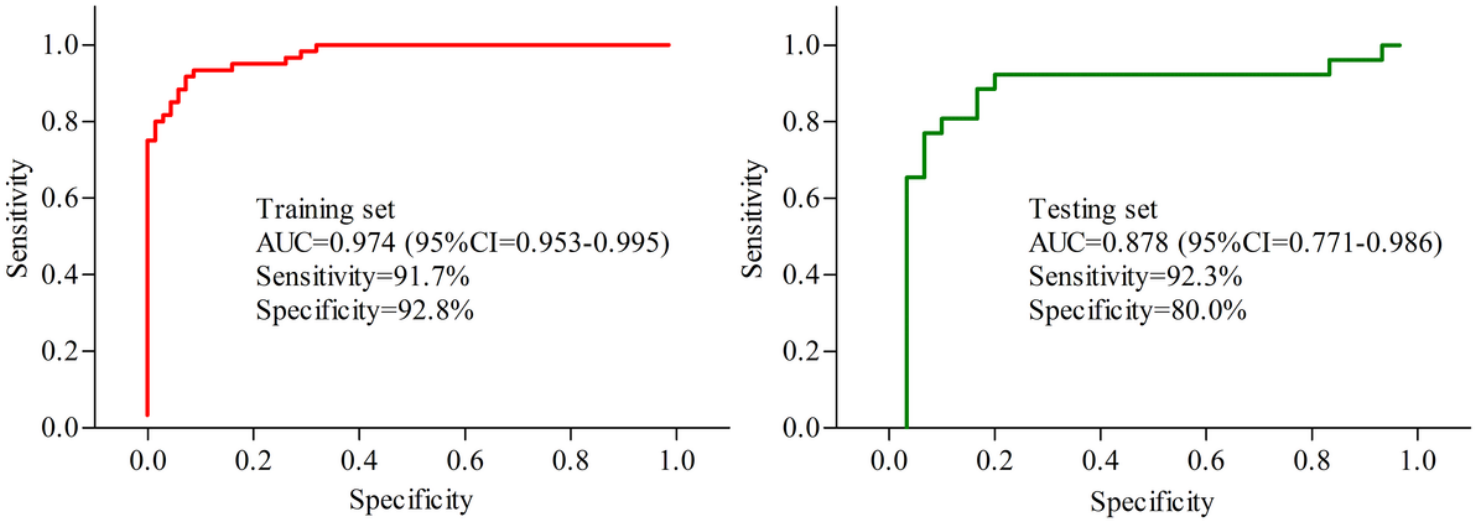

Figure 2

Diagnostic performance of the potential biomarker panel consisting of AAT, ALB and APOA

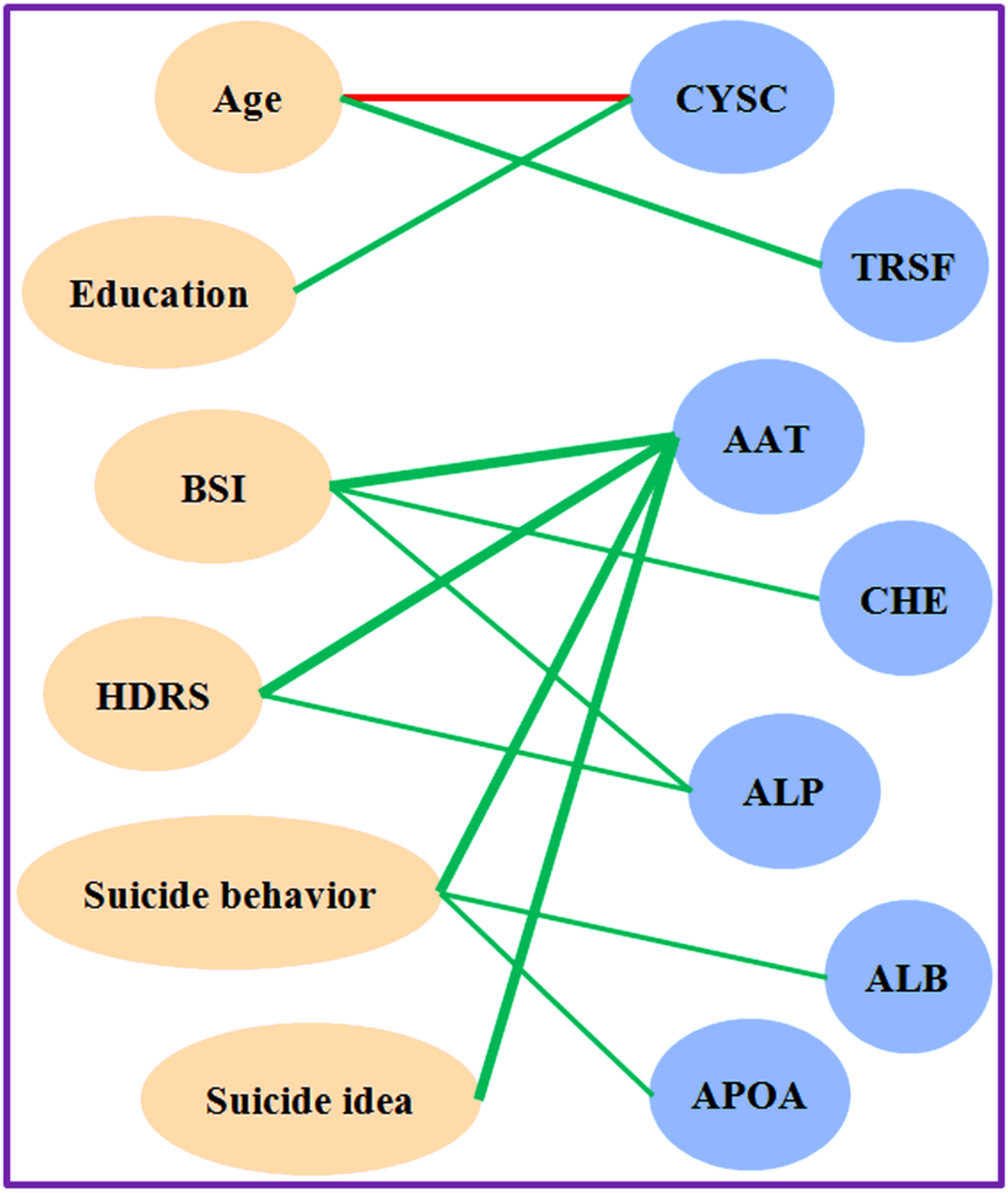

Figure 3

Correlations between demographic data and differential variables between MDD patients and HCs. Green and red line indicated the negative and positive correlation, respectively. The thicker the line, the greater the absolute value of the correlation coefficient.

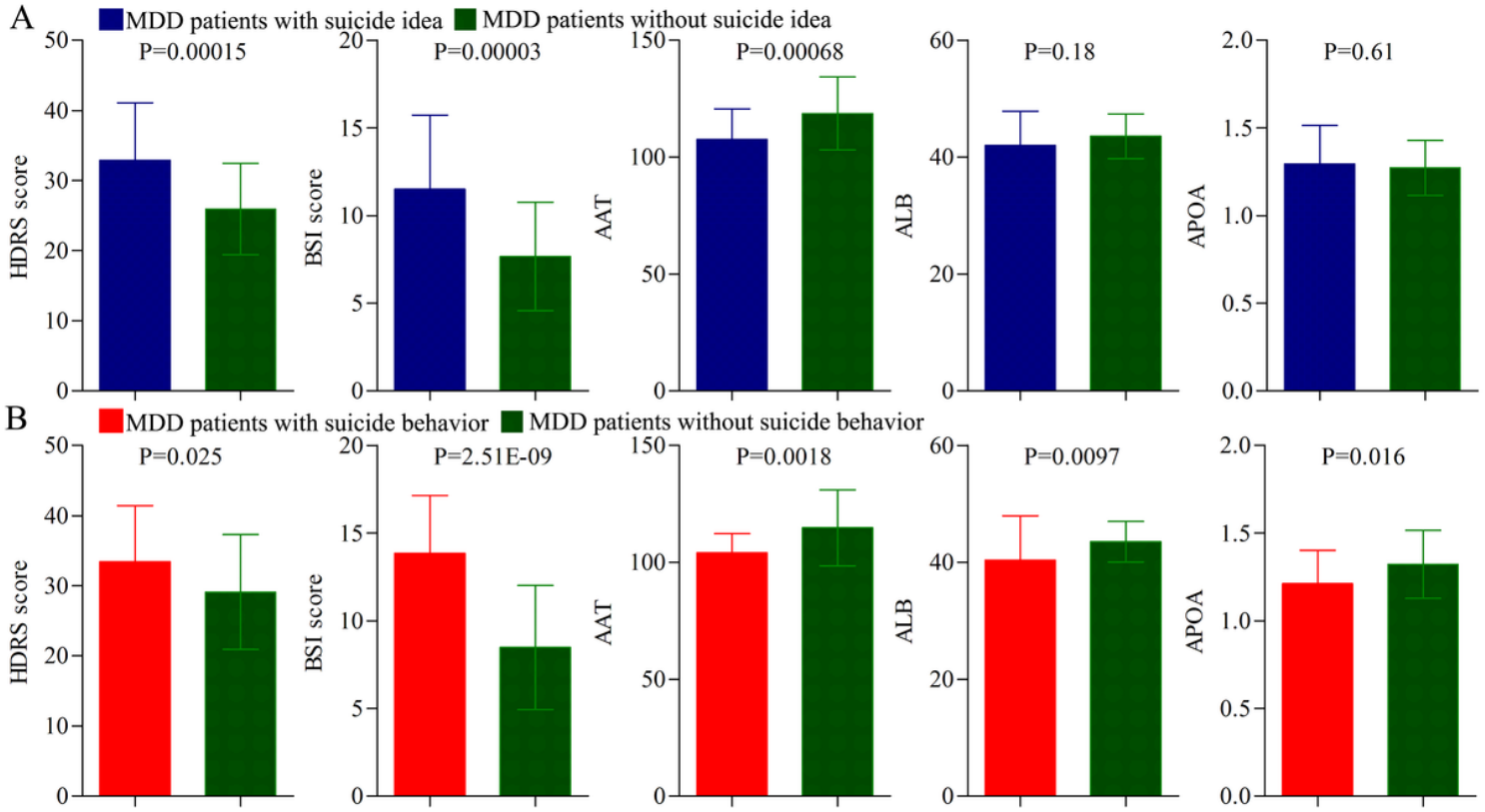

Figure 4

Differential analyses of MDD patients with suicide idea or behavior. A) average HDRS score, BSI score and AAT level were significantly different in MDD patients with suicide idea compared to MDD patients without suicide idea. B) average HDRS score, BSI score, AAT level, ALB and APOA level were significantly different in MDD patients with suicide behavior compared to MDD patients without suicide behavior.

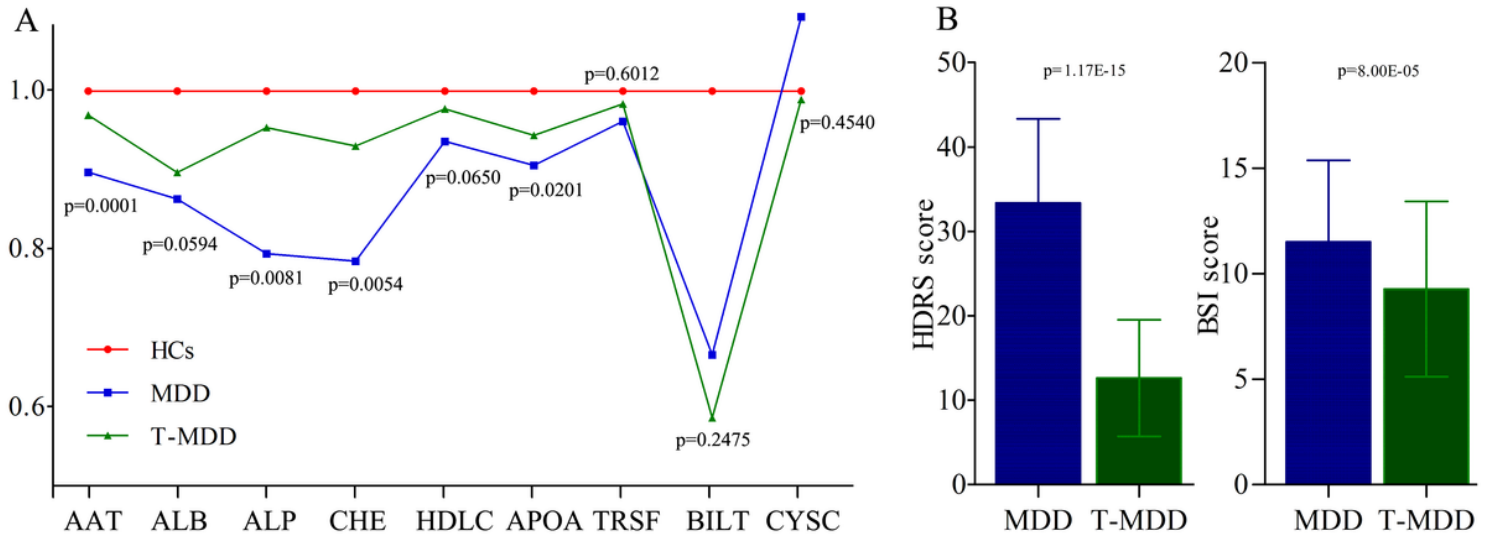

Figure 5

Changes of differential variables, HDRS and BSI scores after treatment. A) eight of nine differential variables in MDD patients were improved after treatment. B) both average HDRS score and BSI score

were significantly decreased after treatment.