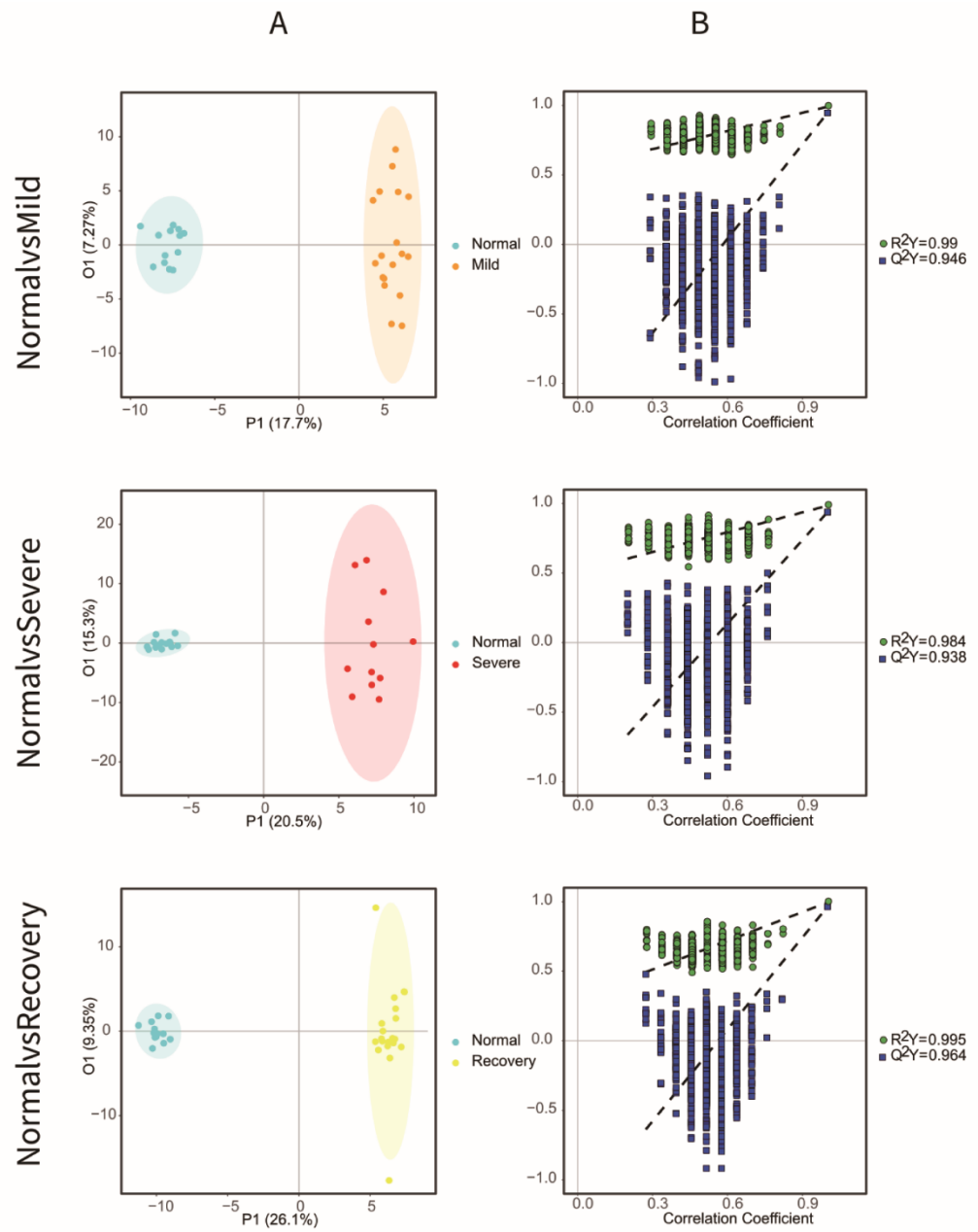

Figure S1. Untargeted metabolism analyses were performed using sera obtained from subjects of different stages: normal, mild, severe, and recovery. (A) OPLS-DA score plots for mild, severe and recovery group, compared to normal group. (B) 999 permutation tests to evaluate the quality of the OPLS-DA model.

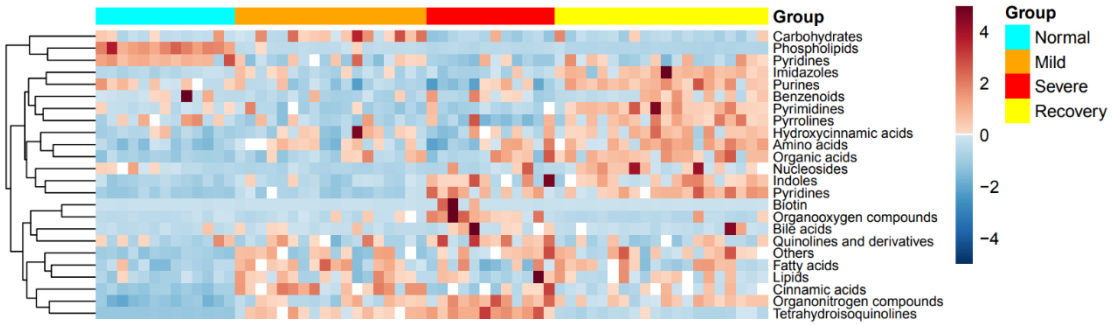

Figure S2. 193 selected metabolites in the discovery cohort by untargeted metabolomics were classified and presented in the heatmap (related to figure 1-C).

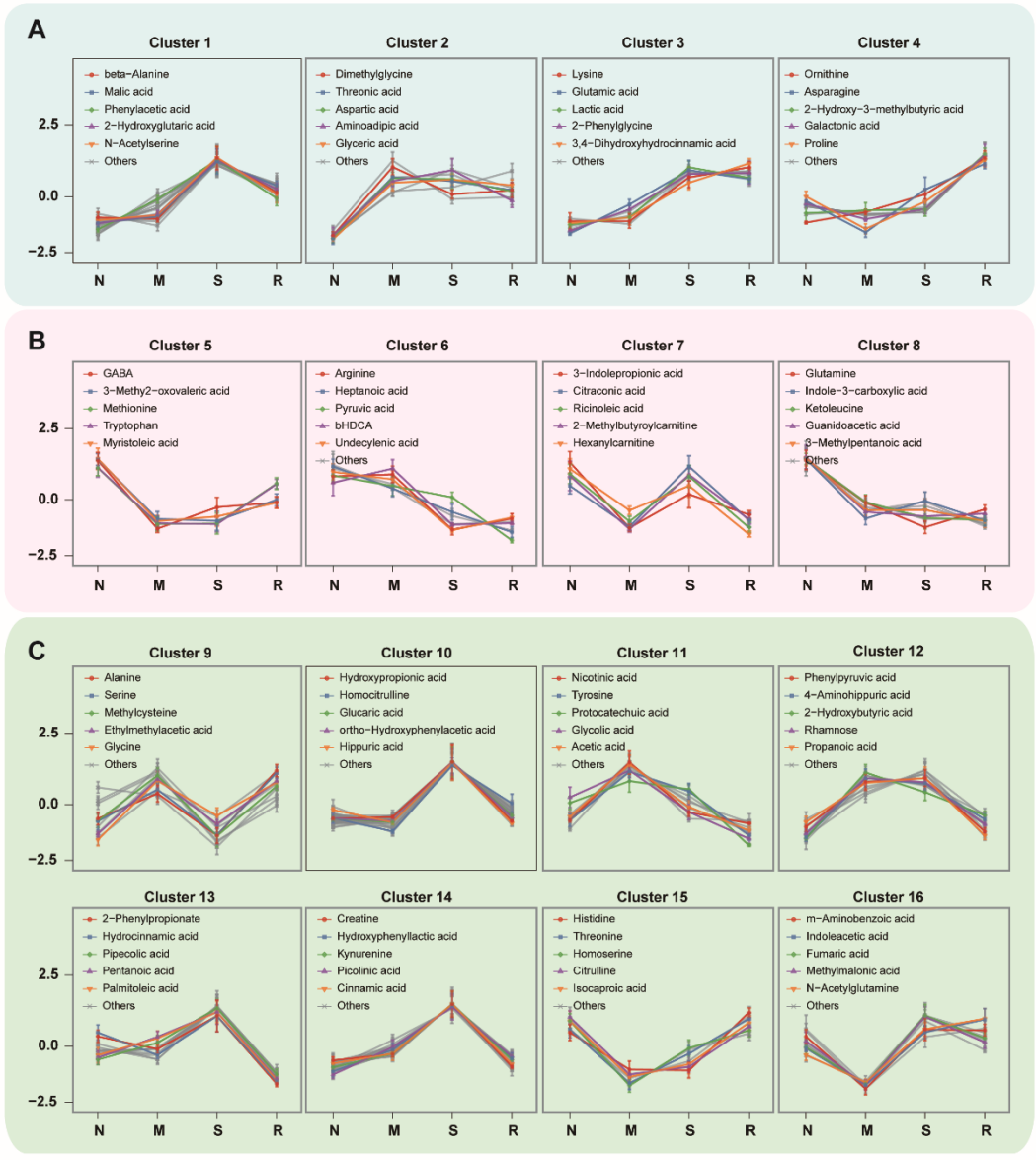

Figure S3. Targeted metabolomic analysis revealed different trends of metabolites in the discovery cohort among different stages. Targeted metabolomic analysis quantified 199 metabolites from sera of the four groups and the data were clustered into 16 discrete clusters using mFuzz, to illustrate the relative expression changes in different groups. All 199 metabolites and the respective cluster of each were listed in table S4. Five metabolites of each cluster were randomly selected and listed at the upper right corner. The 16 clusters were classified into three groups, according to the level of metabolites in recovery groups: (A) higher than normal; (B) lower than normal; (C) on par with normal. The characters on X axis represented different groups: N: Normal; M: Mild; S: Severe; R: Recovery.

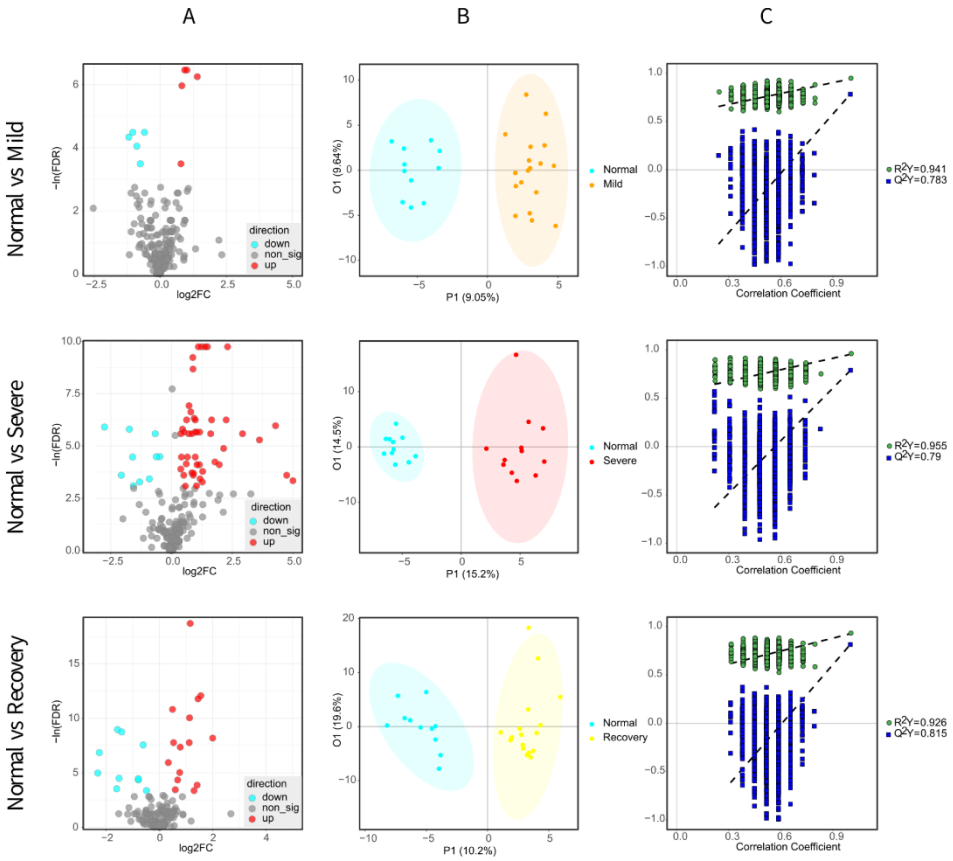

Figure S4. Targeted metabolomic analyses were performed using sera obtained from the discovery cohort. (A) Volcano plots highlighted differential metabolites of subjects in mild, severe and recovery groups, compared to normal group. (B) OPLS-

DA score plots for mild, severe and recovery group, compared to normal group. (C) 999 permutation tests to evaluate the quality of the OPLS-DA model.

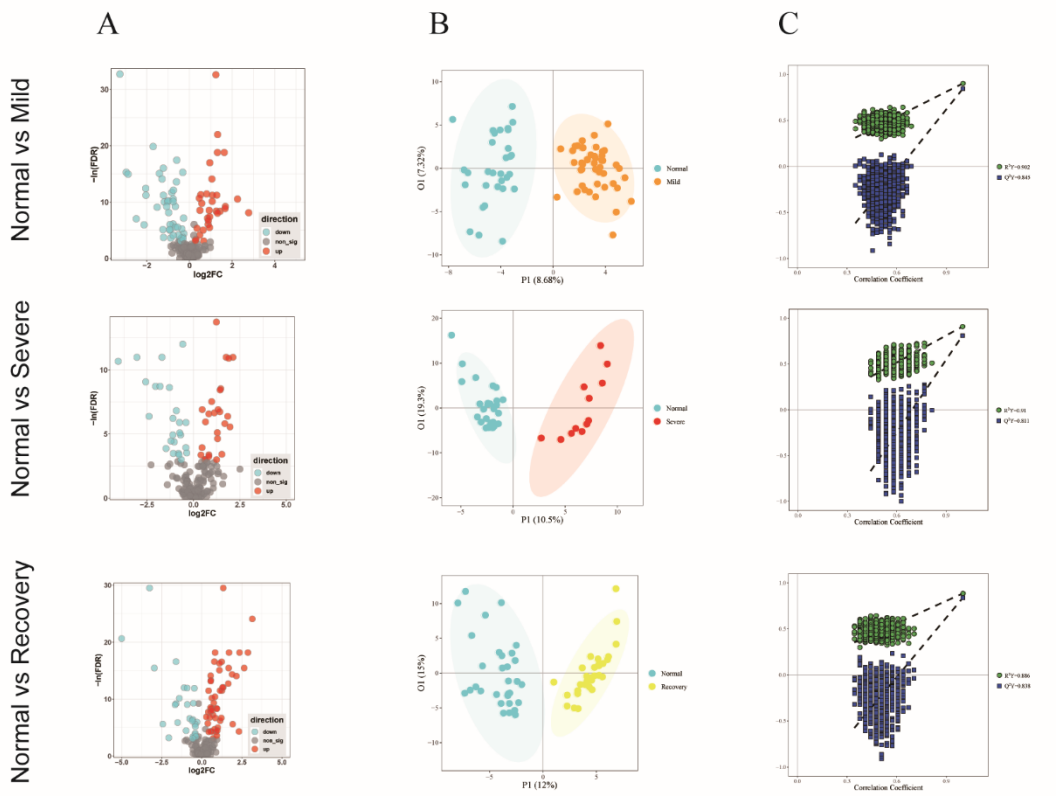

Figure S5. Targeted metabolomic analyses were performed using sera obtained from the validation cohort. (A) Volcano plots highlighted differential metabolites of subjects in mild, severe and recovery groups, compared to normal group. (B) OPLS-DA score plots for mild, severe and recovery group, compared to normal group. (C) 999 permutation tests to evaluate the quality of the OPLS-DA model.

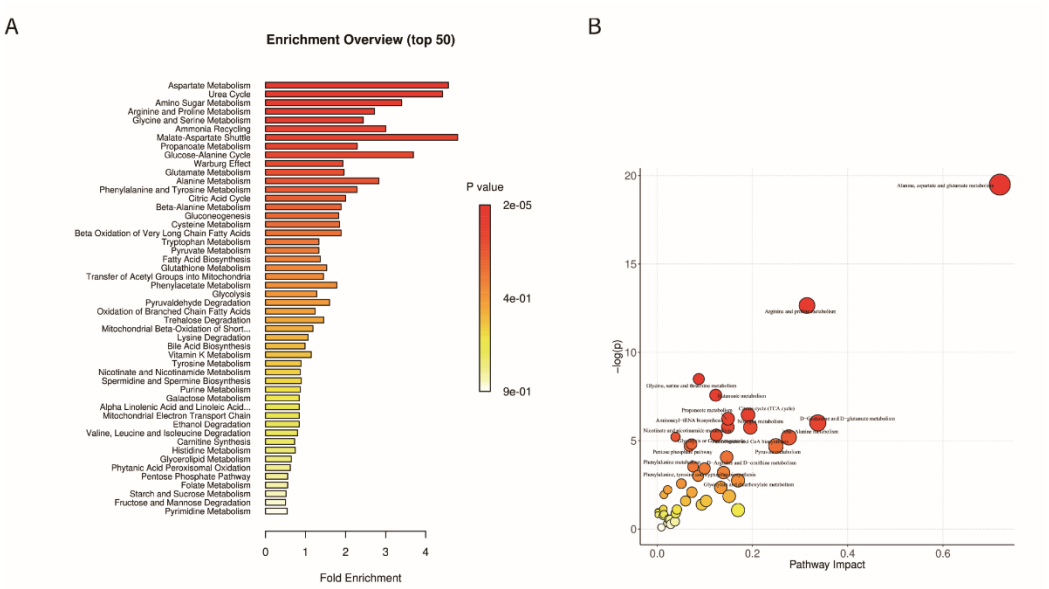

Figure S6. Pathway enrichment analysis of the discovery cohort by targeted metabolomics using SMPDB (A) or KEGG (B) (related to figure 2).

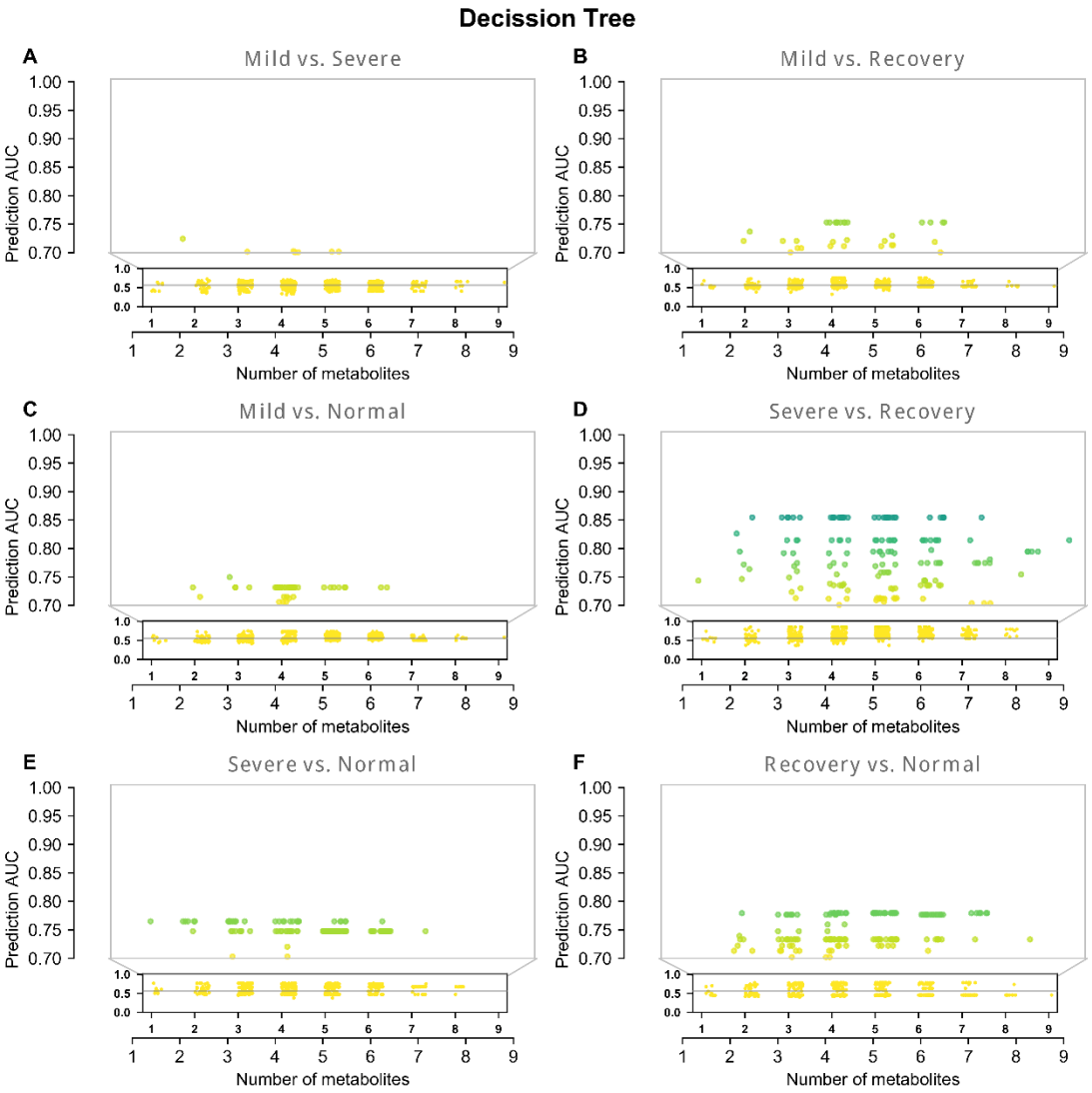

Figure S7. The scatter plots of AUC in distinguishing different stages using 1-9 metabolites in decision tree.

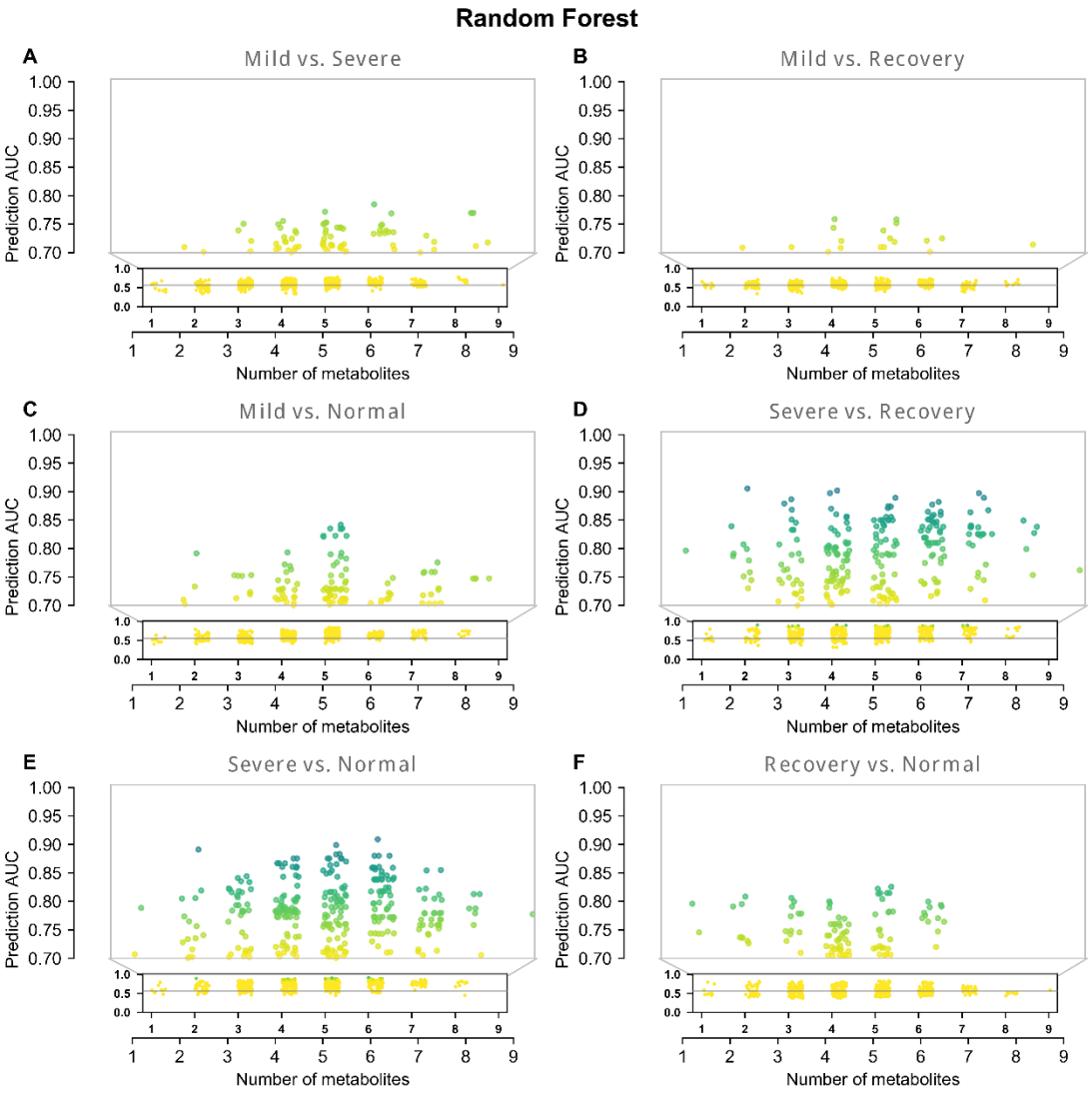

Figure S8. The scatter plots of AUC in distinguishing different stages using 1-9 metabolites in random forest.

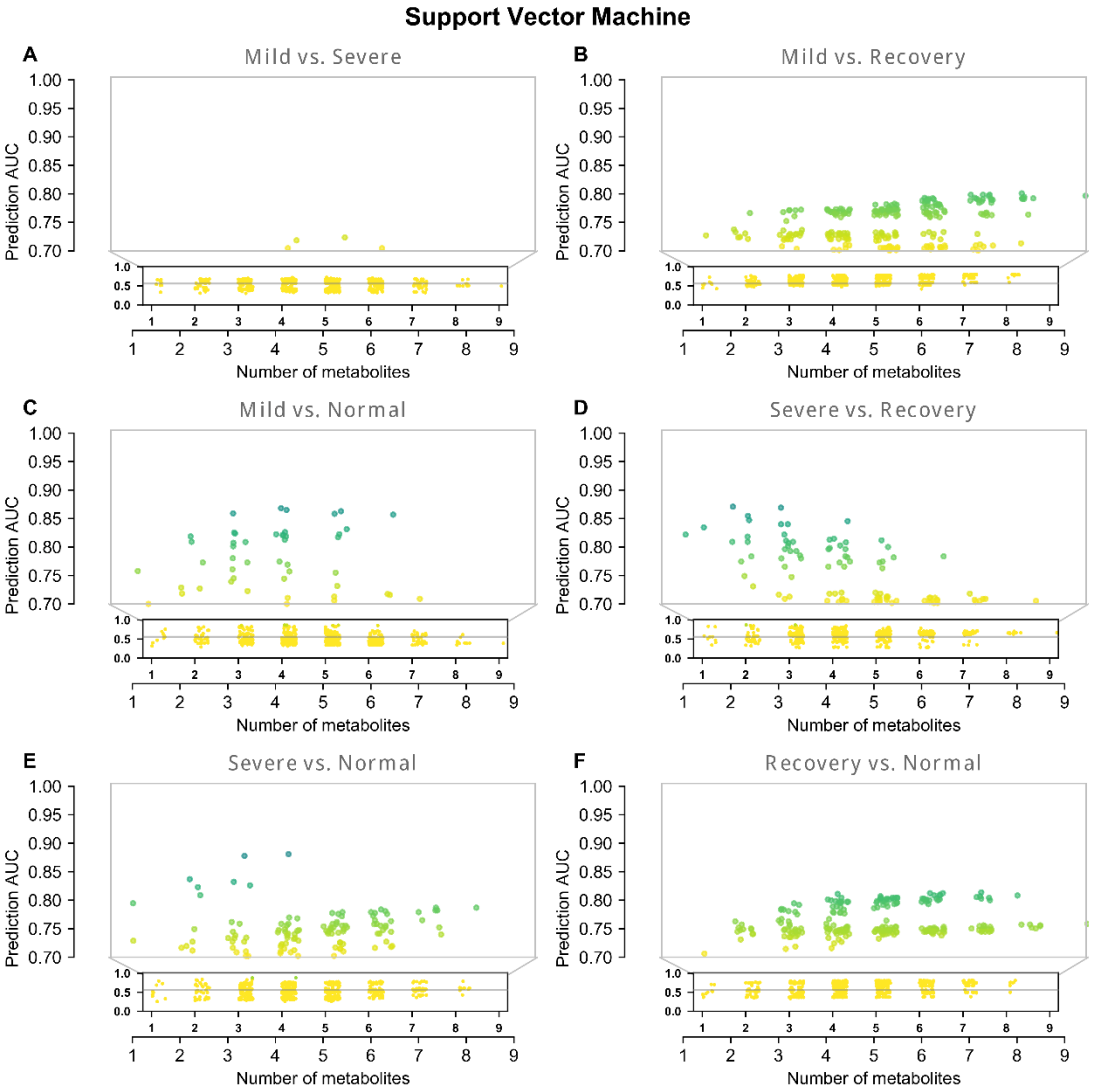

Figure S9. The scatter plots of AUC in distinguishing different stages using 1-9 metabolites in support vector machine.

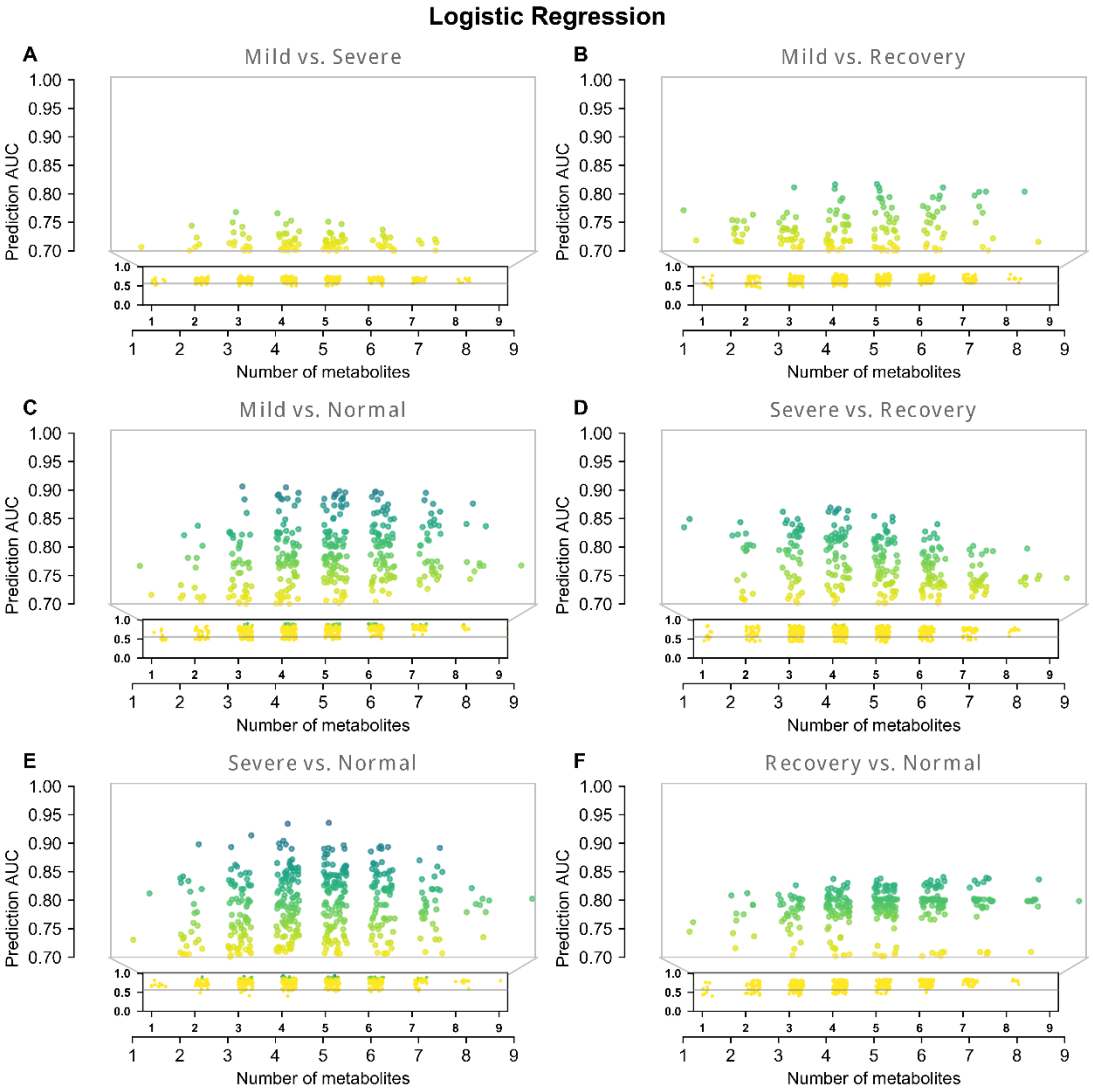

Figure S10. The scatter plots of AUC in distinguishing different stages using 1-9 metabolites in logistic regression.

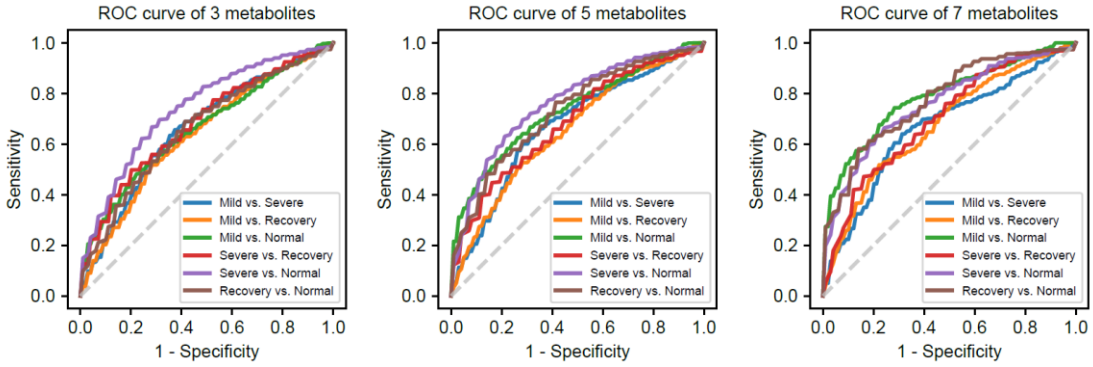

Figure S11. Mean AUC for logistic regression using 1, 3, 5, and 7 metabolites.

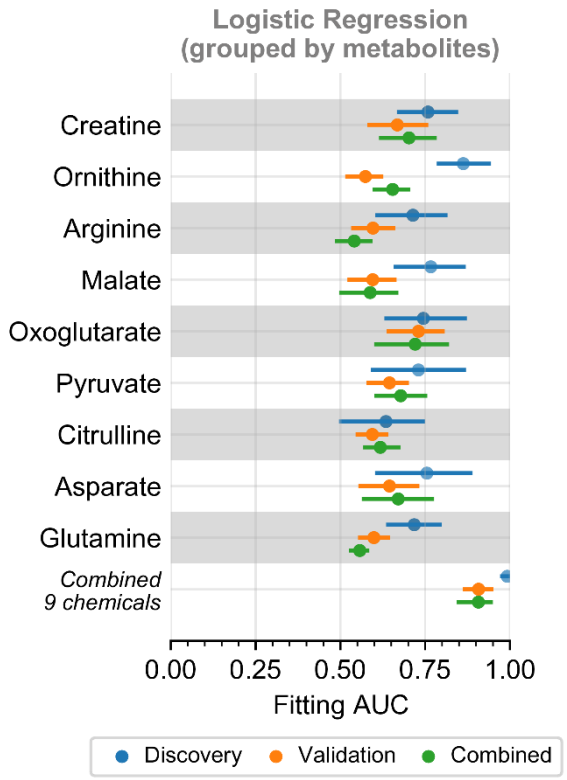

Figure S12. The pooled AUC for the prediction accuracy of disease status using metabolite biomarkers.

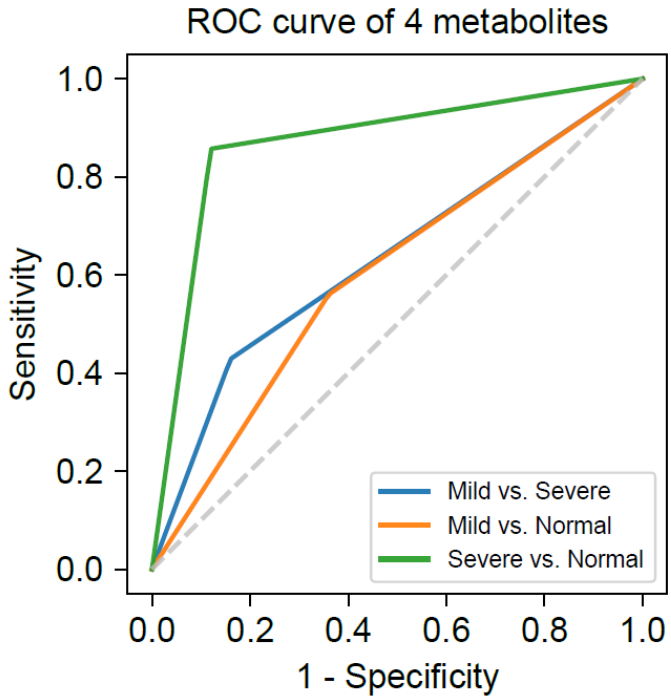

Figure S13. AUC of logistic regression model validated using data in Shen et.al. paper

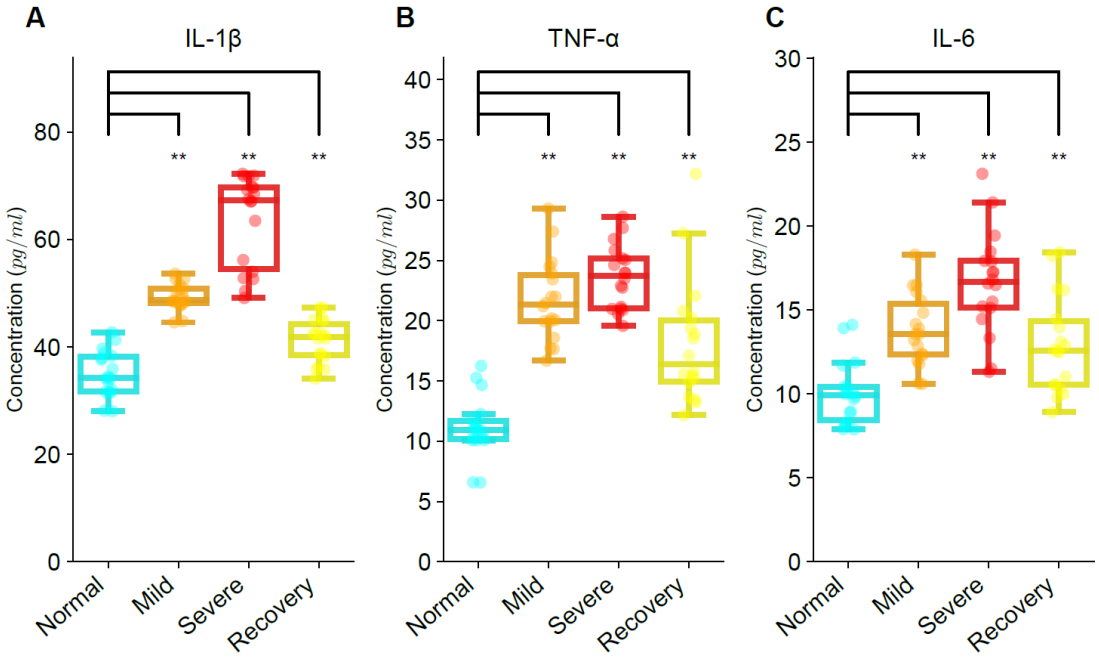

Figure S14. Level of IL-1β, TNF-α and IL-6 detected in sera of different groups in the validation cohort. (A) showed IL-1β. (B) and (C) showed TNF-α, IL-6 respectively.

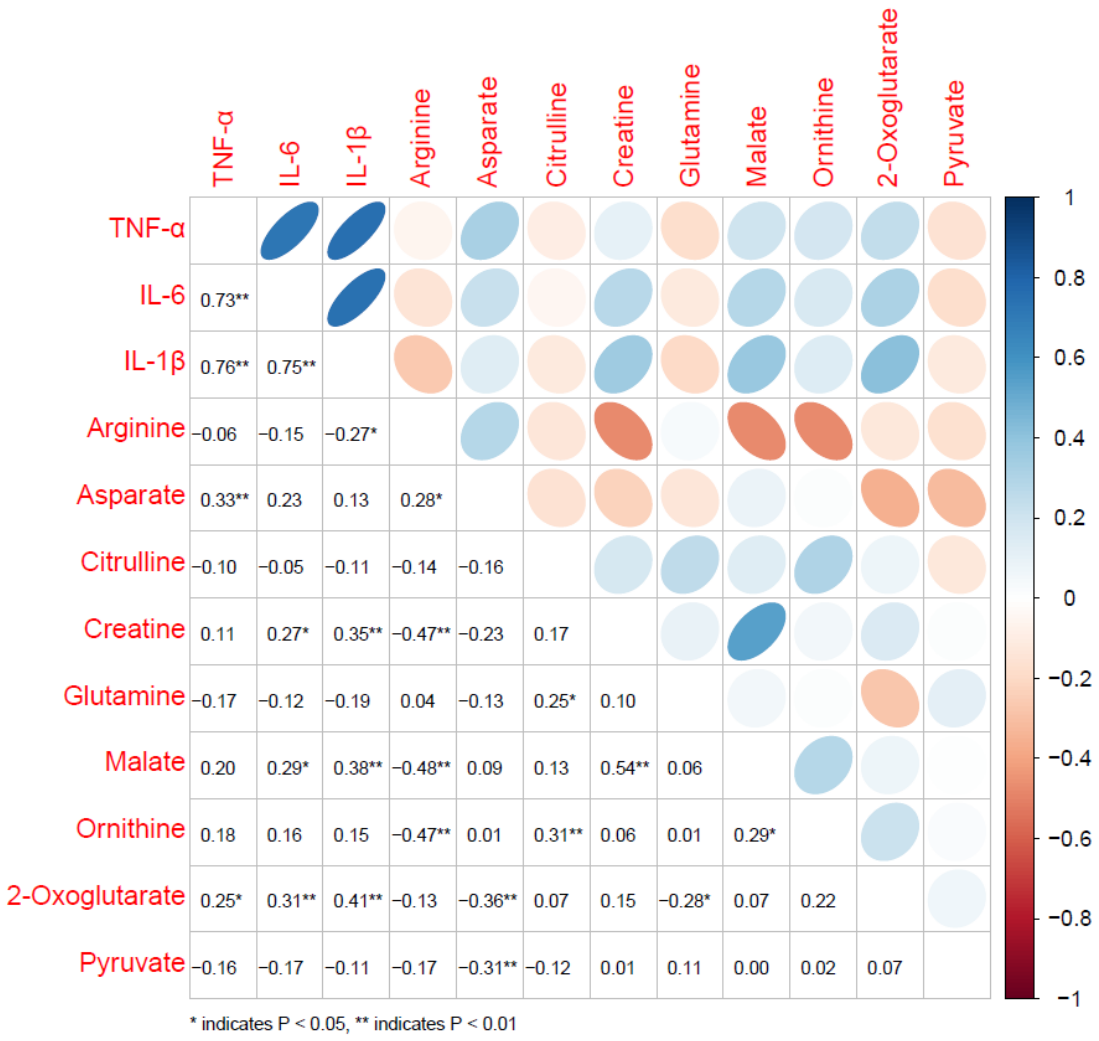

Figure S15. Correlation analysis of the 9 metabolites versus 3 cytokines for patients in normal, mild, severe and recovery group. Among 9 metabolites, asparate was found positively correlated with TNF-α while malate and creatine correlated with IL-6 and IL-1β. 2-oxoglutarate was found to have positive correlations with all three cytokines. The result was obtained by Pearson correlation coefficient analysis.