Prediction of Efficacy of Taeumjowi-Tang for Treatment of Metabolic Risk Factors Based on Machine Learning

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Abstract: Herbal medicine is widely prescribed worldwide. To date, however, studies on the prediction of efficacy of herbal medicine based on machine learning have very rarely been reported. The objectives of this study are to predict the efficacy of Taeumjowi-tang (one of herbal medicines) and evaluate the prediction model in treating metabolic abnormalities. Subjects were divided into an improvement group and a non-improvement group based on the difference before and after oral administration of an herbal medicine. Efficacy models of triglyceride level, high-density lipoprotein (HDL) cholesterol level, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were built using a least absolute shrinkage and selection operator (LASSO) based on variables extracted from face shape, face colors, body circumference, questionnaire, voice, and tongue color. In predicting efficacy for four metabolic risk factors, the efficacy model of HDL cholesterol level showed the best the area under the receiver operating characteristic curve (AUC) value among the four models (AUC = 0.785 (confidence interval = 0.693, 0.877)). The AUC value of the efficacy model of triglyceride level was 0.659 (0.551, 0.768). Efficacy models of DBP and SBP showed AUC values of 0.665 (0.551, 0.78) and 0.54 (0.385, 0.694), respectively. The results may provide a clue to predict whether a drug will be effective for each subject with phenotypic information and to reduce the use of an ineffective drug or its side effects.

Keywords: efficacy prediction; herbal medicine; machine learning; metabolic risk factors; anthropometry

1. Introduction

Generally, obesity and adiposity are related to hypertension, hypertriglyceridemia, hypo-HDL cholesterolemia, type 2 diabetes, cancer, and cardiovascular diseases [1–5]. Therefore, a reduction in obesity decreases the risk of these metabolic abnormalities [1–3]. Herbal medicines are often prescribed for obesity reduction. In traditional Korean medicine, Taeumjowi-tang is one of most well-known herbal medicines, and many studies have reported that Taeumjowi-tang is effective for weight reduction in humans and mice [6–14]. For example, for the assessment of efficacy and safety of Taeumjowi-tang, several studies have performed experiments to identify the changes in anthropometric indices and blood parameters such as body fat mass, weight, waist circumference, fasting glucose concentration, total cholesterol, HDL and LDL cholesterol levels, and triglyceride. These studies have reported that Taeumjowi-tang was effective for reducing weight, total cholesterol levels, and atherogenic index and that adverse effects of this medicine were

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not found [6,10,15]. However, although many studies have been performed, most of these previous studies examined only changes in anthropometric indices and blood parameters after dose intake of herbal medicine. To date, no study has predicted the individual efficacy response to herbal medicine. There are cases where an effect may or may not appear after taking the herbal medicine. Additionally, side effects may also appear after taking herbal medicine or a drug. Therefore, predicting the efficacy of herbal medicine is very important for determining whether it is taken. The objectives of this study were to build prediction models of the efficacy of Taemujowi-tang with the subject’s phenotypic information for personalized treatment of metabolic abnormalities. Through the development of these models, we can predict whether the drug will be effective and reduce the use of an ineffective drug or its side effects. This study is the first to report a prediction model of the efficacy of Taemujowi-tang in traditional medicine or herbal medicine.

2. Materials and Methods

2.1. Subjects

Data used in this study were obtained from the Cheonan Oriental Hospital and Dunsan Oriental Hospital of Daejeon University. The study to collect the data was approved by the Institutional Review Boards at the Cheonan Oriental Hospital and Dunsan Oriental Hospital of Daejeon University (Approval numbers: DJUMC-2018-DR-01 and DJDSKH-18-DR-24) and was conducted in accordance with the Declaration of Helsinki. Written informed consent for participation in the study was obtained from all subjects. Inclusion criteria for subjects were: (1) persons diagnosed with Taeeum-in by the Sasang Constitutional Analysis Tool [16,17]; (2) BMI of 23 or higher; (3) abdominal circumference of 90 cm or more in men and 85 cm or more in women; and (4) people who have risk factors for metabolic syndrome. A total of 206 subjects participated in this study. We excluded subjects with (1) missing or error values regarding blood tests or questionnaire; (2) missing values regarding measurements of anthropometry, facial shape, face color, or tongue color; and (3) missing values regarding demographic information. Furthermore, we excluded male subjects because the number of male subjects was very small for analysis. Ultimately, a total of 98 females were included in the models and analyses for efficacy prediction. The number of subjects in each model is shown in Table 1, and sample selection procedure is shown in Figure 1.

### Table 1. Baseline characteristics of the study subjects according to metabolic risk factors.

| Variables | SBP | DBP | TG | HDL |
|-----------|-----|-----|----|-----|
| Number of subjects | 98  | 50  | 50 | 50  |
| Age (years) | 36.0±10.49 | 34.0±10.49 | 34.0±10.49 | 34.0±10.49 |
| BMI (kg/m²) | 25.0±3.47 | 25.0±3.47 | 25.0±3.47 | 25.0±3.47 |
| Height (cm²) | 159.0±5.84 | 159.0±5.84 | 159.0±5.84 | 159.0±5.84 |
| Weight (kg) | 74.0±10.92 | 74.0±10.92 | 74.0±10.92 | 74.0±10.92 |
| SBP (mmHg) | 127.0±10.65 | 127.0±10.65 | 127.0±10.65 | 127.0±10.65 |
| DBP (mmHg) | 78.0±8.31 | 78.0±8.31 | 78.0±8.31 | 78.0±8.31 |
| Pulse rate (beats per minute) | 75.0±9.13 | 75.0±9.13 | 75.0±9.13 | 75.0±9.13 |
| HDL (mg/dL) | 55.0±11.19 | 55.0±11.19 | 55.0±11.19 | 55.0±11.19 |
| Triglyceride (mg/dL) | 141.0±7.48 | 141.0±7.48 | 141.0±7.48 | 141.0±7.48 |
| LDL (mg/dL) | 123.0±31.12 | 123.0±31.12 | 123.0±31.12 | 123.0±31.12 |
| HDL (mg/dL) | 55.0±11.19 | 55.0±11.19 | 55.0±11.19 | 55.0±11.19 |
| Red Blood Cell (10⁹/L) | 4.4±0.30 | 4.4±0.30 | 4.4±0.30 | 4.4±0.30 |
| Hemoglobin (g/dL) | 13.0±1.04 | 13.0±1.04 | 13.0±1.04 | 13.0±1.04 |
| Fasting blood sugar (mg/dL) | 98.0±15.26 | 98.0±15.26 | 98.0±15.26 | 98.0±15.26 |
| Free thyroxine (mg/dL) | 1.25±0.16 | 1.25±0.16 | 1.25±0.16 | 1.25±0.16 |
| Blood Urea Nitrogen (mg/dL) | 12.0±3.12 | 12.0±3.12 | 12.0±3.12 | 12.0±3.12 |
| Creatinine (mg/dL) | 0.73±0.08 | 0.73±0.08 | 0.73±0.08 | 0.73±0.08 |
| AST (IU/L) | 22.0±8.17 | 22.0±8.17 | 22.0±8.17 | 22.0±8.17 |
| ALT (IU/L) | 23.0±12.3 | 23.0±12.3 | 23.0±12.3 | 23.0±12.3 |
| Total bilirubin (mg/dL) | 0.59±0.25 | 0.59±0.25 | 0.59±0.25 | 0.59±0.25 |
| White blood cell (10⁹/L) | 6.2±1.51 | 6.2±1.51 | 6.2±1.51 | 6.2±1.51 |
| Smoking | Never smoked | 93 (94.9) | 76 (79) | 11 (11) | 46 (46.93) |
| Smoking | 4 (4.08) | 3 (3.75) | 1 (1.06) | 0 (0) | 46 (46.93) |
| Quit smoking | 1 (1.02) | 1 (1.02) | 1 (1.02) | 1 (1.02) | 46 (46.93) |
| Exercise | No | Yes |
|----------|----|-----|
|          | 65 (66.33) | 33 (33.67) |
|          | 53 (66.25) | 27 (33.75) |
|          | 12 (66.67) | 6 (33.33) |
|          | 42 (65.63) | 22 (34.38) |
|          | 23 (67.65) | 11 (32.35) |
|          | 33 (68.75) | 15 (31.25) |
|          | 32 (64.00) | 16 (32.00) |
|          | 35 (70.00) | 18 (36.00) |
|          | 30 (62.5)  | 15 (30.00) |

| SBP_efficacy | No | Yes |
|--------------|----|-----|
|              | 53 (54.08) | 45 (45.92) |
|              | 48 (60) | 32 (40) |
|              | 13 (72.22) | 13 (72.22) |
|              | 25 (39.06) | 25 (39.06) |
|              | 20 (38.2) | 20 (38.2) |
|              | 29 (60.42) | 29 (60.42) |
|              | 16 (32.00) | 16 (32.00) |
|              | 21 (42.00) | 21 (42.00) |
|              | 24 (50.00) | 24 (50.00) |

| DBP_efficacy | No | Yes |
|--------------|----|-----|
|              | -2.35 ± 6.65 | -2.35 ± 6.65 |
|              | -1.45 ± 6.14 | -1.45 ± 6.14 |
|              | -6.33 ± 7.51 | -6.33 ± 7.51 |
|              | 1.33 ± 4.23 | 1.33 ± 4.23 |
|              | -0.26 ± 4.49 | -0.26 ± 4.49 |
|              | -1.75 ± 7.48 | -1.75 ± 7.48 |
|              | -2.92 ± 5.75 | -2.92 ± 5.75 |
|              | -3.14 ± 6.60 | -3.14 ± 6.60 |
|              | -1.52 ± 6.66 | -1.52 ± 6.66 |

* p < 0.05; ** p < 0.01; † p < 0.001. *, ** and † indicate p-values of difference between non-improvement group and improvement group. *, ** and † were obtained from two sample t-test for continuous variables and from Fisher’s exact test for categorical variables. Variables are summarized as the mean ± SD (standard deviation) and the number (percentage) for continuous and categorical variables, respectively. SBP: systolic blood pressure, DBP: diastolic blood pressure, HbA1c: Hemoglobin A1c, TG: Triglyceride, LDL: Low-Density Lipoprotein Cholesterol, HDL: High-Density Lipoprotein Cholesterol, AST: aspartate aminotransferases, ALT: alanine aminotransferase, SBP_efficacy: differences between the improvement group and the non-improvement group in SBP, DBP_efficacy: differences between the improvement group and the non-improvement group in DBP, TG_efficacy: differences between the improvement group and the non-improvement group in TG, HDL_efficacy: differences between the improvement group and the non-improvement group in HDL.

Figure 1. Sample selection procedure.

2.2. Definition

All patients took the Taeumjowi-tang for 12 weeks (three times a day). Patients were divided into an improvement group and a non-improvement group according to the improvement or lack of improvement of metabolic risks after oral administration of herbal medicine (Taeumjowi-tang). Improvement of the triglyceride level was defined as a reduction of more than 6% compared with the triglyceride level at baseline. Improvement of the HDL cholesterol level was defined as an increase of more than 2% compared with the HDL cholesterol level at baseline. For these criteria, we referred to the effects on the triglyceride level by Lovastatin drug and on HDL cholesterol by Pravastatin drug [18]. We defined that Taeumjowi-tang was effective (improvement group) if it worked as much as the minimum values of Lovastatin and Pravastatin efficacy. Additionally, we defined improvement of SBP and DBP as a reduction of more than 10 mmHg and 5 mmHg, respectively, compared to SBP and DBP at baseline [19]. If these criteria were not met, the patients were assigned to the non-improvement group.
2.3. Measurements

Our experiments used several types of variables, such as facial shape and color, voice signal, tongue color, questionnaire, and anthropometry. For facial characteristics and color measurements, the 3D face model of the participant was scanned at various viewing angles using an RGB-D camera (Intel® RealSense™ Depth Module SR300) to extract the morphological profiles and colors of the face [20–22]. Each participant was requested to open his/her eyes, close his/her mouth and maintain a neutral expression in a fixed posture during the 3D scan. The 3D facial features were extracted after image preprocessing, based on the iterative closest point (ICP) algorithm [20]. From the 3D face image, many facial features were selected, such as overall face outline, eyebrow, medial/lateral canthus, pupil, nasal tip/base, and lip fissure, in front and profile view angle. The vertical and horizontal distance variables were calculated using the facial features [16,17,23].

For tongue color measurement, tongue images were acquired by a computerized tongue image acquisition system (TAS-4000, Korea Institute of Oriental Medicine, Daejeon, Korea). The tongue images were divided into root, center, side, and tip areas after the color correction step was performed. Each area was divided into tongue body and coating areas by specific color value thresholding [24]. Since the center and the tip area often had a small proportion of coating area, these areas were analyzed as whole areas, not divided into the tongue body and coating area. Images of the tongue body, coating of each tongue area and teeth marks are shown in the Supplementary Materials (Figures S1 and S2). All the color features are represented by the Commission Internationale de L’éclairage (CIE) L*a*b* color space. The mean values of the three-color components were set to the values representing the characteristics of the tongue in each area. In addition to the color value, the ratio of the coated area and strength of the teeth marks [25] were also used as tongue features. Detailed explanations of facial features and tongue color showed in the Supplementary Materials (Figures S1 and S2).

For voice measurement, voice recording was performed in a room with a noise level below 40 dB. The subjects sat comfortably and were able to maintain the speed and lip opening as they naturally speak. They were asked to pronounce five vowels ("a", "e", "i", "o", "u") with a certain amount of power. Then, a sentence was pronounced twice. We extracted candidate vocal features, including fundamental frequencies, MFCC (Mel-frequency cepstral coefficients), and duration time. A detailed feature list is found in [26].

For anthropometry and questionnaires, body weight and height of subjects were measured to the nearest 0.1 kg and 0.1 cm, respectively, with very lightweight clothing and without shoes, and body mass index was calculated using weight and height. Circumferences of each subject’s body were measured at eight positions: forehead, neck, axilla, chest, ribs, waist, pelvis, and hips. Based on these 8 circumferences, we created several variables (circumference ratios) through calculation of circumference ratios between two positions, such as waist-to-hip circumference ratio and neck-to-waist circumference ratio. Detailed information on this anthropometry measurement has been described in previous studies [27–31]. The questions of questionnaire used in this study are described in Table 2.

| Model     | Variables     | Description                                      |
|-----------|---------------|--------------------------------------------------|
| SBP-efficacy | FDV_52_50    | Vertical distance between 52 and 50 in a frontal face image |
|           | FVV_47_52_81_50 | Vertical distance between 47 and 52/vertical distance between 81 and 50 in a frontal face image |
|           | FVD_81_50_94_194 | Vertical distance between 81 and 50/distance between 94 and 194 in a frontal face image |
|           | FVD_81_51_94_194 | Vertical distance between 81 and 51/distance between 94 and 194 in a frontal face image |
| DBP-efficacy | BodyCenter_a | The mean value of the CIE a* color at the center of the tongue body |
|           | FurCenter_a  | The mean value of the CIE a* color at the center of the coated tongue |
2.4. Statistical Analysis

All statistical analyses were performed by implementation using R 4.0.0 (Arbor Day) and applied to a significance level of $\alpha = 0.05$. Variables were summarized as the mean ± standard deviation (SD) and percentage for continuous variables and categorical variables, respectively. To compare differences between the improvement group and the non-improvement group for SBP, an independent two-sample $t$-test and Fisher’s exact test were performed for continuous variables and categorical variables, respectively. Analyses using the same methods as above for SBP were performed to compare differences between the improvement group and the non-improvement group for each metabolic risk, such as DBP, HDL cholesterol level, and triglyceride level.

To investigate the association of the efficacy response to Taeumjowi-tang for metabolic risks with individual variables of face shape, colors of the face, body circumference, questionnaire, voice, and tongue color, binary logistic regressions were applied in crude form and after adjusting for age and BMI after standardization of data. Odds ratios are
shown with 95% confidence intervals and \( p \)-values for each model. The area under the receiver operating characteristic (ROC) curve (AUC) analyses were applied to evaluate the accuracy of the binary logistic regression models.

To analyze the association between the efficacy response to Taemujowi-tang for metabolic risks and the combined variables of face shape, colors of the face, body circumferences, questionnaire, voice, and tongue color, the least absolute shrinkage and selection operator (LASSO) was applied based on 38 variables. LASSO implemented selecting reliable combined variables among many correlated variables and reducing model complexity. Four LASSO models were established, as follows: Model 1 included the efficacy response to Taemujowi-tang for SBP; Model 2 included the efficacy response to Taemujowi-tang for DBP; Model 3 included the efficacy response to Taemujowi-tang for HDL cholesterol level; Model 4 included the efficacy response to Taemujowi-tang for triglyceride level. To assess the accuracy of the LASSO models, ROC curves were obtained. All variables selected by LASSO in each model are described in Table 2.

3. Results

Figure 2 shows the prediction results for efficacy models of four metabolic risk factors. In the experiments using a combination of variables selected from different variable sets, the AUC values for efficacy models of four metabolic risk factors ranged from 0.54 to 0.785. The efficacy model of the HDL cholesterol level showed the best AUC value among the four models (AUC = 0.785 (confidence interval = 0.693, 0.877)). The AUC value of the efficacy model of triglyceride level was 0.659 (0.551, 0.768), while the efficacy model of DBP showed an AUC value of 0.665 (0.551, 0.78) and the efficacy model of SBP indicated the lowest AUC value (AUC = 0.54 (0.385, 0.694)).

![Figure 2](image-url)
Selected variables for the efficacy model differed according to the four metabolic risk factors. All variables selected by LASSO variable selection in each model of efficacy prediction are described in Table 3. Specifically, most of the included variables in each model for efficacy prediction showed a difference before and after treatment (namely, the difference according to efficacy response to oral administration). The efficacy model of triglyceride level included 5 variables. R83_84 was more strongly associated with the efficacy response to treatment ($p = 0.006$, odds ratio (OR) = 3.01 (1.37, 6.61), and AUC = 0.64 (0.53, 0.75)) than other indices within this model, and Q23, FHD_25_125_53_153, and sMFCC4 were associated with efficacy response ($p = 0.016$ and AUC = 0.48 (0.35, 0.60); $p = 0.03$, OR = 0.62 (0.40, 0.95), and AUC = 0.58 (0.47, 0.69); $p = 0.031$, OR = 1.6 (1.04, 2.45), and AUC = 0.61 (0.49, 0.72)). The efficacy model of HDL included 10 variables. Among these variables, Q5 and Q6 were more strongly associated with the efficacy response than other indices within the model ($p = 0.003$ and AUC = 0.53 (0.41, 0.65); $p = 0.001$ and AUC = 0.54 (0.41, 0.66)). PAi_72_73 and ChRD_b_avg, indicating angle and color in specific regions in the face, were highly associated with the efficacy response ($p = 0.009$, OR = 0.54 (0.34, 0.86), and AUC = 0.61 (0.5, 0.73); $p = 0.002$, OR = 2.08 (1.3, 3.35), and AUC = 0.67 (0.56, 0.78)). The efficacy model of DBP included a total of 6 variables. The Q10 variable was more strongly associated with the efficacy response than other indices included in this model ($p = 0.003$, AUC = 0.51 (0.38, 0.64)). In addition, the BodyCenter_a, FurCenter_a, FurRoot_a, and TotalRatio variables were highly associated with the efficacy response ($p = 0.017$, OR = 0.54 (0.33, 0.90), and AUC = 0.60 (0.48, 0.72); $p = 0.018$, OR = 0.59 (0.38, 0.91), and AUC = 0.6 (0.48, 0.72); $p = 0.019$, OR = 0.59 (0.38, 0.92), and AUC = 0.59 (0.47, 0.72); $p = 0.01$, OR = 1.83 (1.16, 2.90), and AUC = 0.61 (0.49, 0.72). Finally, the efficacy model of SBP included 4 variables. FVD_52_50, FVD_81_50_94_194 and FVD_81_51_94_194 were associated with the efficacy response ($p = 0.031$, OR = 1.83 (1.06, 3.17), and AUC = 0.61 (0.45, 0.76); $p = 0.014$, OR = 2.03 (1.15, 3.58), and AUC = 0.66 (0.51, 0.82); $p = 0.014$, OR = 2.10 (1.16, 3.80), and AUC = 0.63 (0.50, 0.77)). However, FVV_47_52_81_50 was not associated with the efficacy response in this model ($p = 0.9$, OR = 0.57 [0.30, 1.09], and AUC = 0.55 (0.42, 0.69)).

| Model         | Variables                        | Non-Improvement | Improvement | OR (95% CI) | p-Value | AUC (95%) |
|---------------|----------------------------------|-----------------|-------------|-------------|---------|-----------|
| SBP-efficacy  | FDV_52_50                        | 71.68 ± 3.81    | 73.96 ± 4.07 | 1.83 (1.06, 3.17) | 0.031   | 0.61 (0.45, 0.76) |
|               | FVV_47_52_81_50                   | 5.42 ± 1.50     | 4.76 ± 1.07  | 0.57 (0.30, 1.09) | 0.090   | 0.55 (0.42, 0.69) |
|               | FVD_81_50_94_194                 | 0.17 ± 0.01     | 0.18 ± 0.01  | 2.03 (1.15, 3.35) | 0.014   | 0.66 (0.51, 0.82) |
|               | FVD_81_51_94_194                 | 0.52 ± 0.03     | 0.54 ± 0.02  | 2.10 (1.16, 3.80) | 0.014   | 0.63 (0.50, 0.77) |
| DBP-efficacy  | BodyCenter_a                     | 28.42 ± 1.94    | 27.44 ± 1.61 | 0.54 (0.33, 0.90) | 0.017   | 0.60 (0.48, 0.72) |
|               | FurCenter_a                      | 19.43 ± 0.78    | 18.97 ± 0.98 | 0.59 (0.38, 0.91) | 0.018   | 0.6 (0.48, 0.72)  |
|               | FurRoot_a                        | 17.83 ± 1.16    | 17.19 ± 1.35 | 0.59 (0.38, 0.92) | 0.019   | 0.59 (0.47, 0.72) |
|               | Tip_a                            | 30.69 ± 4.12    | 28.75 ± 4.26 | 0.62 (0.40, 0.97) | 0.035   | 0.6 (0.48, 0.72)  |
|               | TotalRatio                       | 28.39 ± 12.33   | 36.69 ± 16.56 | 1.83 (1.16, 2.90) | 0.010   | 0.61 (0.49, 0.72) |
|               | Q_10                             |                 |              |              |         | 0.003     | 0.51 (0.38, 0.64) |
|               | Express                          | 29 (45.31)      | 6 (17.65)    | 1            |         |           |
|               | Moderate                         | 30 (46.88)      | 18 (52.94)   | 2.90 (1.01, 8.33) | 0.048   |           |
|               | Hide                             | 5 (7.81)        | 10 (29.41)   | 9.67 (2.41, 38.71) | 0.001   |           |
| TG-efficacy   | FHD_25_125_53_153                | 0.68 ± 0.04     | 0.67 ± 0.03  | 0.62 (0.40, 0.95) | 0.030   | 0.58 (0.47, 0.69) |
|               | ChLD_a_avg                       | 149.72 ± 1.90   | 148.99 ± 2.07 | 0.66 (0.43, 1.01) | 0.053   | 0.59 (0.48, 0.71) |
|               | R83_84                           | 0.93 ± 0.04     | 0.96 ± 0.07  | 3.01 (1.37, 6.61) | 0.006   | 0.64 (0.53, 0.75) |
|               | sMFCC4                           | −7.77 ± 3.02    | −6.29 ± 3.48 | 1.60 (1.04, 2.45) | 0.031   | 0.61 (0.49, 0.72) |
|               | Q_23                             |                 |              |              |         | 0.016     | 0.48 (0.35, 0.60) |
|               | Sausage-shaped with a hard and   | 2 (4.17)        | 5 (10.00)    | 1            |         |           |
|               | uneven surface                   |                 |              |              |         |           |
|               | Sausage-shaped with cracks       | 4 (8.33)        | 12 (24.00)   | 1.2 (0.16, 8.8) | 0.858   |           |
|               | Soft chocolate bar              | 28 (58.33)      | 29 (58.00)   | 0.41 (0.07, 2.31) | 0.315   |           |
|               | Mushy pasta                      | 7 (14.58)       | 3 (6.00)     | 0.17 (0.02, 1.44) | 0.104   |           |
### Variables

| Variables | Mean ± SD | Number (Percentage) | Statistical Test |
|-----------|-----------|---------------------|------------------|
| **Bits of gruel** | | | |
| FHD_33_133_43_143 | 1.13 ± 0.04 | 1 (2.00) | 0.09 (0.37, 0.94) | 0.027 | 0.59 (0.48, 0.70) |
| FA_53_94 | 86.08 ± 2.56 | 1 (2.00) | 1.69 (1.09, 2.61) | 0.018 | 0.60 (0.49, 0.71) |
| FA_94_43 | 80.66 ± 2.80 | 1 (2.00) | 1.53 (1.00, 2.35) | 0.049 | 0.57 (0.45, 0.68) |
| PAi_72_73 | 71.39 ± 4.40 | 1 (2.00) | 0.54 (0.34, 0.86) | 0.009 | 0.61 (0.5, 0.73) |
| FHD_43_143_94_194 | 0.94 ± 0.02 | 1 (2.00) | 1.57 (1.02, 2.41) | 0.039 | 0.59 (0.48, 0.70) |
| ChRD_L_avg | 146.24 ± 8.79 | 1 (2.00) | 0.64 (0.41, 0.98) | 0.041 | 0.55 (0.43, 0.66) |
| ChRD_b_avg | 109.81 ± 1.99 | 1 (2.00) | 2.08 (1.3, 3.35) | 0.002 | 0.67 (0.56, 0.78) |
| **FA_53_94** | 86.08 ± 2.56 | 1 (2.00) | 1.69 (1.09, 2.61) | 0.018 | 0.60 (0.49, 0.71) |
| **FA_94_43** | 80.66 ± 2.80 | 1 (2.00) | 1.53 (1.00, 2.35) | 0.049 | 0.57 (0.45, 0.68) |
| **PAi_72_73** | 71.39 ± 4.40 | 1 (2.00) | 0.54 (0.34, 0.86) | 0.009 | 0.61 (0.5, 0.73) |
| **FHD_43_143_94_194** | 0.94 ± 0.02 | 1 (2.00) | 1.57 (1.02, 2.41) | 0.039 | 0.59 (0.48, 0.70) |
| **ChRD_L_avg** | 146.24 ± 8.79 | 1 (2.00) | 0.64 (0.41, 0.98) | 0.041 | 0.55 (0.43, 0.66) |
| **ChRD_b_avg** | 109.81 ± 1.99 | 1 (2.00) | 2.08 (1.3, 3.35) | 0.002 | 0.67 (0.56, 0.78) |
| **Extrovert** | 25 (50.00) | 10 (20.83) | 1 | |
| **Introvert** | 18 (36.00) | 20 (41.67) | 2.78 (1.05, 7.34) | 0.039 | |
| **Moderate** | 7 (14.00) | 37 (77.08) | 0.001 | 0.53 (0.41, 0.65) | |
| **Energetic** | 31 (62.00) | 12 (25.00) | 1 | |
| **Moderate** | 13 (26.00) | 23 (47.92) | 4.57 (1.76, 11.84) | 0.002 | |
| **Quiet** | 6 (12.00) | 13 (27.08) | 5.6 (1.73, 18.12) | 0.004 | |
| **Q_6** | 31 (62.00) | 12 (25.00) | 1 | |
| **A lot** | 10 (20.00) | 21 (43.75) | 1 | |
| **Moderate** | 23 (46.00) | 16 (33.33) | 0.33 (0.12, 0.89) | 0.028 | |
| **A little** | 15 (30.00) | 7 (14.58) | 0.22 (0.07, 0.72) | 0.012 | |
| **None** | 2 (4.00) | 4 (8.33) | 0.95 (0.15, 6.10) | 0.959 | |

**p**-values were obtained from logistic regression analyses. Odds ratios (OR) are represented with 95% confidence intervals. Area under the curves (AUC) are represented with 95% confidence intervals based on leave-one-out cross validation.

### Discussion

Taeumjowi-tang is a popular herbal product in Korea and is generally used for weight loss [6–10,32] and changes in several lipid profiles [6,11,13,14]. Until now, there have been no studies reporting prediction models or algorithms for the efficacy of Taeumjowi-tang or other herbal medicines for an individual. However, several studies have examined the efficacy of Taeumjowi-tang. To examine the association of oral administration of Taeumjowi-tang with anthropometric and blood parameters, many studies have proven that the efficacy of Taeumjowi-tang is useful for weight reduction or changes in lipid profiles in humans and mice [6–14]. For example, Yoo et al. [6] examined changes in anthropometric indices and blood parameters after dose intake of Taeumjowi-tang in obese Korean children. They found that anthropometric indices, such as weight, subscapular skin-fold thickness, abdominal skin-fold thickness, body fat mass, body mass index, percent body fat, relative body fat, and blood parameters including total cholesterol, atherogenic index, thyrotropin, and leptin significantly decreased. Additionally, Yong et al. [10] observed an effect of Taeumjowi-tang on obese female patients and proved that anthropometric indices, such as weight, body fat, muscle volume increase, BMI, and body fat ratio change, were significantly decreased after dose intake of Taeumjowi-tang. Kim and Jo [11] examined the association between the intake of Taeumjowi-tang and hypertriglyceridemia in Korean females and found that the triglyceride level was reduced from 432 mg/dL to 113 mg/dL after oral administration of Taeumjowi-tang. Park et al. [12] reviewed the efficacy of Taeumjowi-tang related to blood parameters, cells, body and organ weight, BMI, waist-hip circumference ratio, waist circumference, food intake, and bioelectrical impedance analysis. Seo et al. [13] examined the efficacy of Taeumjowi-tang in obese Korean males and females through a comparison of subjects before and after oral administration of Taeumjowi-tang. They found 15% weight loss, 16% BMI reduction, 26% fat mass reduction, 12% reduction in total cholesterol, and 35% reduction in triglyceride level, but no reduction in HDL cholesterol. Cho et al. [32] examined the effect of combined electroacupuncture therapy and oral administration of Taeumjowi-tang and reported that...
body weight, BMI, percent fat mass, and waist-to-hip circumference ratio were significantly decreased after treatment. Li et al. [14] tested the safety and efficacy of Taeumjowi-tang in a randomized, double-blind, placebo-controlled clinical trial on obese subjects. They observed that total cholesterol level, LDL cholesterol level, weight, and waist circumference were significantly decreased after 12 weeks of oral administration. Additionally, the efficacy of Taeumjowi-tang has been demonstrated in animal experiments. Several previous studies have examined the effect of Taeumjowi-tang for the treatment of obesity and its comorbidities in obese mice [7–9]. For example, Park et al. [9] examined the efficacy of Taeumjowi-tang for the treatment of obesity and atopic dermatitis induced by a high-fat diet and 1-fluoro-2,4-dinitrobenzene in mice and suggested that Taeumjowi-tang was useful for the clinical management and treatment of comorbid obesity-atopic dermatitis because the effect may be caused by the regulation of HIF-1α expression. Kim et al. [8] investigated the efficacy of Taeumjowi-tang on liver proteome alteration in mice based on two-dimensional electrophoresis combined with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, and they reported that Taeumjowi-tang could reduce obesity by modulating fatty acid metabolic proteins and genes. However, unlike the studies mentioned above, some studies have reported that oral administration of Taeumjowi-tang has no effect on changes in lipid profiles or anthropometric and body fat composition indices [33,34]. Specifically, Park et al. [33] argued that oral administration of Taeumjowi-tang had no effect on changes in BMI, waist circumference, hip circumference, waist-to-hip circumference ratio, visceral fat mass, subcutaneous fat mass, total cholesterol, HDL cholesterol, or triglyceride through a double-blind, randomized, placebo-controlled study. Additionally, Kim et al. [34] reported that blood pressure, HDL cholesterol, LDL cholesterol, and triglyceride were not changed after oral administration of Taeumjowi-tang for 8 weeks, although weight, waist-to-hip ratio, and BMI were decreased significantly.

In terms of facial variables used in our study, facial characteristics (shape) and complexion (color of face) were often used to diagnose diseases or prescribe herbal medicine, such as Taeumjowi-tang [35–37]. For example, Park et al. [35] investigated the association of facial complexion with age, BMI, and systolic blood pressure for cold- and heat-prescription, such as Taeumjowi-tang, and documented significant differences in complexion between cold-prescription and heat-prescription subjects. This implies that prescriptions such as Taeumjowi-tang may differ according to individual patterns and that the efficacy of herbal medicine may differ according to individuals.

This study has several limitations. First, the number of subjects used in our models was small due to the difficulty of a large-scale clinical trial study for efficacy prediction. Second, we cannot guarantee that our findings are similar to those of other ethnic groups or countries because anthropometry, facial shape, facial color, and socioeconomic and environmental characteristics differ according to countries and ethnicity. Last, although we suggested several prediction models of efficacy for treatment of metabolic risk factors, performance of the efficacy model of SBP was very low. Only the performance of HDL efficacy model is thought to have predictive power. Therefore, more research is needed to improve the performance of these models. Despite these limitations, our results are valuable for predicting whether a drug will be effective before treatment with herbal medicines and for reducing the side effects.

In conclusion, we demonstrated the possibility of predicting the individual efficacy of herbal medicine through examination of four models for prediction of efficacy of herbal medicine for personalized treatment of metabolic risk factors. Additionally, we found several indices that showed the differences before and after treatment according to the efficacy response to oral administration. Therefore, our findings suggested that our model may properly predict the efficacy of herbal medicine for the treatment of hypertriglyceridemia and hypo-HDL cholesterololemia given the evidence of the efficacy of Taeumjowi-tang.
**Supplementary Materials:** The following are available online at www.mdpi.com/article/10.3390/app11089741/s1, Figure S1: Position of facial features in front and profile view angle, Figure S2: Position of tongue features

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