Application of machine learning algorithms to identify risk factors for depression in type 2 diabetes mellitus patients: A Taiwan diabetes registry study

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Abstract

Background: We analyzed variables reported during routine clinical practice using a registrational database to estimate risk factors for depression in people with type 2 diabetes mellitus.

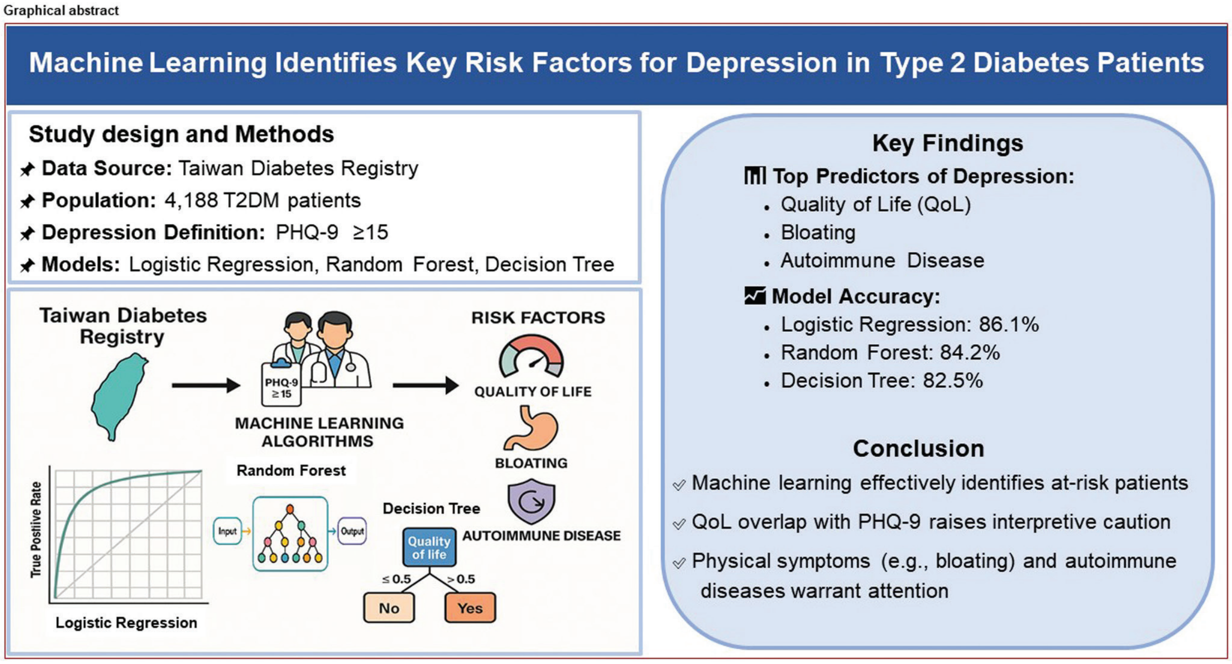
Methods: A Patient Health Questionnaire (PHQ-9) score of 15 was selected as the cut-off for clinically meaningful depression. Missing data was either filled in with a median value, the *k*-nearest neighbors' method, or the entire variable was removed. Logistic regression, random forest, and decision tree machine learning models were used to decide which factors were most relevant to depression. The accuracy of each algorithm was evaluated with a testing set.

Results: When all variables were included in the logistic regression model, the area under the receiver operating characteristic curve was 0.81. In the random forest model, the most important factor was quality of life (QoL). Upon removing QoL-related variables, bloating, and autoimmune disease became the greatest contributing factors. Model accuracy was 83.1%. In the decision tree model, QoL was also observed as the most decisive factor. Upon removing QoL variables, bloating was the first node. Model accuracy was 82.5%.

Conclusion: QoL, bloating, and autoimmune disease were the most important factors associated with depression in type 2 diabetes mellitus patients.

Keywords: Depression; Risk factor; Taiwan; Type 2 diabetes mellitus

Graphical abstract



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Lay Summary: This study used data from the Taiwan Diabetes Registry to explore what factors may increase the risk of depression in people with type 2 diabetes. Researchers applied machine learning techniques—including logistic regression, random forest, and decision tree models—to analyze a wide range of health and lifestyle information. Depression was defined as a score of 15 or higher on the Patient Health Questionnaire (PHQ-9). Among all the factors studied, poor quality of life (QoL) was found to be the strongest predictor of depression. When QoL-related items were removed from the analysis, bloating and autoimmune diseases emerged as key contributors. These results suggest that both physical symptoms and overall life satisfaction play a critical role in the mental health of people with diabetes. The machine learning models were able to predict depression with around 82%–83% accuracy, highlighting their potential usefulness in clinical settings for identifying at-risk patients.

1. INTRODUCTION

A higher incidence of major depressive disorder has been observed in patients with diabetes mellitus.[1,2] The underlying etiology of depression can be multi-faceted and reflects a complicated interplay between genetic and environmental factors.[3] Prior studies have demonstrated risk factors for depression in diabetes mellitus patients to be severe hypoglycemia, diabetes neuropathy, taking anti-diabetic medications, alterations in brain volume and blood flow, and chronic inflammation-related neurodegeneration.[4–6] In the present study, we analyzed the Taiwan Diabetes Registry database for variables reported during routine clinical care to evaluate risk factors for depression in people with type 2 diabetes. This data can help inform clinicians, who can then provide patients with appropriate interventions or mental health consultations in their daily practice to more comprehensively care for patients with diabetes in Taiwan.

2. METHODS

2.1. Taiwan Diabetes Registry database

The Taiwan Diabetes Registry was established by the Diabetes Association of the Republic of China (Taiwan) in October 2015 and involved 14 medical centers, 44 regional and local hospitals, and 37 general practice clinics. Diagnosis was based on clinical criteria at the discretion of the treating physician. Other diseases were self-reported by each patient. After obtaining written informed consent from patients, clinical diabetes educators collected clinical information and various disease-related medical records in a web-based electronic portal. This platform allowed healthcare providers to record and track the clinical course of treatment and outcomes in the diabetes registry. Follow-up information was updated annually. The information recorded in the platform included general diabetes characteristics, personal and family history, disease history, living habits (smoking, drinking, diet, and activity level), results of physical examinations (height, weight, blood pressure, waist, and hip circumference), results of laboratory examinations (lipids, blood glucose, glycated hemoglobin, renal and liver function, and urine tests), feet assessment results, cardiovascular and microvascular diabetes complications, diabetes education and self-management status, hospitalization history, and medications used. At enrollment, patients were required to complete two quality of life (QoL)-related questionnaires: the Patient Health Questionnaire (PHQ-9) and the EuroQol five dimensions questionnaire (EQ-5D). Both are standardized instruments for measuring health-related QoL and assess five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Our study was approved by the Joint Institutional Review Board in Taiwan (protocol number: TDR20-4) and the institutional review board at Taipei Veterans General Hospital (IRB number: 2015-08-003AC).

2.2. Definition of depression

Collected as part of the registry data, the PHQ-9 score is a widely adapted tool for screening, diagnosing, monitoring, and measuring the severity of depression. It contains nine Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria for depression: depressed mood; markedly diminished interest or pleasure in most or all activities; significant weight loss (or poor appetite) or weight gain; insomnia or hypersomnia; psychomotor retardation; fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt; diminished ability to think or concentrate, or indecisiveness; and recurrent thoughts of death (not just fear of dying), or suicidal ideation, plan, or attempt. Each item was scored from 0 (not at all) to 3 (nearly every day). The PHQ-9 score is the sum of the scores from all nine items. The higher the score, the more severe the depressive symptoms.

The clinical utility of the PHQ-9 score was validated in a cohort of 6000 patients from eight primary care clinics and seven obstetrics-gynecology clinics in the United States.[7] Using professional mental health interviews, which is the gold standard for diagnosing depression, Kroenke et al[7] determined that a PHQ-9 score of 10 or higher indicated depression with both a sensitivity and specificity of 88%. Based on this validation study, PHQ-9 scores of 5, 10, 15, and 20 are considered to represent mild, moderate, moderately severe, and severe depression, respectively. Regarding the optimal cut-off score for diagnosing depression, a meta-analysis conducted by Manea et al[8] showed that six studies using 15 as a cut-off score had a specificity of 0.96 (95% confidence interval [CI]: 0.94-0.97). In the present exploratory study, we therefore used a PHQ-9 score of 15 as the cut-off value for major depression.

2.3. Data preparation

Because the present study focuses on depression in people with type 2 diabetes mellitus, variables directly related to type 1 diabetes, including gestational age, birth weight, and vaccination history were excluded from the analysis. Those without PHQ-9 data were also excluded. Among the remaining variables, 87 cases were missing data. Removing the cases with missing data would be one way to resolve the issue, but a reduced sample size would negatively impact model training. Instead, we filled in missing values using a median or *k*-nearest neighbors algorithm, depending on the nature of each particular variable (Supplement Table 1, http://links.lww.com/JCMA/A332). After data cleaning, 4188 patients with 194 variables were included

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for further analysis. The data were divided into a training set (80% of the cohort) and a testing set (20% of the cohort). This ratio is often chosen because it provides a good balance between training and testing data; the model gets sufficient data to learn patterns (80%) and enough data to validate its performance (20%). These sets were not stratified.

2.4. Machine learning algorithms

We used three commonly adapted machine learning algorithms, including logistic regression, random forest, and decision tree models. For the logistic regression model, all variables were considered numeric, and categorical variables were seen as numerical data. For the decision tree algorithm, a classification rather than regression decision tree was used. The model was tested with different hyperparameters settings, and the one with best performance was selected.

Analysis was conducted in R Version 4.2.1 (R Foundation, Indianapolis, IN), and figures were produced using the package ggplot2 (Wickham 2009).

3. RESULTS

3.1. Participants

At the data cut-off, 4501 patients were in the database. Among these, 37 patients were missing PHQ-9 scores and were therefore excluded. After data cleaning (see Section 2.3), 4188 patients with 194 variables were included for further analysis. Only 36 (0.86%) patients had a PHQ-9 score of 15 or higher. Table 1 shows the baseline characteristics of depressed and non-depressed patients.

3.2. Logistic regression model

Initially, all variables were put into the logistic regression model, and the full model had an accuracy of 85.7%. Then, a stepwise model was used to select variables that contributed most to the model. Variables selected in the stepwise method were: sex, marital status, occupation, education, city of residence, number of children, income, obesity, hemodialysis, thirst, cardiovascular disease, eye complications, skin complications, smoking habit, low salt diet, vegetarian diet, hepatitis B virus infection, autoimmune disease, angina, peripheral vascular disease, right eye retinal laser surgery, fundus examination results, normal left eye fundus examination result, macular degeneration, proliferative diabetic retinopathy, kidney transplant, bloating, constipation, diarrhea, hypoglycemia severity, heart rate, weight, body mass index, alanine aminotransferase, regular insulin use, QoL, angiotensin-converting enzyme inhibitor use, diuretics use, angiotensin receptor blocker use, β-blocker use, metformin use, gliclazide use, phosphodiesterase inhibitor use, antithrombin use, and vitamin K agonist use. The accuracy of the stepwise model was 86.1%, which was comparable to the full model. The area under the receiver operating characteristic curve was 0.81 (Fig. 1).

Table 1

Baseline characteristics of depressed and non-depressed subjects

	Depressed	Non-depressed
Number	36	4152
Age (y)	55.0 ± 15.1	58.0 ± 13.8
Male (%)	49.1	51.4
BMI (kg/m^2)	27.0 ± 5.4	26.8 ± 7.5
DM duration (y)	4.3 ± 8.0	3.8 ± 7.6
HbA1c (%)	8.66 ± 1.57	8.21 ± 1.17

BMI = body mass index; DM = diabetes mellitus; HbA1c = hemoglobin A1c.

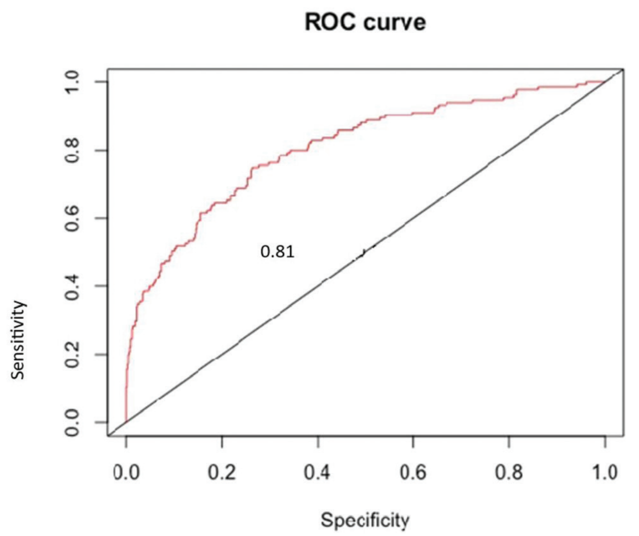

Fig. 1 Stepwise logistic regression model ROC. The stepwise logistic regression model selects variables that contribute most to the model. The accuracy of this method was 86.11%, which is slightly higher than the results of the unselected logistic regression (accuracy of 85.73%). The AUC is 0.806, indicating good discriminatory power. AUC = area under the curve; ROC = receiver operating characteristic.

Because EQ-5D questions partly overlap with those from the PHQ-9, we removed QoL-related variables and then repeated the logistic regression. The full model with all variables except for QoL-related variables yielded an accuracy of 81.3%. We then did a forward stepwise logistic regression, and the following variables were selected (in order of significance): bloating, autoimmune disease, long-acting insulin use, care unit, constipation, hemodialysis, diarrhea, hypoglycemia severity, vegetarian diet, sex, number of children, coronary artery disease, alanine aminotransferase, care at local hospital, no follow-up visits, right eye retinal laser surgery, systolic blood pressure, occupation, diastolic blood pressure, thirst, left eye fundus exam results, sleep duration, β-blocker use, self-care status, education, age, local health center care, obesity, waist measurement, macular degeneration, angiotensin receptor blocker use, diuretics use, left eye retinal laser surgery, colorectal cancer, adenosine diphosphate receptor inhibitor use, phosphodiesterase inhibitor, normal left eye fundus examination result, heart rate, glycated hemoglobin, prostate cancer, hypoglycemia, eye complications, heart failure, stage III chronic kidney disease, forgetting to take medications, cardiovascular disease, angiotensin-converting enzyme inhibitor use, city of residence, niacin use, metformin use, peripheral vascular disease, gastric cancer, gliclazide use, gestational diabetes mellitus, normal right eye fundus examination results, fibrate use, residence status, marital status, kidney transplant, dialysis, clinic care, urinary tract cancer, and nighttime meals. The accuracy of prediction was 82.0%. The area under the receiver operating characteristic curve was 0.585 for the full model (excluding QoL variables) and 0.587 for the forward stepwise model.

3.3. Random forest model

The random forest model yielded a prediction accuracy of 84.2%. By calculating the mean decrease accuracy, we determined which variable caused the greatest reduction in model accuracy following its removal. The two variables that ranked highest were "I feel more worried and anxious than most people I know (QoL S-11)" and "I am afraid that I may not take responsibility for my family in the future (QoL S-10)" (Fig. 2A).

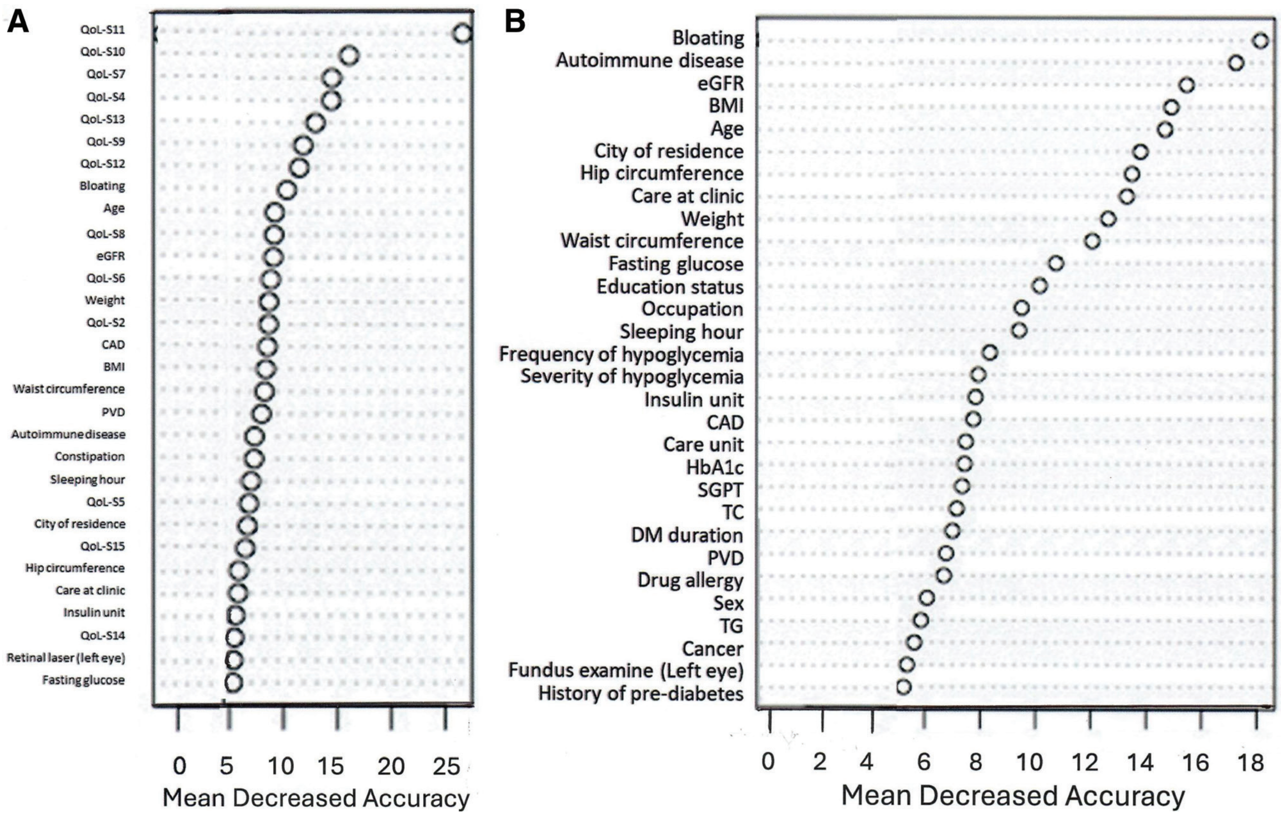

Fig. 2 Variable importance according to the random forest model. (A) Using all variables. This figure illustrates the mean decrease in accuracy for each variable in the random forest model. The two variables that contribute most to accuracy reduction are "QoL-S11: I feel more worried and anxious than most people I know" and "QoL-S10: I am afraid that I may not take responsibility for the family in the future." (B) After removing QoL variables. This figure shows the importance of variables in the random forest model after excluding QoL-related variables. The factors with the highest importance are bloating, autoimmune disease, eGFR, BMI, age, and city of residence. BMI = body mass index; CAD = coronary artery disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; PVD = peripheral vascular disease; QoL = quality of life; QoL-1 = "I think my DM is well controlled"; QoL-S2 = "I often feel afraid that my disease may get worse"; QoL-S4 = "I feel that DM interferes with what I wanted to do"; QoL-S5 = "I am worried about the risk of hypoglycemia"; QoL-S6 = "Dealing with DM is more difficult than before"; QoL-S7 = "Dealing with DM makes me exhausted"; QoL-S8 = "I feel pressure because of DM"; QoL-S9 = "I think the treatment for DM is too complicated"; QoL-S10 = "I worry that I will not fulfill my responsibility to my family in the future"; QoL-S11 = "I feel more nervous and anxious compared to most people I know"; QoL-S12 = "Diet control causes me a lot of trouble in daily life"; QoL-S13 = "I worry that I may bring trouble to my family and children"; QoL-S15 = "I worry that treatment may cause body weight gain"; SGPT = serum glutamate pyruvate transaminase; TC = total cholesterol; TG = triglyceride.

Upon removing the QoL-related variables and putting all remaining variables in the random forest model, the accuracy was 83.1%. Bloating, autoimmune disease, estimated glomerular filtration rate, body mass index, age, and city of residence then became the factors of highest importance (Fig. 2B).

3.4. Decision tree model

Similar to the other algorithms, in the decision tree model, the QoL questionnaire prompt "I feel more worried and anxious than most people I know" contributed most to predicting depression, followed by "I feel diabetes is hindering me from doing what I really wanted to do" (Fig. 3A). Because these questions are very similar to PHQ-9 questions, QoL-related variables were removed and the decision tree was re-constructed. Boating, autoimmune disease, city of residence, and right eye proliferative diabetic retinopathy all contributed to predicting depression (Fig. 3B). The accuracy of the decision tree model excluding QoL questions was 82.5%.

4. DISCUSSION

This study investigates the application of machine learning algorithms to identify risk factors for depression in patients with type 2 diabetes mellitus using data from the Taiwan Diabetes Registry. We employed various machine learning models, including logistic regression, random forest, and decision trees, to analyze clinical variables and their association with depression, defined by a PHQ-9 score of 15 or higher.

Key findings reveal that QoL, bloating, and autoimmune diseases are significant predictors of depression in this population. The random forest model achieved an accuracy of 84.2%, while the decision tree model reached 82.5% when excluding QoL variables. This study highlights the importance of QoL and indicates that bloating and autoimmune disorders may be risk factors for depression in patients with type 2 diabetes, suggesting a complex interplay between physical health and mental well-being.

Through a comprehensive analysis of a large dataset and the identification of specific clinical factors that have not been extensively studied in relation to depression in diabetes patients, we demonstrate an opportunity for targeted interventions and improved diabetes patient care in Taiwan.

Compared to the general population, prevalence rates of depression are nearly two times higher in people with type 2 diabetes mellitus.[9] Meanwhile, depression has also been reported to increase the risk of developing type 2 diabetes mellitus by

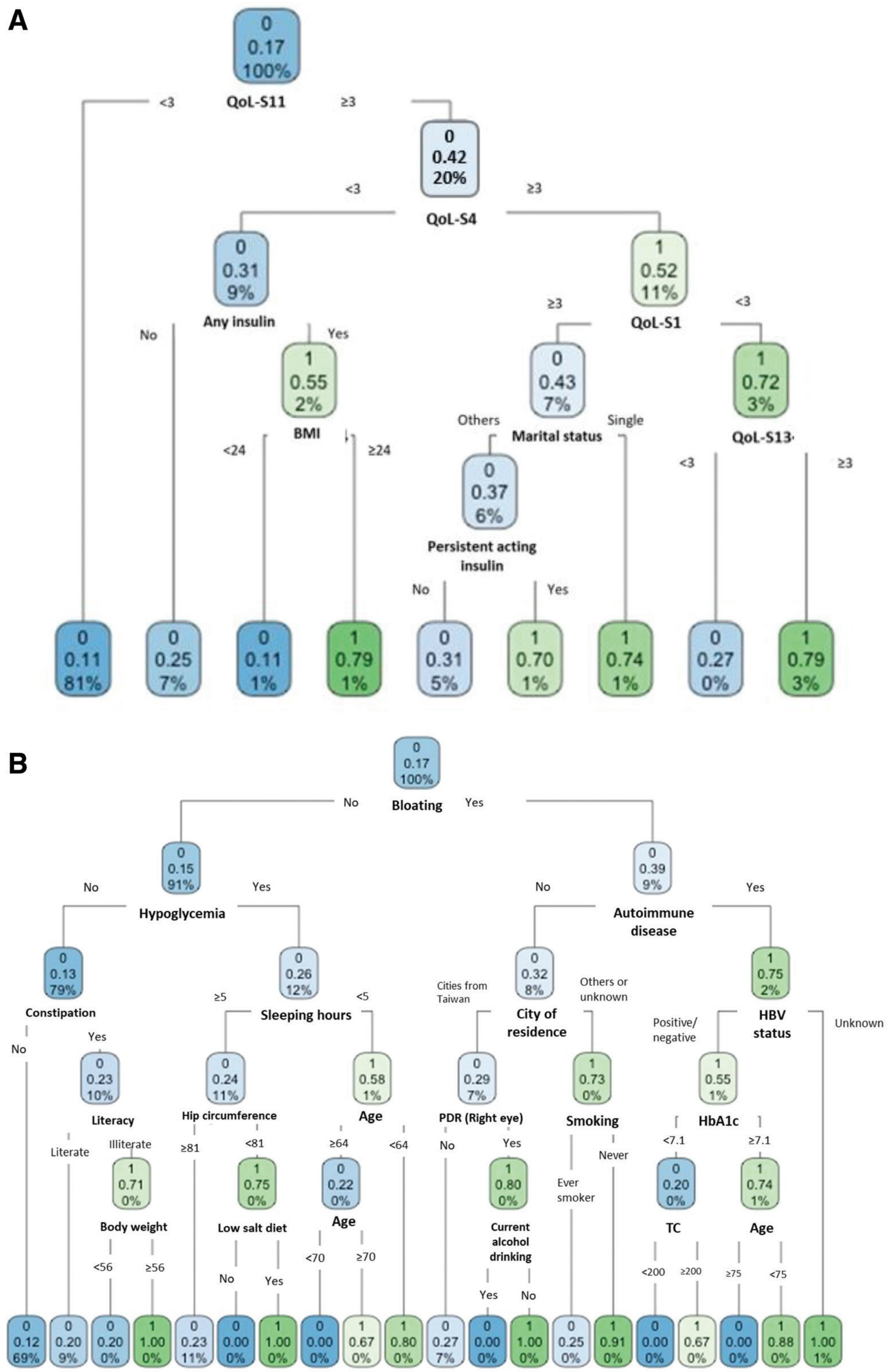

Fig. 3 Decision tree model. (A) Using all variables. This figure shows the importance of QoL questions in the decision tree model. The question "QoL-S11: I feel more worried and anxious than most people I know" contributes most to predicting depression, followed by "QoL-S4: I feel diabetes is hindering me from doing what I really wanted to do." QoL prompts were rated as follows: 1 = strongly disagree; 2 = disagree; 3 = agree; 4 = strongly agree; 5 = cannot or refused to answer. QoL-1 = "I think my DM is well controlled"; QoL-S4 = "I feel that diabetes mellitus interferes with what I wanted to do"; QoL-S11 = "I feel more nervous and anxious compared to most people I know"; QoL-S13 = "I worry that I may bring trouble to my family and children". (B) Excluding quality of life questions. This figure presents the decision tree model after removing QoL variables. The factors that contribute most to the prediction model are bloating, autoimmune disease, city of residence, and PDR of the right eye. The accuracy of this model, excluding QoL questions, is 82.45%. HbA1c = hemoglobin A1c; PDR = proliferative diabetic retinopathy; QoL = quality of life; TC = total cholesterol.

60%.[10] Stress has been proposed as a link between diabetes mellitus and depression.[2] Chronic stress is associated with corticotropin-releasing factor, adrenocorticotropic hormone, and cortisol secretion from the hypothalamus-pituitary-adrenocortical axis, as well as downstream catecholamine secretion by the adrenal medulla. In addition, it has been proposed that stress can mediate cytokine production and inflammatory responses.[11,12] Dysregulation of the stress system has been linked to a range of disorders including metabolic diseases such as obesity, metabolic syndrome, type 2 diabetes mellitus, hypertension, and cardiovascular diseases, as well as behavioral disorders like anxiety, depression, eating disorders, and sleep disorders.[2,13,14]

Environmental factors reported both in people with depression and those with type 2 diabetes mellitus include low socioeconomic status,[15,16] poor sleep, and lack of physical exercise.[2] Other common risk factors for depression in diabetes mellitus patients include body mass index, physical activity, current smoking habit, sleep duration, skipping breakfast, severe hypoglycemia, diabetes neuropathy, history of foot ulcers, and taking anti-diabetic medications.[4–6] Many of these risk factors are included in our learning model. Among the three machine learning models employed, QoL parameters seemed to be most highly correlated with depression; when QoL-related variables were removed from the models, the accuracy and area under the receiver operating characteristic curve values dropped significantly. Besides QoL, other factors with high importance in the random forest and decision tree models included bloating and the presence of autoimmune disorders. Those with bloating symptoms and concomitant autoimmune diseases are thus more likely to have depression. To the best of our knowledge, this is the first time these characteristics have been identified as associated with depression in patients with diabetes.

Bloating is one of the manifestations of autonomic diabetic neuropathy.[17] Although the co-existence of peripheral diabetic neuropathy and depression is being increasingly recognized,[18,19] whether autonomic neuropathy also correlates with depression is still uncertain. Depression is associated with alterations in autonomic control, and patients diagnosed with major depressive disorders exhibit autonomic dysfunction.[20,21] This possible link between the two diseases requires further investigation.

Rheumatoid arthritis is a type of autoimmune disease. According to prior studies, a high proportion of rheumatoid arthritis patients also suffer from depression symptoms, and the incidence of depression in people with rheumatoid arthritis is up to three times higher than in the general population.[22] Pain and physical impairment are often thought of as causes of depression in these patients.[23] In addition, neuroinflammation might be linked to cytokine secretion, including interleukin (IL)-1, tumor necrosis factor-alpha (TNF-α), and IL-6, in rheumatoid arthritis or other autoimmune diseases, and thus may play a role in concomitant depressive disorders.[24–26]

In addition to the three major predictors identified, our analysis found that the rate of depression increases among individuals with a higher body mass index (greater than 24), those over the age of 70, and individuals residing outside of Taiwan or with unknown residency. These findings align with previous studies indicating that higher body mass index and older age are associated with an increased likelihood of depression in individuals with type 2 diabetes mellitus.[4–6] While obesity is recognized as a risk factor for type 2 diabetes in existing literature, the body mass index cut-off for depression identified in our study is relatively low. This reflects the lower overweight and obesity thresholds typically observed in Asian populations.

The strength of this study lies in the quality and comprehensiveness of the Taiwan Diabetes Registry database, which includes data from patients with diabetes mellitus receiving treatment across various medical institutions in Taiwan. The database encompasses a wide range of clinical variables, including family history, personal history, treatment details, and results from diabetes-related laboratory tests and physical examinations.

Despite the strengths of this study, there are several notable limitations. One considerable limitation is the low incidence rate of depression within the cohort, with less than 1% of patients meeting the criteria for clinically meaningful depression. This low prevalence may hinder effective model construction, even with a large database. Selection bias could also play a role, as registry participants are required to have regular consultations with diabetes educators and dietitians. Consequently, individuals who are less compliant or engaged in their care may be underrepresented, potentially skewing the perceived rates of depression among those with type 2 diabetes.

High rates of missing data regarding hypoglycemia severity and insulin units could also introduce bias into the model. The database does not record the use or duration of medications for depression, anxiety, insomnia, or other psychiatric disorders. Furthermore, the broad timeframe for data collection means that changes in treatment paradigms over time could not be accounted for in the analysis. There is also the potential for inaccuracies in diagnoses, including depression, autoimmune diseases, and type 2 diabetes, particularly those based on self-reported questionnaires.

Moreover, this study does not consider well-known factors associated with depression that were not recorded, such as experiences of physical or emotional abuse, major trauma, and exposure to certain drugs (including illicit substances, antiviral medications, isotretinoin, and corticosteroids). Stressful life events—such as bereavement, the loss of a beloved pet, or pregnancy—were also not included. These unmeasured variables may limit the comprehensiveness of our findings and their applicability to the broader population.

Depression in diabetes patients is often underdiagnosed and is an important aspect of comprehensive diabetes care. Bloating and autoimmune disorders were determined to be risk factors for depression in people with type 2 diabetes mellitus. However, the underlying mechanisms and pathophysiology require further study.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://links.lww.com/

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