Acupuncture and Herbal Medicine

Interpretable machine learning reveals key dose trajectory patterns predicting success of acupuncture-assisted methadone tapering

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Abstract

Objective: Long-term methadone maintenance treatment (MMT) requires gradual dose reduction to mitigate adverse effects; prior research has shown that acupuncture facilitates dose tapering and alleviates opioid cravings. Although medication dosage parameters hold significant clinical value in addiction medicine, the impact of early outpatient dose data on therapeutic effects currently remains unclear. This study aimed to construct a methadone dose reduction prediction model and analyze the clinical value of historical dose trajectories.

Methods: Data from two randomized trials (N = 197 patients across six Chinese MMT clinics) were analyzed, with participants grouped into the acupuncture and non-acupuncture cohorts. The primary outcome was combined outcome comprising methadone dose reduction and craving score changes. Pre-intervention dose trajectories were derived *via* cluster analysis and merged with baseline features. Five machine learning models were trained using SHapley Additive exPlanations (SHAP) to explain the feature contributions. Subgroup analyses linking trajectories to the effects of acupuncture were conducted.

Results: Methadone dose data were clustered into three trajectories. Model training included nine features from 11 variables. The CatBoost model achieved the best performance on the test set (area under the curve = 0.7531, accuracy = 0.8205). The SHAP summary plot revealed that the three most influential factors in methadone dose reduction were intervention type, body mass index, and dosage trajectory. Subgroup analysis showed that trajectory class 2 exhibited significantly better efficacy than class 0 at weeks 2 and 4 of acupuncture (week 2: risk difference, 20.4%, P = 0.015; week 4: risk difference, 27.5%, P = 0.013).

Conclusions: In this study, we established a trajectory-based prediction model for MMT dose reduction and demonstrated the clinical value of historical trajectories. The results suggest that acupuncture optimally supports patients with dynamic "rise-then-decline" trajectories, advancing personalized MMT strategies.

Keywords: Acupuncture, Machine learning, Methadone maintenance treatment, Predictive model, Trajectory analysis

Introduction

Methadone maintenance treatment (MMT) can prevent and relieve the strong desire to use drugs among individuals suffering from addiction and is therefore a widely used and effective interventional treatment for individuals addicted to traditional opioid drugs worldwide[1–2]. However, long-term use can lead to side effects, including adverse physical effects (eg, sleep complaints, constipation)[3–4], cognitive function and memory impairment[5–6]. and even drug dependence[7]. Consequently, many MMT clients undergo methadone dose reduction. However, increased cravings for opioids and withdrawal symptoms during methadone tapering affect adherence to MMT, which increases the risk of relapse. Owing to the current lack of effective drug-assisted methods for methadone dose reduction, non-pharmacological therapies are important. Our previous systematic studies demonstrated the effectiveness of acupuncture as a non-drug solution[8–10]. Some clinical studies have further shown that electro-acupuncture can improve psychiatric symptoms and prevent relapse during opioid withdrawal[11–12]. Our previous randomized controlled trials (RCTs)[13–14] also demonstrated the advantages of acupuncture in facilitating reductions in the daily dose of methadone and decreasing opioid cravings. Recent multiomics and

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How to cite this article: Fan BC, Chen YM, Chen C, Zhang PM, Zeng JC, Lu LM. Interpretable machine learning reveals key dose trajectory patterns predicting success of acupuncture-assisted methadone tapering. Acupunct Herb Med 2025;5(4):469–479. doi: 10.1097/HM9.0000000000000177

Received 28 July 2025 / Accepted 19 November 2025

single-cell RNA transcriptomic analyses have further provided molecular evidence supporting the clinical efficacy of acupuncture-assisted methadone reduction[15].

Drug dosage data are paramount in the field of addiction medicine; as such, some studies have explored opioid dosage reduction using machine learning (ML) techniques to analyze and predict opioid dosage and overdose risk[16–22]. ML is particularly valuable in this context, as it can handle the complex nonlinear relationships that are commonly present in medical dosage and response data[23]. In addition, the dose trajectory is also an important clinical feature requiring examination. Changes in methadone dosage over time, termed the dose trajectory, are clinically relevant because they reflect patient responses to treatment and indicate potential challenges or success in tapering methadone doses. One study used cluster analysis to explore the relationship between the clinical use trajectory of opioids and adverse events[24]. Exploring whether pre-intervention dose trajectories can be used to judge the efficacy of interventions provides new perspectives for the comprehensive analysis of factors that influence the prognosis of methadone dose reduction. Meanwhile, "intelligent acupuncture" is beginning to optimize clinical decision-making, utilizing artificial intelligence and data-driven methods to enhance acupuncture diagnosis, prescription design, and treatment evaluation[25–26]. Through ML and clustering techniques, the present study aimed to demonstrate the clinical value of pre-intervention dose trajectories and identify specific pre-intervention methadone dose trajectories that optimize the efficacy of acupuncture in patients with MMT, providing a reference for optimizing the clinical practice strategy of acupuncture for methadone dose reduction. This study comprised a secondary analyze of our two previous RCTs[13–14].

Methods and materials

Data source

The study data were derived from two parallel-arm RCTs (RCT-I: ChiCTR1900026357 and RCT-II: ChiCTR2200058123), which aimed to determine the efficacy of acupuncture for methadone reduction in patients undergoing MMT (trial information and protocol are shown in the Supplementary Methods, https://links.lww.com/AHM/A198). This secondary analysis included data from outpatient electronic records before the trial and baseline patient data at trial initiation. Data were collected between November 2017 and April 2023, which included the 85 consecutive weeks before the trial. The initial data analysis for the present report was conducted from August 1, 2023, to March 26, 2024. This *post hoc* analysis of de-identified data complied with the *Declaration of Helsinki* and was approved by the Guangzhou University of Chinese Medicine Institutional Review Board (YJ-KY-2025-035), which waived the requirement for informed consent.

Participants

The participants in these two studies were all patients enrolled from six MMT clinics in China. Participants were randomly assigned in a 1:1 ratio, and fulfilled the diagnostic criteria for opioid use disorders as defined by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders[27]. Each participant provided written informed consent to participate in the randomized clinical trials. Key exclusion criteria included having a history of mental illness other than drug dependence and receiving other treatments that may have affected the effectiveness evaluation of the present intervention during the previous three months. The inclusion and exclusion criteria are detailed in the Supplementary Methods, https://links.lww.com/AHM/A198.

Interventions

The experimental groups in both trials received acupuncture in addition to conventional treatment, with intervention durations of 6 and 8 weeks, respectively. The acupuncture point groups underwent acupuncture based on Jin's three-needle therapy (Dingshen-zhen, Sishen-zhen, and Shouzhi-zhen). Acupuncture was performed three times weekly, with each session lasting for 30 minutes. To ensure standardization and reliability, all acupuncturists were licensed professionals with at least 5 years of clinical experience who had undergone unified training before the trials. Acupuncture procedures were performed according to a standardized protocol, adherence to which was monitored regularly. Details of the acupuncture points and insertion depths are provided in the Supplementary Methods (https://links.lww.com/AHM/A198). The control groups in RCT-I and RCT-II received conventional treatment and sham acupuncture in addition to conventional treatment, respectively (Supplementary Methods, https://links.lww.com/AHM/A198).

Assessments

Outcomes

The primary outcome metrics for both RCT-I and RCT-II were methadone dose reduction and the visual analog scale (VAS) score for drug cravings. The clinical benefits of these two metrics, defined as a mean methadone dose reduction of ≥ 20% compared with the baseline value[13–14,28–30]. and a decrease in the VAS score for opioid cravings by ≥4 points[31–32] from that at baseline, were considered to reflect the minimum clinically important difference. Details regarding the judgment criteria are presented in the Supplementary Methods (https://links.lww.com/AHM/A198). In this study, we defined the composite efficacy of methadone reduction as follows: if both of the above metrics achieved clinical benefit, the treatment was considered effective; otherwise, it was considered ineffective. Data were evaluated based on the intervention results at week 6.

Predictors

Data were selected from the full analysis set of the clinical trials in which the analysis sample contained complete data. Predictors were derived from clinical trial data and outpatient electronic records. The clinical trial data included patients' baseline characteristics, such as

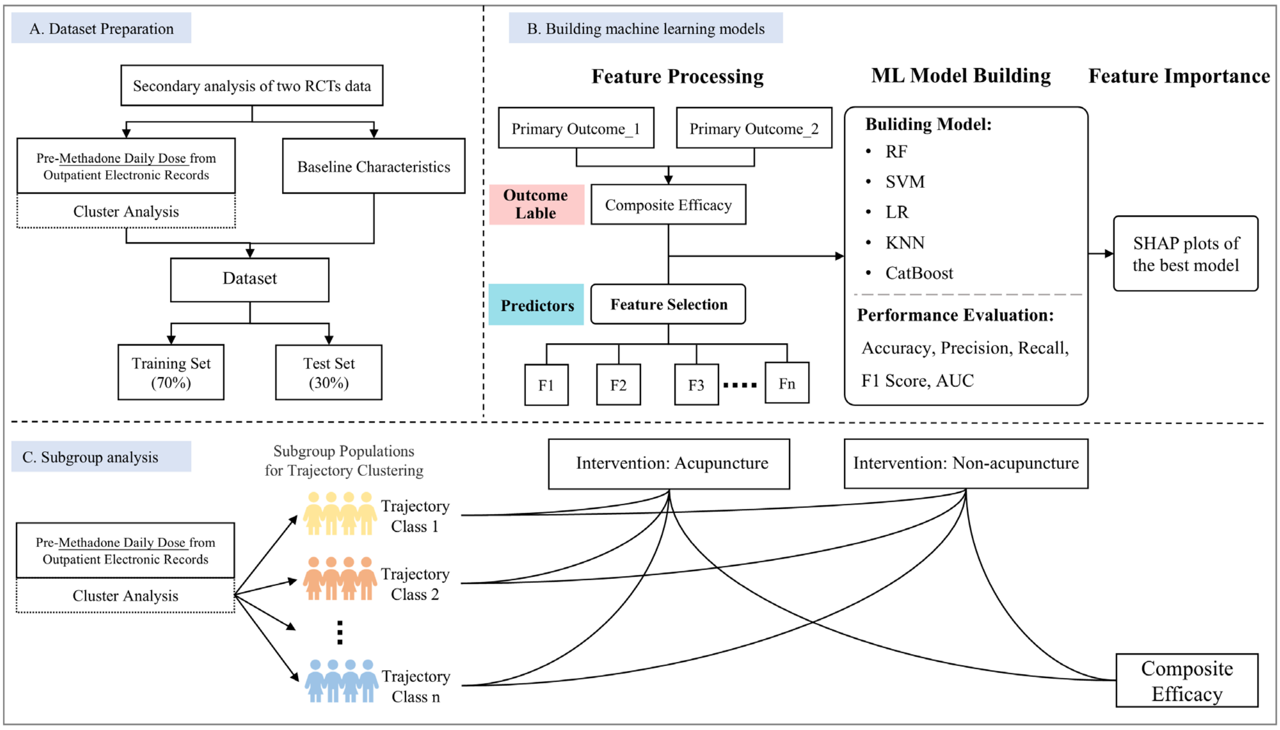

Figure 1. Flowchart summary of the study methodology. AUC: Area under the curve; CatBoost: CatBoost classifier; F1, F2, F3,..., Fn: Clinical variables as input features for ML models; KNN: K-nearest neighbor; LR: Logistic regression; ML: Machine learning; Primary Outcome_1: Methadone dose reduction; Primary Outcome_2: Visual analog score for drug craving; RF: Random forest; SHAP: SHapley Additive exPlanations; SVM: Support vector machine.

sex, age, body mass index (BMI), marital status, occupation, education level, initial drug dosage, years of opioid use, and drug route. Data were collected at trial enrollment. This study integrated and analyzed two previously-published RCTs[13–14]. Because the acupuncture groups had similar intervention protocols, the acupuncture group data from RCT-I and RCT-II were combined into a new acupuncture group. The sham acupuncture group in RCT-II simulated actual acupuncture; therefore, this group was merged with the conventional group in RCT-I to form a non-acupuncture group. The only difference between the two groups was the use of acupuncture as an intervention method. Outpatient electronic records were used to retrieve the patients' methadone daily dose data for 85 weeks before treatment initiation, as obtained from the electronic records of the MMT outpatient clinics. The patients' pre-intervention dosing data were clustered to form historical dose trajectory categories. The baseline characteristics, interventions, and pre-intervention dose trajectory categories were used as predictors.

Statistical analysis

All statistical analyses were conducted using Python, version 3.8.0 (Python Software Foundation), and models were built using the ML libraries scikit-learn[33], K-shape[34], and SHapley Additive exPlanations (SHAP)[35]. GraphPad Prism version 10.2.3 (GraphPad Software Inc., La Jolla, CA, USA) was used to graph the results. All analyses were conducted using Statistical Package for Social Sciences version 25 (IBM, Armonk, NY, USA). All P values were two-sided, and statistical significance was set at $P < 0.05$. An overall flowchart of the analysis is presented in Figure 1. The study was divided into three steps: In step 1, the time-series data were clustered and merged with the baseline data for feature selection; In step 2, five models were constructed for the dataset, and SHAP analysis was performed on the best-performing model among the support vector machine, random forest, logistic regression, k-nearest neighbor, and CatBoost classifiers (CatBoost); In step 3, the relationship between acupuncture therapy and the pre-intervention dose trajectory category were analyzed.

Dose trajectory clustering

We used the unsupervised K-shape ML clustering algorithm to perform cluster analysis of the methadone dose trajectories. Owing to the large differences in methadone doses among the original data of the MMT patients, all data were subjected to Z-score standardization (Supplementary Figure S1, https://links.lww.com/AHM/A198). Details regarding the K-shape clustering algorithm and standardized processing are presented in the Supplementary Methods (https://links.lww.com/AHM/A198). This study applied three indicators (Calinski–Harabasz, silhouette coefficient, and elbow method) to determine the optimal cluster value, k, of the methadone trajectory in patients undergoing MMT. The process of selection of the three evaluation criteria is detailed in the Supplementary Methods (https://links.lww.com/AHM/A198).

Model training and evaluation

Ten variables were used as input features for the ML model. We used a zero-importance feature algorithm and collinearity analysis to select the features (Supplementary Methods, https://links.lww.com/AHM/A198). The screened predictors and their data formed a new dataset that was subsequently divided into the training (70%) and test (30%) sets. We subsequently constructed five ML models to predict the composite efficacy of methadone reduction in patients undergoing MMT. All the models were trained using 10-fold cross-validation, while Bayesian optimization was conducted to evaluate the best model hyperparameters. The search space for each parameter was predefined. The optimization procedure began with several randomly sampled parameter combinations to fit the initial surrogate model. At each iteration, the surrogate model predicted the performance of the candidate parameter sets, and the acquisition function selected the most promising parameters for evaluation. This process was repeated until convergence was achieved.

Five performance evaluation variables were applied to analyze the performance of the selected ML models: the area under the receiver operating characteristic curve (AUC), accuracy, precision, recall, and F1 score.

Predictor importance

We applied the SHAP method to interpret the predictive model to further analyze the relationship between the predictors and outcome metrics. This is a generalized technique for assessing the importance of predictors in ML predictive models. The SHAP values demonstrate the importance of each predictor and quantify the contribution of each predictor to the model output, thereby providing insights beyond solely predictive accuracy. Details regarding the SHAP method are provided in the Supplementary Methods (https://links.lww.com/AHM/A198).

Subgroup analysis

We conducted a subgroup analysis to further investigate the relationship between acupuncture therapy and different methadone dose trajectories, and identify the optimal pre-intervention methadone dose trajectory for acupuncture efficacy. We further conducted chi-square tests (Pearson, Fisher exact, and Wald chi-square tests) on data from three time points (weeks 2, 4, and 6) to analyze the differences in efficacy at each time point. To assess dose trajectory efficacy differences, we considered the correlation between intervention and time, using generalized estimating equations with robust standard errors and an exchangeable working correlation structure. We applied Bonferroni correction to ensure the reliability of the results which showed significance.

RESULTS

Sample distribution

Among the 251 patients enrolled across the two trials, 11 were included in both trials, and 43 lacked pre-intervention outpatient data. This study therefore included 197 patients, including 100 (50.8%) in the acupuncture group and 97 (49.2%) in the non-acupuncture group. All included patients had complete outpatient medication records with no missing data. Supplementary Figure S2 (https://links.lww.com/AHM/A198) shows a flowchart of the participant selection process. Table 1 provides a comprehensive overview of the baseline clinical variables and treatment outcomes in both groups. No significant difference existed in the baseline data; differences were noted in the outcome indicators between the two groups.

Historical trajectories

Historical methadone dose data were clustered into three trajectories. Patients' pre-intervention methadone intake data were converted to average weekly doses, and the dose history data were clustered to form trajectory categories that were used as features to construct effective prediction models. After standard processing and comprehensive evaluation, the optimal k_{pro} value was determined to be 3. The results of this analysis are summarized in Supplementary Figure S3 (https://links.lww.com/AHM/A198) and are visualized in Figure 2. Over the 85 weeks preceding treatment: Trajectory 0 showed a gradual decrease from an early peak, followed by a substantial drop and a slight rebound; Trajectory 1 exhibited a brief phase of rapid dose reduction, followed by a quick rebound and maintenance at approximately the original dosage level; and Trajectory 2 showed a consistent increase historically, followed by a recent steady decline back toward the initial dosage. These distinct historical patterns may indicate different stabilities and tapering propensities, facilitating the interpretation of outcome differences between the acupuncture and non-acupuncture groups.

Model evaluation and performance

Feature selection

Collinearity analysis identified no significant correlations between any of the 10 features. The zero-importance feature selection method excluded sex, educational level, and drug route. Supplementary Table S1, Figures S4 and S5 (https://links.lww.com/AHM/A198) present the feature selection analyses. Nine features were used as final inputs to train the ML models (intervention, age, BMI, marital status, occupation, initial drug dosage, trajectory category, educational level, and years of opioid use). These eight predictors and their data formed a new dataset, which was divided into training (n = 158) and test (n = 39) sets. The data distributions are presented in Supplementary Table S2 (https://links.lww.com/AHM/A198). Excluding the intervention, the variable distributions did not differ between the two sub-datasets.

Predictive performance of the ML models

The prediction performances of the five ML models are presented in Table 2 and the final optimal parameters for each model are summarized in Supplementary Table S3 (https://links.lww.com/AHM/A198). In the test set, the accuracy and precision of the models were 66%–82% and 40%–85%, respectively. Among the models, CatBoost exhibits the best performance (accuracy:

Table 1.

Participant characteristics at baseline (original data set) and treatment outcomes

Characteristic	Acupuncture group (*n* = 100)	Non-acupuncture group (*n* = 97)	χ^2/*t*/*Z*	*P*
Age (M [P25, P75]), years	50.00 (46.00, 54.75)	49.00 (45.50, 55.00)	–0.105	0.916
Sex, *N* (%)				
Male	84 (84.0)	87 (89.7)		
Female	16 (16.0)	10 (10.3)		
BMI ($\bar{x} \pm$ s), kg/m^2	23.02 ± 3.32	23.24 ± 3.55	–0.489	0.625
Occupation, *N* (%)			0.003	0.956
Employed	54 (54.0)	52 (53.6)		
Unemployed	46 (46.0)	45 (46.4)		
Marital status, *N* (%)			0.074	0.964
Married	39 (39.0)	36 (37.1)		
Single	50 (50.0)	50 (51.5)		
Divorced	11 (11.0)	11 (11.3)		
Education level, *N* (%)			0.003	0.957
Primary or middle school	77 (77.0)	75 (77.3)		
High school or university	23 (23.0)	22 (22.7)		
Initial drug dosage (M [P25, P75]), mL	34.50 (15.50, 50.00)	35.00 (15.50, 50.00)	–0.208	0.835
Years of opioid use (M [P25, P75]), years	15.00 (10.00, 20.00)	13.00 (8.00, 21.00)	–0.851	0.395
Primary route of previous opioid use, *N* (%)				
Injection	79 (79.0)	78 (80.4)		
Nasal or oral	21 (21.0)	19 (19.6)		
Composite efficacy, *N* (%)			28.399	<0.001
Effective	50 (50.0)	14 (14.4)		
Ineffective	50 (50.0)	83 (85.6)		

BMI: Body mass index (calculated as weight in kilograms divided by height in meters squared); CI: Confidence interval; MMT: Methadone maintenance treatment.
Composite efficacy includes two aspects: effective reduction in methadone dose and improvement in opioid craving score.

0.8205, AUC: 0.7531, recall: 0.5000, precision: 0.8571, and F1 score: 0.6316). The performance of each model in the training set is presented in Supplementary Table S4, Figures S6 and S7 (https://links.lww.com/AHM/A198) provide additional information regarding model training. Given the superior overall performance of the CatBoost model, this was preferred for predicting the composite efficacy of methadone reduction.

Further exploration of the prediction model

To further clarify the role of the predictors in the prediction model, we applied the SHAP method to assess their importance. Figure 3A presents the features of the model ranked based on SHAP values. The top three features were intervention, BMI, and trajectory. The summary plot illustrates the positive and negative effects of these characteristics on the composite efficacy of methadone dose reduction in patients undergoing MMT. Dependency plots were further generated to show the individual differences and overall distributional trends for each feature (Figure 3B). Among the categorical variables, the intervention and trajectory categories showed clear differences. Among the continuous variables, trends in BMI and duration of drug use exhibited a nonlinear relationship with treatment efficacy.

Subgroup analysis

A comparison of the composite efficacy metrics between the acupuncture and non-acupuncture groups within each methadone dose trajectory category revealed a superior composite efficacy of methadone dose reduction in the acupuncture group than in the non-acupuncture group across all categories (Figure 4). Under natural conditions (non-acupuncture), the three trajectory groups exhibited distinct outcome patterns, as follows: trajectory 0 showed no improvement by week 4, but reached an approximately 10% effectiveness rate by week 6; trajectory 1 showed no notable improvement throughout the period; and trajectory 2 demonstrated a gradual increase in the proportion of effective cases, reaching approximately 20% by week 6. In contrast, following acupuncture intervention, all three trajectories showed significant improvements. Trajectory 1, which showed no natural improvement, demonstrated the largest response to acupuncture (final effectiveness rate of 60%), whereas trajectories 0 and 2 achieved approximately 40% effectiveness by week six. These findings indicate that acupuncture not only enhances the existing benefits in trajectories 0 and 2 but also revitalizes the treatment response in trajectory 1.

Across the three trajectories, the difference in efficacy between the acupuncture and non-acupuncture

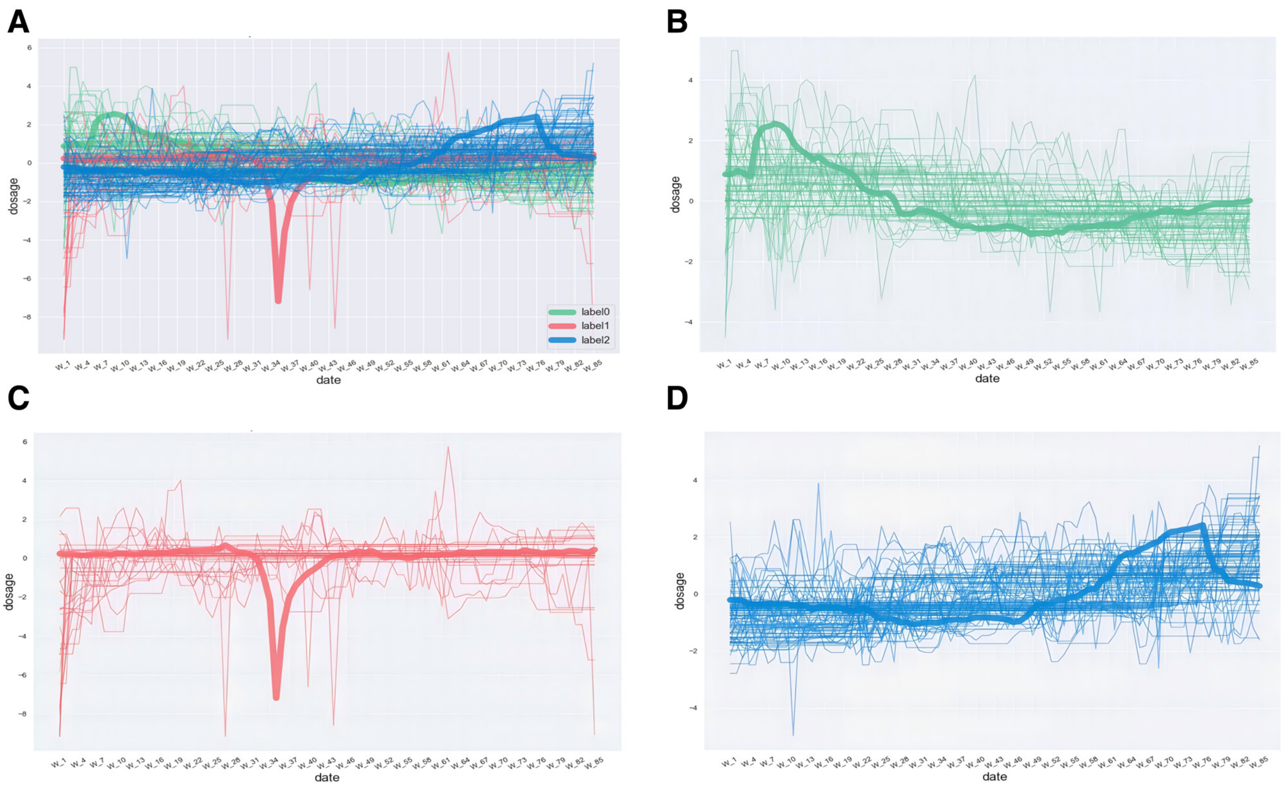

Figure 2. Trajectory clustering for time-series data for patients undergoing MMT. Green: trajectory 0; red: trajectory 1; blue: trajectory 2; vertical axis: standardized methadone dose; horizontal axis: MMT duration (weeks). MMT: Methadone maintenance treatment.

Table 2.

Performance of the machine learning models in the test data

Model	Accuracy	AUC	Precision	Recall	F1-Score
RF	0.7436	0.8272	0.5625	0.7500	0.6429
SVM	0.7179	0.4614	0.6667	0.1667	0.2667
LR	0.6667	0.7407	0.4286	0.2500	0.3158
KNN	0.6667	0.5201	0.4000	0.1667	0.2353
CatBoost	0.8205	0.7531	0.8571	0.5000	0.6316

AUC: Area under the curve; CatBoost: CatBoost classifier; KNN: K-nearest neighbor; LR: Logistic regression; RF: Random forest; SVM: Support vector machine.

groups peaked at week 6, with the largest difference observed in trajectory 1 (15 [62.5%] *vs.* 0 [0]; risk difference, 62.5% [97.5% CI, 31.2% to 78.8%]; $P < 0.001$, Supplementary Tables S5–S7, https://links.lww.com/AHM/A198).

As shown in Figure 4D and Supplementary Table S8 (https://links.lww.com/AHM/A198), the acupuncture group showed no interaction effect between the composite efficacy of the three trajectories and time (Wald χ^2 Trajectory Category * Time = 9.007, *P* [Trajectory Category*Time] = 0.061). Therefore, we further explored the trajectory differences at individual time points. The composite efficacy rates between the three trajectories differed at weeks 2 and 4 (χ^2/Fisher = 7.343, $P = 0.018$; χ^2/Fisher = 7.15, $P = 0.029$), with the composite efficacy of trajectory 2 being higher than that of trajectory 0 (week 2: 9 [23.1%] *vs.* 1 [2.7%], risk difference, 20.4% [97.5% CI, 5.1%–35.8%], $P = 0.015$; week 4: 16 [41.0%] *vs.* 5 [13.5%], risk difference, 27.5% [97.5% CI, 7.4%–44.8%], $P = 0.013$; Supplementary Table S9, https://links.lww.com/AHM/A198). The non-acupuncture group showed no significant differences across the three trajectories (Figure 4E and Supplementary Table S10, https://links.lww.com/AHM/A198).

Discussion

This secondary analysis of two prior RCTs revealed that dose trajectory was a key predictor of the composite efficacy of methadone reduction. Patients whose dosage trajectory initially increased before subsequently decreasing experienced the effects more rapidly than those whose dosage trajectory initially decreased before subsequently increasing, particularly during the early stages of the acupuncture intervention.

Reducing methadone dosage is a major focus of drug addiction research. Previous clinical trials have investigated successful dosage reduction patterns after MMT[36] and have explored the clinical efficacy of other interventions to assist in methadone dosage reduction.

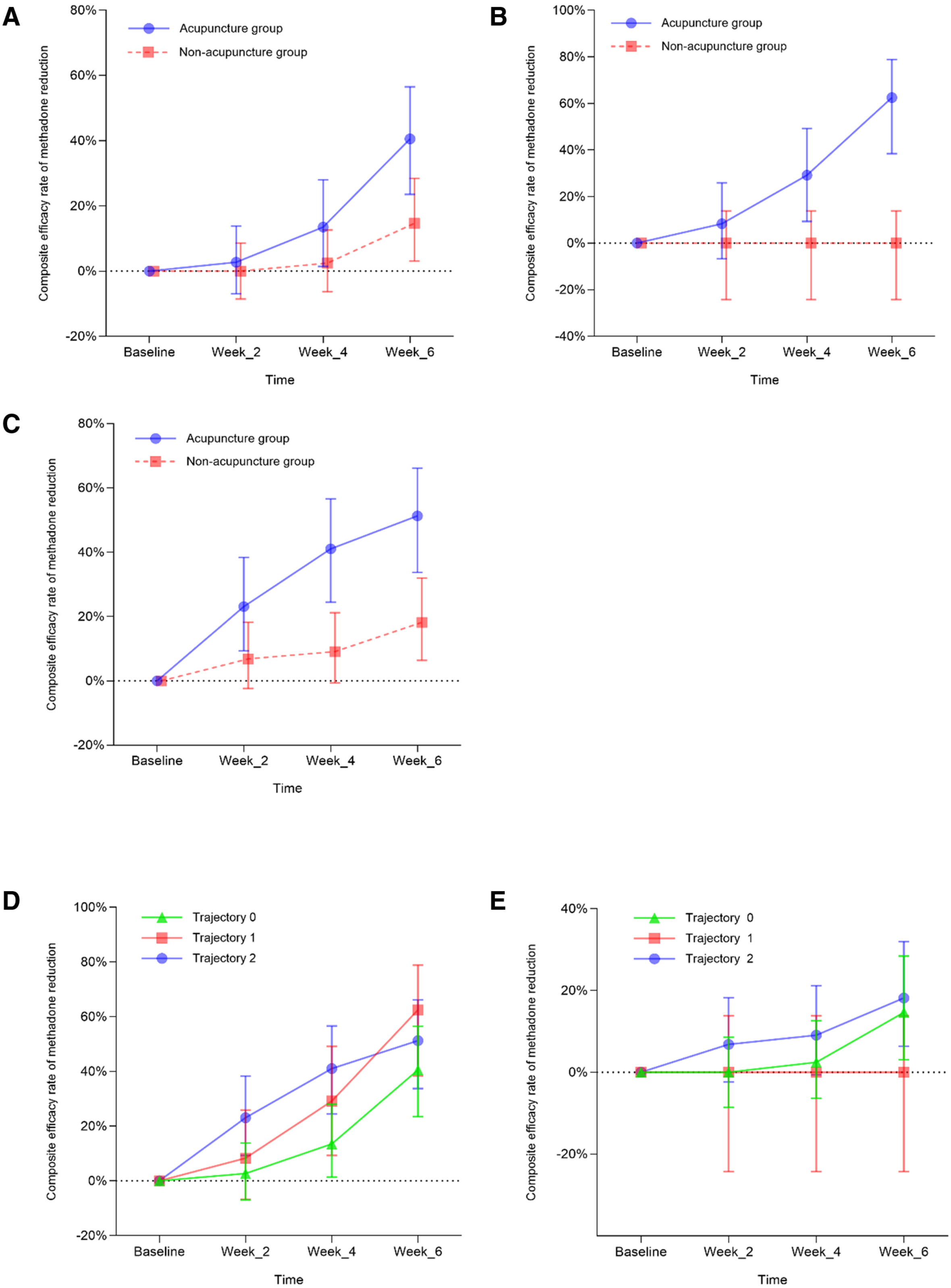

Figure 3. SHAP analysis of the model feature importance. (A) SHAP values of the predictors. The importance of each feature is ranked along the vertical axis in descending order, from top to bottom. Each point in the feature represents a single outpatient MMT case in the dataset. The position of the point on the horizontal axis indicates the degree to which the feature affects the model's prediction of the composite efficacy (the higher the value, the greater the effect on the prediction). The color of the point reflects the feature value for that case. For example, for categorical variables (eg, intervention, trajectory categories), blue and red dots correspond to 0 and 1; while blue, purple, and red dots correspond to 0, 1, and 2, respectively. For numerical variables (eg, age, educational level, and years of opioid use), blue and red dots represent lower and higher values, respectively. Overlapping points located at the same horizontal position are dispersed vertically to indicate the density of the distribution of the sample at that SHAP value. (B) SHAP-dependence plots of the features. Each scatter plot in the figure shows the marginal effect of a feature on SHAP values. Each point corresponds to one patient undergoing MMT. The horizontal and vertical axes respectively represent the feature value and the corresponding SHAP value (which indicates the contribution of the feature to the model prediction). BMI: Body mass index; MMT: Methadone maintenance treatment; SHAP: SHapley Additive exPlanations.

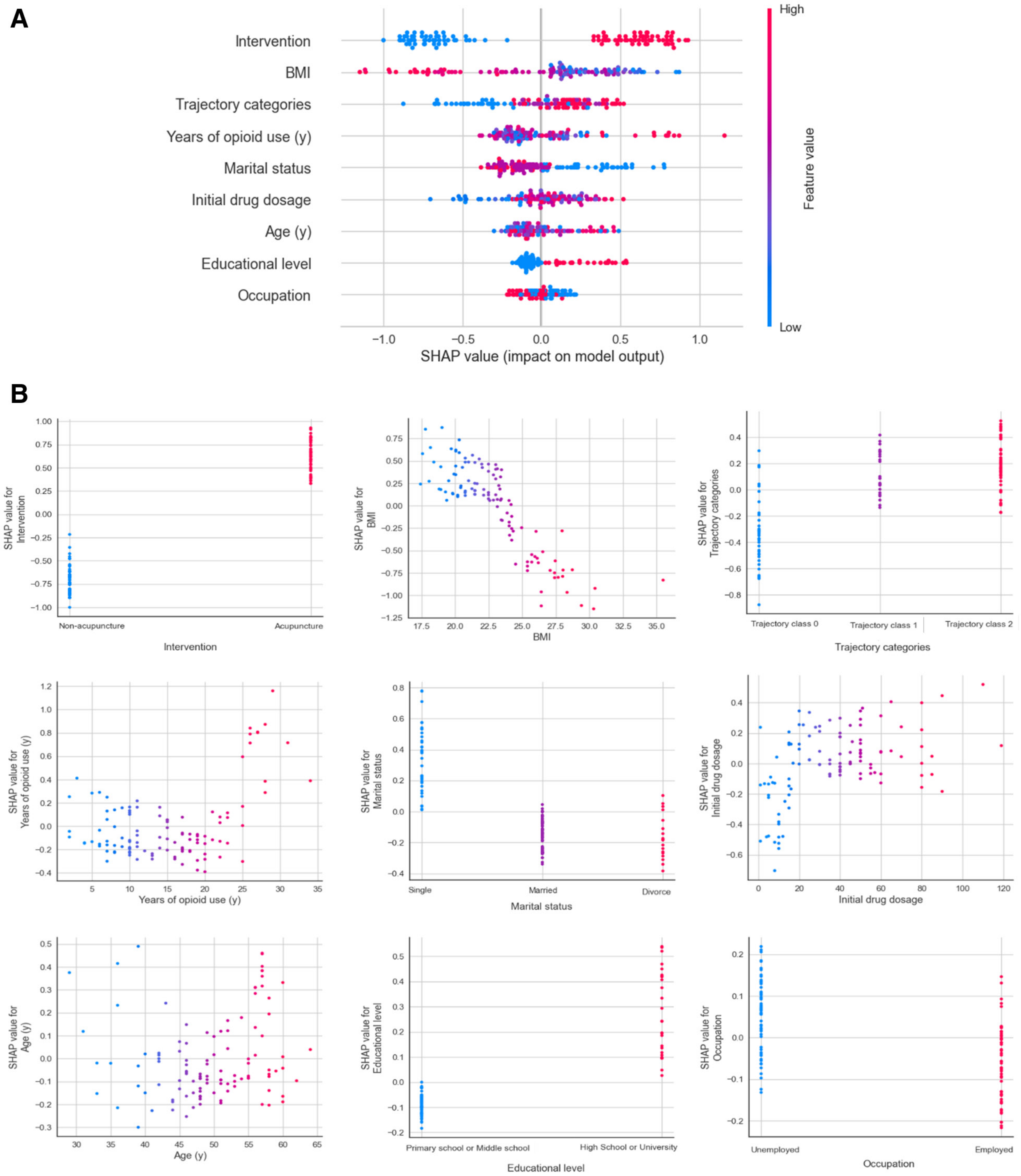

Figure 4. Composite efficacy rates of methadone reduction for the three dose trajectories according to trajectory category and intervention type. Composite efficacy rates of patients undergoing MMT on trajectories 0 (A), 1 (B), and 2 (C) at three separate time points. Composite efficacy rates at three time points after acupuncture (D) and non-acupuncture (E) treatments in patients with three dose trajectories. The composite efficacy rate for methadone dose reduction is defined as the proportion of participants who simultaneously achieved a methadone dose reduction of ≥20% and an improvement in VAS score of ≥4 points compared with those at baseline. In the line graphs, error bars represent the 95% confidence interval (CI). CI: Confidence interval; MMT: Methadone maintenance treatment; VAS: Visual analog scale.

We previously demonstrated that acupuncture not only effectively promotes reductions in methadone dosage to achieve clinical benefits but also alleviates methadone-induced adverse effects and improves patient quality of life and psychological health[9,13–14]. Clinical data can be used to identify factors influencing the effective dose of methadone[37], while artificial intelligence analysis has been shown to uncover correlations to explore the causes of drug addiction and abuse[16] and assess the risk of drug overdose[17,19]. In addition, in-depth analysis may reveal the links between clinical time-series data and clinical events, to better evaluate the relationship between the trajectory of opioid use, its effectiveness, and adverse events[24]. These analyses enable experts to develop effective treatment regimens and regulatory policies[28]. In the present study, we incorporated these analytical perspectives into an ML framework. Among the different predictive models evaluated, the CatBoost algorithm demonstrated the most balanced and reliable performance, with its accuracy and AUC values outperforming those of the other models. This could be attributed to the suitability of the algorithm for clinical datasets, as it efficiently handles categorical variables, exhibits a strong resistance to overfitting, and maintains stable performance even under conditions of a small sample size and high data heterogeneity[38–39].

Our visualization results indicate that historical dose trajectories significantly affect efficacy predictions. The distribution of trajectory 2 in the positive region of the SHAP values indicates that this trajectory positively influenced the efficacy prediction of the model. Conversely, the distribution of trajectory 0 suggests that this trajectory negatively affected model efficacy. In the natural condition without acupuncture intervention, only patients in trajectory 2 showed a modest spontaneous improvement, whereas those in trajectories 0 and 1 exhibited minimal or no efficacy changes. The subgroup analysis, which revealed higher efficacy rates in patients with trajectory 2 than in those with trajectory 0 at weeks 2 and 4 of acupuncture intervention, supported these findings. We believe that patients following trajectory 2 may have experienced increased opioid cravings and worsening withdrawal symptoms during prolonged periods of low-dose treatment, necessitating dose escalation for symptom management. However, the intolerable adverse effects of long-term high-dose methadone require dosage tapering. During this period, further methadone reduction exacerbates withdrawal symptoms[40]. Acupuncture effectively alleviates these symptoms by regulating the nervous system and promoting the release of endorphins[41]. Therefore, patients undergoing MMT with this dose trajectory adapt to dose reduction more quickly after receiving acupuncture interventions and thereby progress more effectively in their dosage reduction. In contrast, patients with trajectory 0 also experienced dose increases following prolonged low-dose treatment but remained in the phase of gradual dose escalation during the acupuncture intervention. These patients may have been more dependent on methadone, which could have led to a lower response to acupuncture. However, acupuncture therapy can gradually improve the overall patient status[13–14]. Consequently, with continued acupuncture treatment, the efficacy increases in later stages, eventually approaching that of patients with trajectory 2.

For trajectory 1, which included patients who showed no efficacy improvement under natural conditions, acupuncture treatment "revitalized" the clinical response, resulting in a marked increase in effectiveness. This finding indicates that acupuncture can restore treatment responsiveness even in patients with stable or refractory dosing trajectories. Subgroup analysis further indicated that for patients in trajectory 1 undergoing MMT, conventional treatment showed limited effectiveness in dose reduction, whereas the acupuncture group exhibited significant therapeutic advantages. These findings highlight distinct outcome characteristics before and after acupuncture. Acupuncture not only enhances existing benefits for patients following trajectories 0 and 2, but also restores responsiveness in trajectory 1.

These results indicate that individualized treatment strategies can be optimized according to the patient dose trajectories. For patients with an "increase–decrease" trajectory (trajectory 2), early integration of acupuncture may facilitate a more rapid dose reduction. For those with a "long-term low dose followed by escalation" trajectory (trajectory 0), sustained and continuous acupuncture intervention with careful clinical support may be required. Acupuncture can complement conventional treatments in patients with relatively stable dosing patterns (trajectory 1). Thus, incorporating dose trajectory information into clinical decision-making may improve the success of methadone tapering, highlighting the potential role of acupuncture in personalized MMT strategies.

In addition, the SHAP results revealed that a higher BMI had a greater negative impact on efficacy. We believe this is because obesity reduces the methadone metabolic rate[42], resulting in obese patients being exposed to more severe or longer-lasting withdrawal symptoms, in addition to the poorer sleep quality and constipation commonly experienced by patients undergoing MMT[43–44], making it more difficult to effectively reduce the methadone dose at a higher BMI.

The strengths of this study include the data analysis of two rigorous RCTs with standardized blinding designs, treatment plans, and high-quality data. Moreover, the outpatient medication records used contain a large amount of data over a long period, providing time-series data support for in-depth analyses. Finally, research ideas integrated clinical RCT and outpatient medication record data, expanding the analytical ideas for clinical research and for intelligent decision-making in traditional Chinese medicine[45]. The method for constructing the predictive models in this study was also informative for other studies, including time-series clinical data. However, one limitation of this study was that the data were derived from a special clinical sample with a relatively small sample size. On the one hand, this restricted the exploration of more complex ML methods, such as neural networks, but on the other hand, the limited sample size and heterogeneity may have constrained the generalizability of the model, resulting in the relatively modest AUC. Nevertheless, the overall performance of the model indicates that there is room for improvement. Future studies could expand the sample size and explore advanced strategies, such as ensemble and transfer learning, to further enhance predictive performance. Importantly, the performance of the predictive model did not influence the analysis of trajectory categories or acupuncture efficacy. Therefore, we are confident that our conclusions remain robust.

Conclusions

Overall, this analysis of methadone dose trajectories provides several significant clinical insights. First, this study showed that among patients receiving acupuncture interventions, those with a trajectory of increasing followed by decreasing doses achieved results faster and more easily than those with a trajectory of decreasing followed by increasing doses. Our results demonstrate that modeling based on the dose trajectory category, interventions, and baseline data is feasible, and that the dose trajectory is a key predictor of the composite efficacy of methadone reduction. These findings may help to guide physicians in assessing the efficacy of acupuncture-assisted methadone reduction and contribute to the improvement of acupuncture treatment strategies for opioid addiction.

Conflicts of interest statement

The authors declare no conflict of interest.

Funding

The study was supported by the National Natural Science Foundation of China (82174527, 82405556); the Project of First-Class Universities and High-level Dual Discipline for Guangzhou University of Chinese Medicine (A1-2601-24-414-109Z71, A1-2601-24-415-109Z50, and A1-2601-24-415-109Z76); and Zhongshan Coma and Wake-up Promotion Workshop of Traditional Chinese Medicine (A2-3105-242-109-001). The China Postdoctoral Science Foundation General Project (2024M750464).

Author contributions

All authors participated in design of this study. Baochao Fan and Yiming Chen drafted the manuscript. Liming Lu and Jingchun Zeng revised it. Baochao Fan and Yiming Chen participated in designing the search strategies. Chen Chen and Peiming Zhang participated in the data extraction. Baochao Fan, Yiming Chen and Chen Chen participated in data analyses. Liming Lu arbitrated any disagreements in the process of the study. All authors read and approved the final manuscript.

Ethical approval of studies and informed consent

This *post hoc* analysis of de-identified data complied with the *Declaration of Helsinki* and was approved by the Guangzhou University of Chinese Medicine Institutional Review Board (YJ-KY-2025-035), which waived the requirement for informed consent.

Acknowledgments

The author sincerely thanks the medical and administrative staff of Guangzhou Huiai Hospital, Guangzhou Baiyun District Maternal and Child Health Hospital, Shunde Wu Zhong Pei Hospital, The Third People's Hospital of Foshan, The Third People's Hospital of Zhaoqing, and Zhongshan Second People's Hospital for providing clinical data for this study. Special thanks to Yuting Wang, Yu Dong, Dehui Nie, Chenyang Tao, and Cui Li for their valuable support in data collection and patient management. Ultimately, this work would not have been possible without the cooperation of all the patients participating in the clinical trials, and we are deeply grateful for their contributions.

Data availability

Data supporting the findings of this study will be made available from the corresponding author lulimingleon@126.com.

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