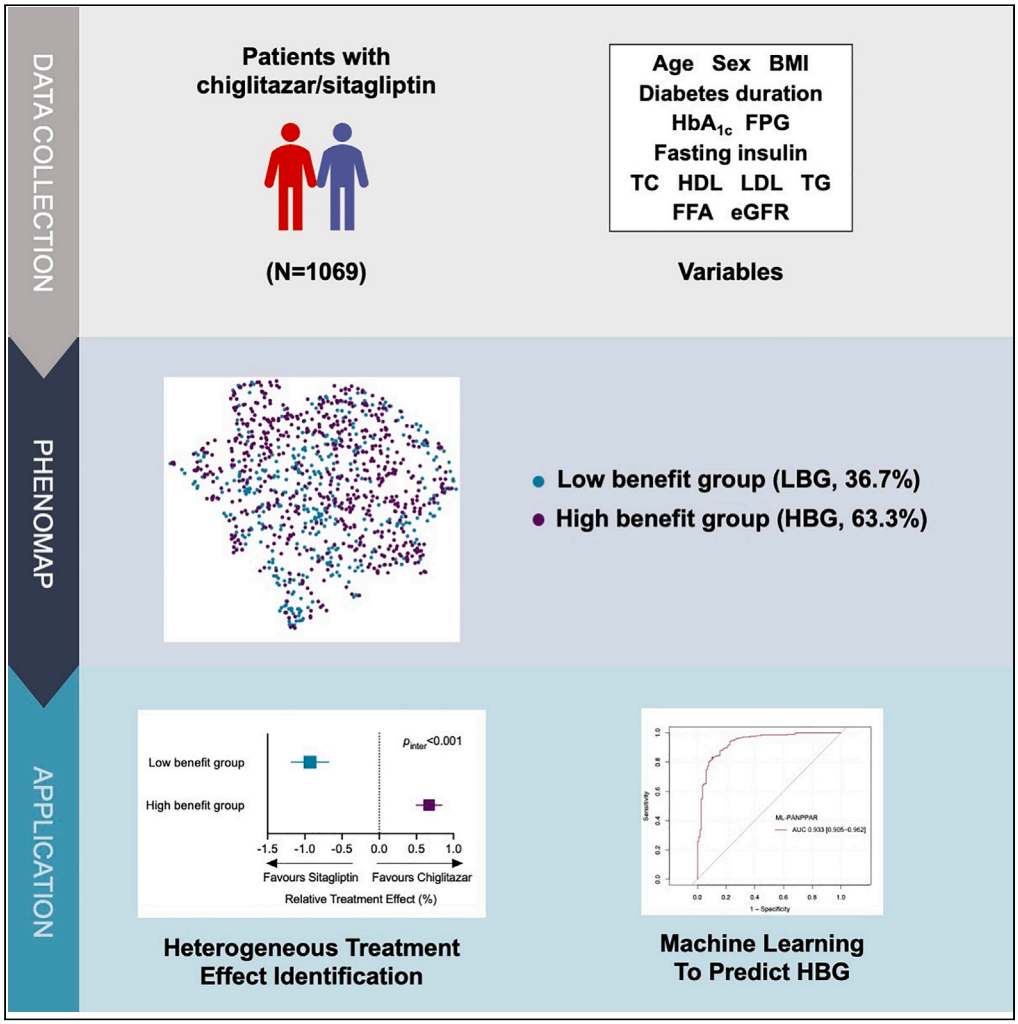
iScience

CellPress
OPEN ACCESS

Article

Personalized glucose-lowering effect of chiglitazar in type 2 diabetes



Qi Huang, Xiantong Zou, Yingli Chen, ..., Jian Zhou, Weiping Jia, Linong Ji

wpjia@sjtu.edu.cn (W.J.)
jiln@bjmu.edu.cn (L.J.)

Highlights

Machine learning applied to personalized glucose-lowering effect of chiglitazar

More patients had a great glycemic response to chiglitazar than sitagliptin

With sex, BMI, HbA_{1c}, HDL, and fasting insulin, responders could be identified

Huang et al., iScience 26, 108195
November 17, 2023
https://doi.org/10.1016/j.isci.2023.108195

iScience

CellPress
OPEN ACCESS

Article

Personalized glucose-lowering effect of chiglitazar in type 2 diabetes

Qi Huang,[1,3] Xiantong Zou,[1,3] Yingli Chen,[1] Leili Gao,[1] Xiaoling Cai,[1] Lingli Zhou,[1] Fei Gao,[2] Jian Zhou,[2] Weiping Jia,[2,*] and Linong Ji[1,4,*]

SUMMARY

Chiglitazar (carfloglitazar) is a peroxisome proliferator-activated receptor pan-agonist presenting non-inferior glucose-lowering efficacy with sitagliptin in patients with type 2 diabetes. To delineate the subgroup of patients with greater benefit from chiglitazar, we conducted a machine learning-based post-hoc analysis in two randomized controlled trials. We established a character phenomap based on 13 variables and estimated HbA_{1c} decline to the effects of chiglitazar in reference to sitagliptin. Out of 1,069 patients, 63.3% were found to have greater reduction in HbA_{1c} levels with chiglitazar, while 36.7% showed greater reduction with sitagliptin. This distinction in treatment response was statistically significant between groups ($p_{interaction}$<0.001). To identify patients who would gain the most glycemic control benefit from chiglitazar, we developed a machine learning model, ML-PANPPAR, which demonstrated robust performance using sex, BMI, HbA_{1c}, HDL, and fasting insulin. The phenomapping-derived tool successfully identified chiglitazar responders and enabled personalized drug allocation in patients with drug-naïve diabetes.

INTRODUCTION

Type 2 diabetes (T2DM) is a chronic and highly heterogeneous progressive condition and current guidelines have recommended a shift from a uniform treatment approach to personalized therapeutic strategies. Precision medicine has emerged as a promising patient-centered concept with the capacity to enhance the management of T2DM by incorporating genetic, lifestyle, and environmental variables.[1] Currently, studies in diabetes subclassification,[2,3] therapy selection,[4] and complications predictions[5] have advanced the field of precision therapeutics.

Identifying individuals with optimal responses to specific anti-diabetic drugs constitutes a crucial aspect of precision therapeutics.[6] Researchers have utilized genetic or clinical features to identify drug responders who are more likely to have better glucose control, fewer adverse effects, or improved cardiorenal outcomes with sulfonylureas,[4] dipeptidylpeptidase 4 (DDP4) inhibitors,[7] glucagon-like peptide 1 (GLP-1) receptor agonists,[8] or sodium-glucose cotransporter 2 (SGLT2) inhibitors.[5,8] The conventional approach to identifying these potential features involves conducting a one-variable-at-a-time subgroup analysis in randomized controlled trials or real-world databases, but results may have limited statistical power and generalizability.[9,10] Instead, a shift toward machine learning technologies, such as gradient forest analysis[11] and phenomapping[12] has shown superiority in the identification of complex patterns and phenotypes. These methods are expected to shape precision medicine in diabetes, although substantial applications and validations are required.

Chiglitazar (carfloglitazar) is a new pan-peroxisome proliferator-activated receptor (pan-PPAR) agonist known for its substantial glucose-lowering effects,[13] with a unique capacity to improve insulin sensitivity and mitigate dyslipidemia.[14–16] In a recent phase 3 trial ChiglitAzar Monotherapy with Sitagliptin (CAMS), chiglitazar demonstrated similar glucose-lowering efficacy when compared to sitagliptin,[17] and it was approved by the Chinese FDA as an anti-diabetic drug in type 2 diabetes for individuals who did not attain satisfactory glycemic control through lifestyle therapy.

Chiglitazar and sitagliptin operate through distinct physiological mechanisms to achieve their glucose-lowering effects. Therefore, we hypothesized the existence of a subpopulation that may exhibit a more favorable response to chiglitazar compared to sitagliptin. The application of precision medicine may assist in identifying these individuals and revealing their potential clinical characteristics. In our study, we aimed to develop machine learning-based tools for the personalized assessment of the glucose-lowering efficacy of chiglitazar and identify the subgroup that could gain greater benefits from its use. It may provide valuable insights into the precision selection of chiglitazar in clinical practice.

[1]Department of Endocrinology and Metabolism, Peking University People's Hospital, Beijing 100044, China
[2]Department of Endocrinology and Metabolism, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai Clinical Center for Diabetes, Shanghai Diabetes Institute, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai 200233, China
[3]These authors contributed equally
[4]Lead contact
*Correspondence: wpjia@sjtu.edu.cn (W.J.), jiln@bjmu.edu.cn (L.J.)
https://doi.org/10.1016/j.isci.2023.108195

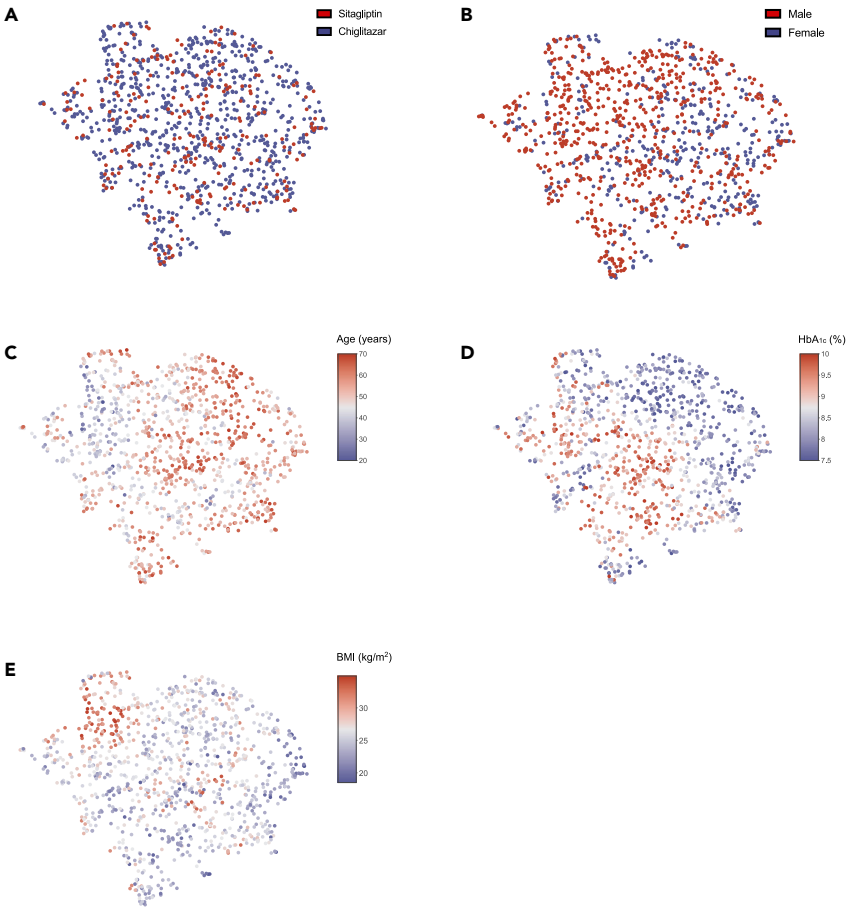


Figure 1. Phenotypical architecture of the study population

(A–E) The graphs illustrate the distribution of patient characteristics, such as (A) treatment arm allocation, (B) sex, (C) age, (D) HbA_{1c}, and (E) BMI within the topological space representing all patients (N = 1069) in study. Each point represents an individual participant, and the distance between points is determined by the Gower distance, calculated from pre-randomization features, with shorter distances indicating greater similarity.

RESULTS

Baseline characteristic of the study population

We included a total of 1,069 patients who had received at least one dose of either chiglitazar (N = 822, 76.9%) or sitagliptin (N = 248, 23.1%) (Table S1). In the overall population, the mean age was 51.0 ± 9.6 years, with 62.7% being male. The mean HbA_{1c} level was 8.6 ± 0.7% (70 ± 7.6 mmol/mol), and the mean duration of diabetes was 1.4 years. No significant differences in baseline characteristics were observed between the two treatment groups.

At week 24, the least-squares mean of HbA1c was 1.43% (95%CI 1.35 to 1.50) [15.6 mmol/mol (14.7–16.4)] with chiglitazar and 1.38% (95%CI 1.24 to 1.51) [15.0 mmol/mol (13.5–16.5)] with sitagliptin ($p > 0.05$). The proportions of patients reaching HbA_{1c} <7.0% (53 mmol/mol) were also similar between the two treatment groups (Figure S1).

Individualized treatment effect of the study population

Figure 1 displays a visual representation of the topological structure of the entire participant cohort. The allocation of treatments appeared to be evenly distributed across the sample (Figure 1A) However, there was clustering in relation to characteristics such as sex, age, HbA_{1c}, and BMI (Figures 1B–1E). These clusters reflect the inherent heterogeneity within the treatment groups with regard to these demographic features.

We derived the estimation of the difference in the HbA_{1c} decline between chiglitazar and sitagliptin from individualized weighted models. The average relative treatment effect of the whole population was 0.06% (95%CI 0.05 to 0.07) [0.65 mmol/mol (0.55–0.76)] (Figure S2A). No significant correlation was observed between pre-designated treatment allocation and the estimated treatment effects (Figure S2B).

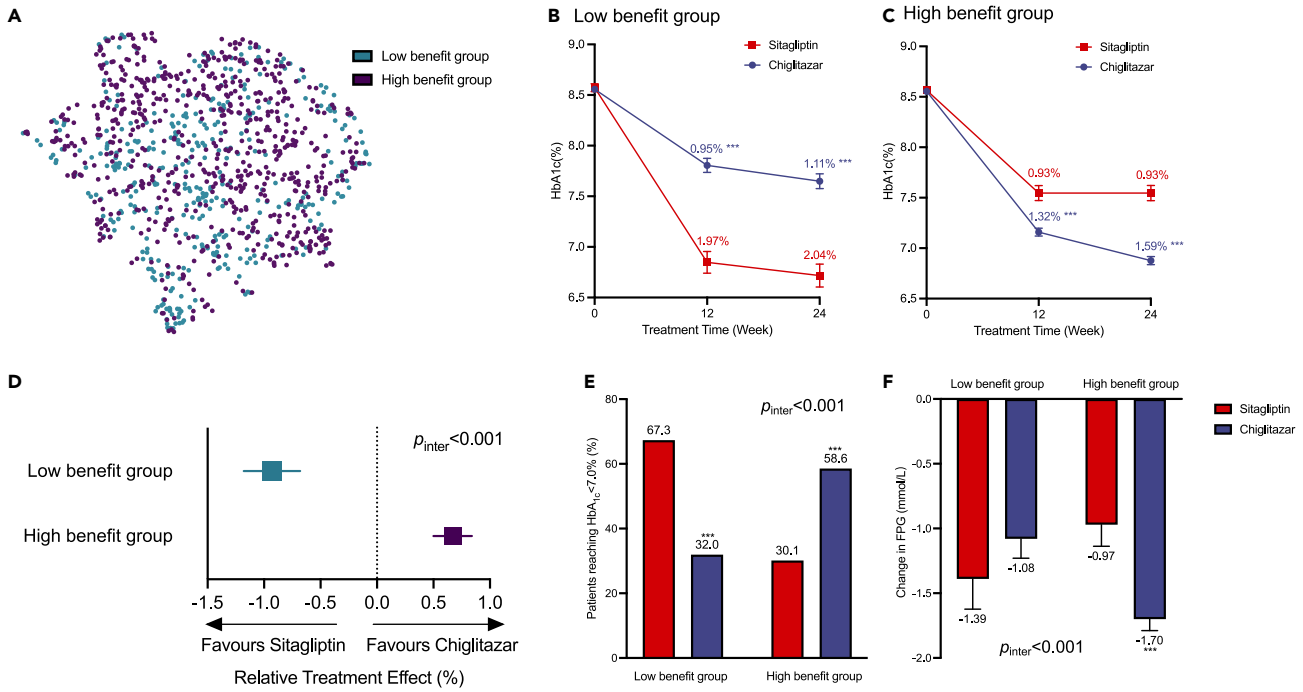


Figure 2. The glucose-lowering efficacy between chiglitazar and sitagliptin in low-benefit group (LBG) and high-benefit group (HBG)

(A) The distribution of patients in the LBG and HBG within the topological space representing all patients (N = 1069) in the study.

(B) The least-squares mean change of HbA1c from baseline to 12 weeks and 24 weeks in LBG, adjusted by baseline stratum and baseline HbA1c.

(C) The least-squares mean change of HbA1c from baseline to 12 weeks and 24 weeks in LBG, adjusted by baseline stratum and baseline HbA1c.

(D) The least-squares mean and 95% CI difference of HbA_{1c} between chiglitazar and sitagliptin at 24 weeks in LBG and HBG, adjusted by age, sex and baseline HbA_{1c}.

(E) The percentages of patients reaching HbA_{1c}<7% (53 mmol/mol) at week 24 in LBG and HBG.

(F) The least-squares mean and standard error of change in FPG in HBG and LBG, adjusted by baseline stratum and baseline FPG. ***, p < 0.001 compared to the sitagliptin arm at the specified time point. The p value for interaction was determined by assessing the treatment-by-group interaction term. Error bar in (B) and (C) shows standard error of the mean.

Glucose-lowering efficacy and secondary outcomes

With the use of the phenomapping-derived model, we identified 677 (63.3%) patients as the high-benefit group (HBG) and 392 (36.7%) as the low-benefit group (LBG). Patients of HBG were more likely to be old, female, had a higher BMI, lower HbA_{1c}, worse lipid profile, and higher levels of insulin resistance (Table S2). The distribution of the HBG and LBG was heterogeneous on the phenomap (Figure 2A). Within the LBG (Figure 2B), the least-squares mean (95% CI) decline of HbA_{1c} of chiglitazar and sitagliptin was 1.11% (0.96–1.25) [12.1 mmol/mol (10.5–13.6)] and 2.04% (1.82–2.26) [22.2 mmol/mol (19.8–24.6)] (relative treatment effect of chiglitazar versus sitagliptin: −0.93% (−1.18 to −0.68) [-10.1 mmol/mol (−12.9 to −7.4)]); In the HBG (Figure 2C), the corresponding figure was 1.59% (1.52–1.68) [17.3 mmol/mol (16.6–18.3)] and 0.93% (0.78–1.08) [10.1 mmol/mol (8.5–11.8)] (relative treatment effect: 0.66% (0.50–0.83) [7.2 mmol/mol (5.5–9.0)]). There was a significant interaction between treatment effect and subgroups (p < 0.001, Figure 2D). Chiglitazar demonstrated a higher proportion of individuals achieving an HbA1c level below 7.0% (53 mmol/mol) and a greater reduction in fasting plasma glucose (FPG) within the HBG (Figures 2E and 2F).

In terms of secondary outcomes, there was no significant heterogeneity observed in changes in HOMA-IR, HDL, and TG at week 24 (Figure S3), although chiglitazar reduced HOMA-IR in a greater magnitude in the HBG. In the safety analysis, a mild increase in mild edema events and a larger decrease in hematocrit were observed with chiglitazar treatment in the HBG (Table S3).

To explore whether patients respond differently to different doses of chiglitazar, we conducted the analysis in patients taking two dosages of chiglitazar, and the phenotypical architecture of patients is presented in Figure S4. Out of 822 participants, the majority (N = 635, 77.6%) showed a greater decline in HbA_{1c} with 48 mg chiglitazar in comparison with 32 mg (p < 0.001, Figure 3). Participants favoring 48 mg dose had older age, similar levels of HOMA-IR, lower HbA_{1c} and FPG and a higher level of LDL at baseline (Table S4).

Identifying responders of chiglitazar using machine learning

We constructed an XGBoost model using 13 baseline features in all patients taking chiglitazar to identify chiglitazar responders, who were patients in the HBG assessed by phenomapping. SHAP analysis showed sex, BMI, fasting insulin, HbA_{1c}, and HDL were the dominating

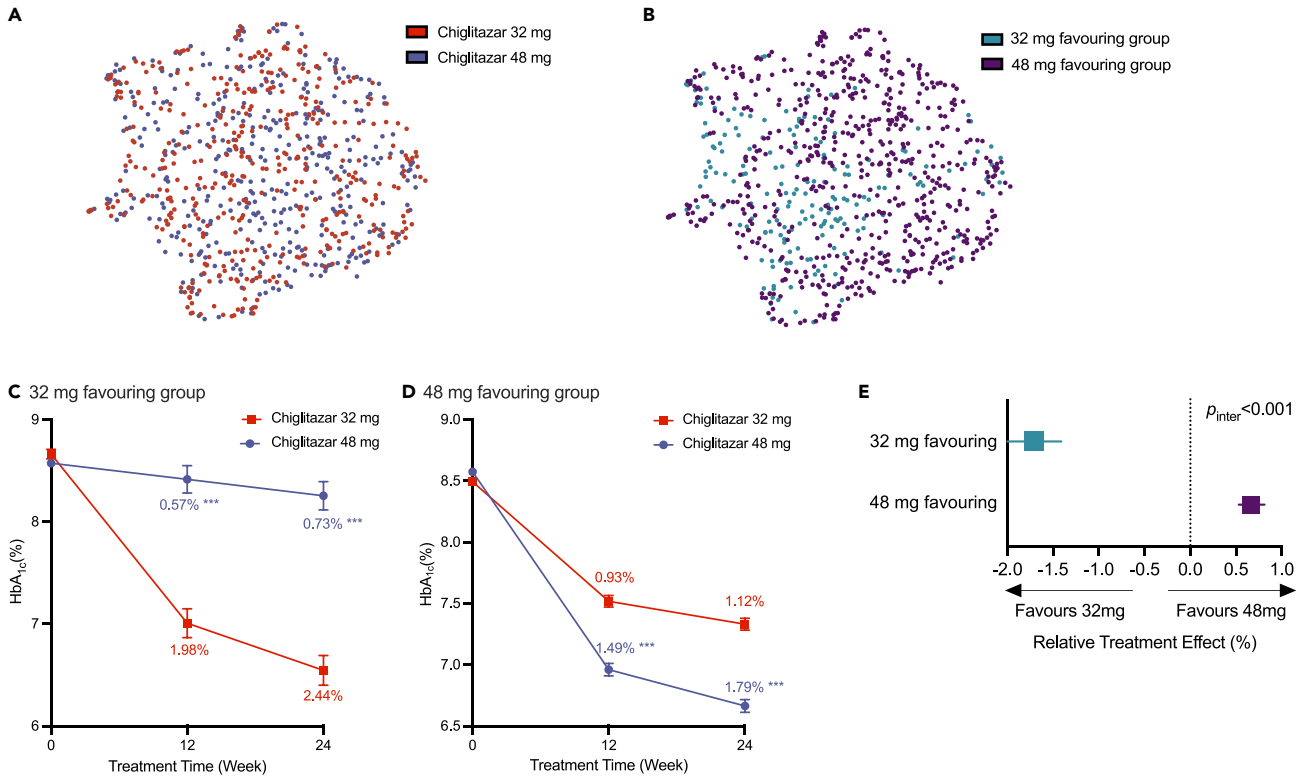


Figure 3. The glucose-lowering efficacy between chiglitazar 48 mg and 32 mg in 32 mg favoring group and 48 mg favoring group

(A) The distribution of patients taking chiglitazar 32 mg and 48 mg within the topological space representing all patients taking chiglitazar (N = 812) in study.
(B) The distribution of patients in 32 mg favoring group and 48 mg favoring group within the topological space representing all patients taking chiglitazar in study.
(C) The relative decline of HbA_{1c} between chiglitazar 48 mg and chiglitazar 32 mg at 24 weeks in 32 mg favoring group adjusted by age, sex and baseline HbA_{1c}.
(D) The relative decline of HbA_{1c} between chiglitazar 48 mg and chiglitazar 32 mg at 24 weeks in 48 mg favoring group adjusted by age, sex and baseline HbA_{1c}.
(E) The least-squares mean and 95% CI difference of HbA_{1c} between chiglitazar 48 mg and 32 mg in 32 mg favoring group and 48 mg favoring group, adjusted by baseline stratum and baseline HbA_{1c}. ***, $p < 0.001$ compared to arm chiglitazar 32 mg at the specified time point. The p value for interaction was determined by assessing the treatment-by-group interaction term. Error bar in (C) and (D) shows standard error of the mean.

features (Figure 4A). We rebuilt a model called ML-PANPPAR which incorporated these 5 most important features. This model demonstrated excellent discrimination (ROC-AUC 0.933 [95%CI 0.905 to 0.962]) and ideal calibration (p = 0.460 for Hosmer-Lemeshow test) in the internal validation dataset (Figures 4B and 4C). The optimal cut-off value of 0.726 had a high sensitivity of 0.896 and a specificity of 0.830. This implement showed high net benefits across the range of prevalence of chiglitazar responders (Figure 4D).

We hypothesized sex was an important feature in determining a patient's response to chiglitazar due to the gender disparity between HBG and LBG and the high SHAP value of sex in the machine learning analysis. We estimated the relative treatment effect by sex in all participants before and after matched by sex using the IPTW method (Table S5). There was a significant interaction between sex and treatment effect only after matching (p = 0.031), and the positive effect of chiglitazar versus sitagliptin was only observed in females (Figure S5).

DISCUSSION

Our study implemented a phenomapping-derived tool to unveil the intricate clinical characteristics associated with drug responses and identify subpopulations exhibiting an improved response to the pan-PPAR agonist chiglitazar. We developed a machine learning-based tool ML-PANPPAR for clinical application.

Machine learning methods have gained extensive success in uncovering responders to anti-diabetic treatments. Our analysis added a new dimension to the understanding of the response to chiglitazar by discovering a comprehensive subpopulation that had better glycemic responses. The conventional method to dissect drug-responsive subpopulation is to conduct one-variable-at-a-time subgroup analysis, however, the conclusion used to be weakened due to the limited statistical power.[9,10] The false discovery rate of heterogeneous treatment effect in exploratory subgroup analysis can reach up to 75% and even 33% in confirmatory subgroup analysis.[18] Predictive approaches offer a solution by using multiple variables to predict drug responses for each individual.[19] Nonetheless, this approach still presents challenges in obtaining a robust estimation, particularly when taking into account the abundance of variables and their potential interaction effects.[20] Instead, phenomapping-based approach addresses this challenge by directly estimating the treatment effect differences between two drugs,

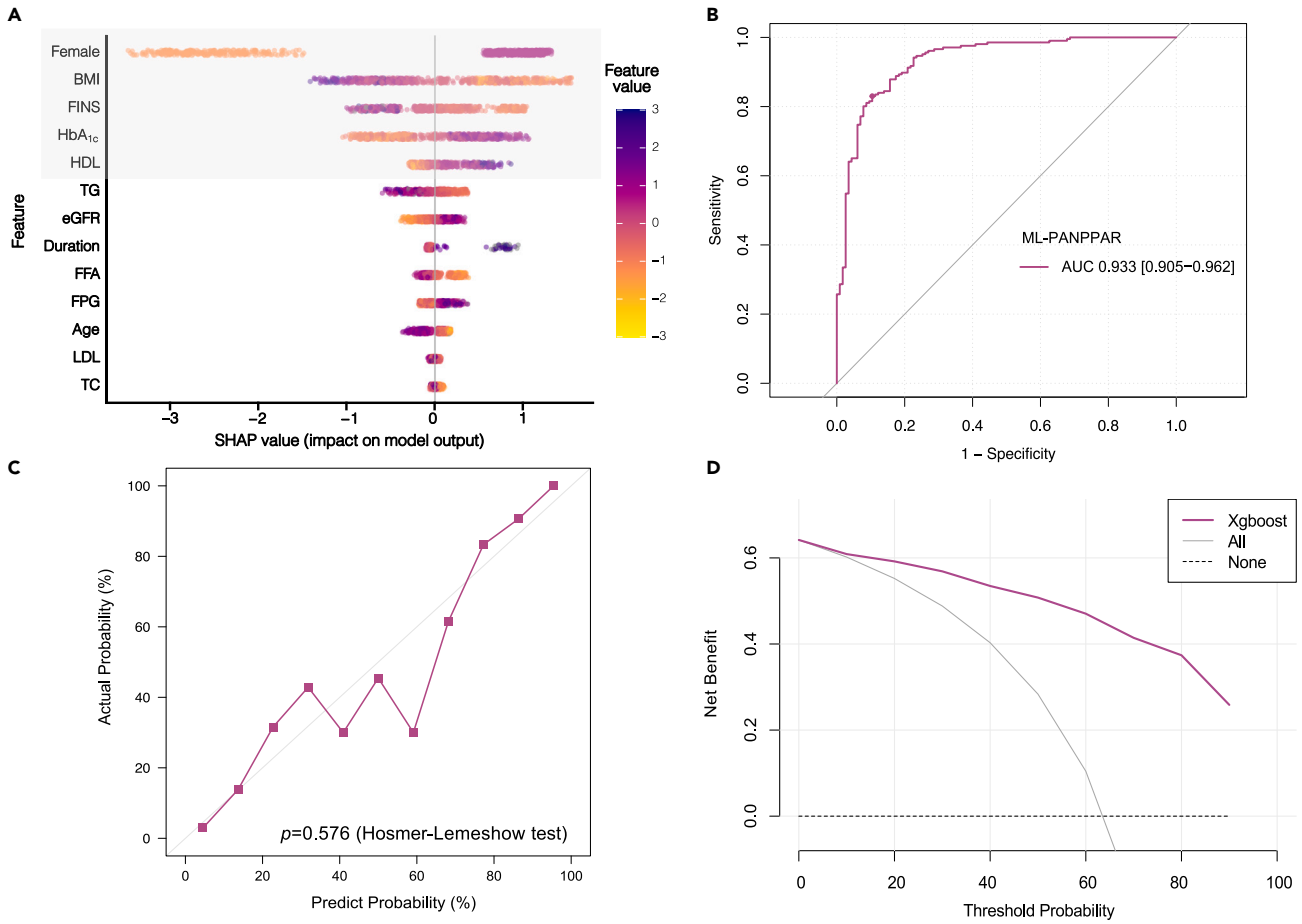


Figure 4. Variable selection and model performance of ML-PANPPAR to predict patients with high glucose response to chiglitazar

(A) The SHAP summary plot reflecting the importance of 13 variables in the XGBoost model. The y axis indicates the predictors ranking in descending order of importance. The y axis ranks the predictors in descending order of importance, while the x axis indicates the impact on the model output. Larger values denote a more significant positive influence on the prediction. The legend employs a gradient color scheme to represent different values of each variable. The points within the graph correspond to individual study participants. Among all the variables in the model, the top 5 features were selected to construct the ML-PANPPAR prediction model.

(B) Receiver operating characteristic of ML-PANPPAR.

(C) Calibration plot of ML-PANPPAR: The gray line represents the ideal calibration, while the purple line depicts the actual calibration. The discrepancy between the actual and ideal calibration was assessed using the Hosmer-Lemeshow test, with $p > 0.05$ indicating no significant difference.

(D) Decision curve illustrating the net benefit of ML-PANPPAR at a given threshold probability (the probability of patients falling into the high-benefit group). The dashed line represents the net benefit when no patients are intervened with, while the gray line assumes the net benefit when intervening with no patients. The purple line assumes the net benefit using ML-PANPPAR. BMI, body mass index. FINS, fasting insulin. HbA_{1c}, glycemic hemoglobin. HDL, high-density lipoprotein cholesterol. TG, triglycerides. eGFR, estimated glomerular filtration rate. FFA, free fatty acids. LDL, low-density lipoprotein cholesterol. TC, total cholesterol.

avoiding the necessity to assess interactions between treatments and covariates.[21] Furthermore, the robustness of the estimations was improved through the incorporation of parameter weights assigned to each participant, which were calculated based on information from all other participants.[22]

The phenomap in our study suggested a complex phenotypical structure among participants. The clustered distributions of demographic features, including glycemic and lipid profiles, suggested potential differential effects on drug responses. We explored features affecting drug response by comparing HBG and LBG and found females, higher BMI individuals, those with lower HDL, and higher insulin resistance markers had better responses to chiglitazar. This is in concordance with other clinical trial data that a greater long-term response to PPARγ agonist was observed in females with obesity.[23,24] It should be noted that there appeared to be a tendency for a higher incidence of edema in the high-benefit group, although the majority of cases were mild. Although sitagliptin and chiglitazar achieved similar glycemic reductions overall, they employed distinct pharmacological mechanisms to lower blood glucose. Chiglitazar activates PPARs, forms complexes with retinoid X receptors (RXRs) and binds to specific DNA sequences known as PPAR response elements (PPREs), leading the upregulation of genes involved in insulin sensitization and inflammation such as angiopoietin-like 4 (ANGPTL4),[25] pyruvate dehydrogenase kinase 4 (PDK4),[26] and

retinol-binding protein 4 (RBP-4).[27] In contrast, sitagliptin increases the levels of endogenous incretin hormones like GLP-1, leading to enhanced insulin secretion.[28] Sitagliptin has a modest effect on improving insulin resistance,[29] and a previous study identified a negative association between insulin resistance and glycemic response to DPP-4 inhibitor therapy.[7] Similar to our study, a propensity score-matched analysis on a retrospective cohort found that in patients with adequate HbA_{1c} control, TZD users had significantly better insulin sensitivity compared with DPP-4 inhibitor users, whereas DPP-4 inhibitor users secreted more insulin than TZD users.[30] Our study indicates that, in patients with obesity and higher insulin resistance, chiglitazar may be a preferable choice to consider over sitagliptin.

Our exploratory analysis revealed a significant interaction between sex and treatment response after IPTW matching, suggesting that sex is a crucial factor in determining drug efficacy. The sex-specific effect observed in this context could potentially be elucidated by the influence of sex hormones on PPARs. Estrogen has a positive effect on the expression and function of PPARγ *in vitro* but testosterone and dihydrotestosterone do not have the same impact.[31] There was a paradoxical influence of androgen levels, where testosterone deficiency in men increased insulin resistance and visceral adipose tissue, while low androgen levels in women reduced risk of insulin resistance and adipose accumulation.[32] It was also proposed that PPAR agonists may have a slower clearance rate in female humans as a result of gender differences in the expression of CYP2C8, a key enzyme in the metabolism of PPARγ agonists.[33] Further research is still needed to disclose the sex disparity.

A pharmacokinetics study indicated that a daily dose above 48 mg provided sufficient activation of all PPAR subtypes, resulting in more balanced metabolic effects.[15] Our analysis on 32 mg and 48 mg of chiglitazar also revealed most participants may benefit from a higher dose and around 20% of participants may obtain more benefit with a smaller dose. Participants favoring 48 mg showed lower HbA_{1c} and higher LDL levels, although there was no difference between BMI, insulin resistance, and triglycerides. This was consistent with the CAMP study that in participants with baseline HbA_{1c}>8.5% (69 mmol/mol), HbA_{1c} declined similarly in between two doses and in another subgroup with baseline HbA_{1c}<8.5% (69 mmol/mol), 48 mg performed much better than 32 mg in glucose lowering.[14] Although the relation between PPAR activation pattern and glucose efficacy remained unknown, the baseline glucose and lipid level may affect the patient's response to different dosages of chiglitazar, implying the need for precision drug therapy. Given that a substantial proportion of patients (68%) who exhibited a preference for 32 mg of chiglitazar were anticipated to be LBG (Table S4), whose primary choice would be sitagliptin, we opted not to develop a machine learning-based predictive model for identifying different doses.

We constructed the ML-PANPPAR tool with the aim of simplifying the identification of individuals who may respond favorably to chiglitazar treatment. The model provided new insights into the complex underlying mechanisms that contribute to glycemic response. It provided reassurance that factors such as sex, BMI, HbA_{1c}, HDL levels, and insulin levels, which are indicative of insulin resistance, played a role in determining responses to chiglitazar. We minimized the predicting variables of ML-PANPPAR for clinical usability, and our algorithm demonstrated excellent internal performance. For patients who experienced inadequate glycemic control despite diet and exercise, ML-PANPPAR is the first algorithm to predict their glycemic responses to chiglitazar based on sex, BMI, HbA_{1c}, fasting insulin, and HDL level prior to treatment. This could assist healthcare providers in making precise treatment decisions for this medication in their daily clinical practice. The ML-PANPPAR model was publicly available on http://diabetesmodels.com:9001/index?type=3.

In conclusion, our study emphasizes the potential of chiglitazar to improve glycemic control within a distinct subgroup of type 2 diabetes characterized by insulin resistance and obesity. The machine learning model ML-PANPPAR, derived from phenomapping, emerges as a valuable tool for precision drug selection to decide whether a patient should initiate chiglitazar or sitagliptin. However, further validation through evidence-based external studies is imperative for the clinical implementation of ML-PANPPAR in the future. Our research represents a significant stride in promoting the integration of artificial intelligence into the realm of precision pharmacotherapy for type 2 diabetes.

Limitations of the study

There are some limitations in our study. Firstly, we were only able to replicate our results in CMAS and CMAP studies without external validation. Our results should be validated in more high-quality randomized trials with long-term endpoints. Moreover, our analysis only recruited Chinese patients with drug-naïve type 2 diabetes without taking other medications, which limited its generalizability to other races and patients on different therapeutic regimes. Our study only compared the treatment effect with sitagliptin and further comparison with other anti-diabetic agents especially metformin, glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors are necessary. Then, our study only used phenomapping-derived method to estimate the treatment effect, other machine learning methods, such as gradient tree analysis and causal forest were untapped. The features used in our model were limited, making it challenging to identify other biological determinants of glycemic responses. For example, a study has indicated that the addition of DPP4 inhibitors might significantly improve oxidative stress, which could be a key pathway for enhancing β-cell responsiveness34 and some hormone levels, such as serum apelin35 and prolactin36, would affect the glycemic response to metformin. We could use genomic, metabolomic, and proteomic variables as predictors to achieve a precise estimation of drug responses in the future. Finally, the phenotypical interrelationship among participants was complex to interpret and explainability should be improved.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2023.108195.

ACKNOWLEDGMENTS

This study was partly funded by Beijing Nova Cross program (Z211100002121169) (to X.Zo.), Shanghai Research Center for Endocrine and Metabolic Diseases (2022ZZ01002 to W.J), Beijing Nova Program of Science and Technology (Z191100001119026 to X.Zo.), Peking University People's Hospital Research And Development Funds (RDH2021-10 to X.Zo.), the National Natural Science Foundation of China (81970708 to L.J); Clinical Medicine Plus X - Young Scholars Project, Peking University, the Fundamental Research Funds for the Central Universities (PKU2022LCXQ004 to X.Zo.), Beijing Municipal Science and Technology Commission (Z201100005520013 to L.J).

AUTHOR CONTRIBUTIONS

Q.H. and X.Zo. designed the study. Q.H conducted the analysis and drafted the manuscript. X.Zo., L.J., and W.J. revised the manuscript. Y.C, L.G, X.C., L.Z., F.G., and J.Z. were involved in the data conception and the interpretation of the results. All authors reviewed and approved the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no conflict of interest.

Received: July 8, 2023
Revised: September 13, 2023
Accepted: October 10, 2023
Published: October 12, 2023

REFERENCES

1. Chung, W.K., Erion, K., Florez, J.C., Hattersley, A.T., Hivert, M.F., Lee, C.G., McCarthy, M.I., Nolan, J.J., Norris, J.M., Pearson, E.R., et al. (2020). Precision Medicine in Diabetes: A Consensus Report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care *43*, 1617–1635. https://doi.org/10.2337/dci20-0022.
2. Ahlqvist, E., Storm, P., Käräjämäki, A., Martinell, M., Dorkhan, M., Carlsson, A., Vikman, P., Prasad, R.B., Aly, D.M., Almgren, P., et al. (2018). Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol. *6*, 361–369. https://doi.org/10.1016/S2213-8587(18)30051-2.
3. Zou, X., Zhou, X., Zhu, Z., and Ji, L. (2019). Novel subgroups of patients with adult-onset diabetes in Chinese and US populations. Lancet Diabetes Endocrinol. *7*, 9–11. https://doi.org/10.1016/S2213-8587(18)30316-4.
4. Dennis, J.M., Shields, B.M., Henley, W.E., Jones, A.G., and Hattersley, A.T. (2019). Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: an analysis using clinical trial data. Lancet Diabetes Endocrinol. *7*, 442–451. https://doi.org/10.1016/S2213-8587(19)30087-7.
5. Zou, X., Huang, Q., Luo, Y., Ren, Q., Han, X., Zhou, X., and Ji, L. (2022). The efficacy of canagliflozin in diabetes subgroups stratified by data-driven clustering or a supervised machine learning method: a post hoc analysis of canagliflozin clinical trial data. Diabetologia *65*, 1424–1435. https://doi.org/10.1007/s00125-022-05748-9.
6. Dennis, J.M. (2020). Precision medicine in type 2 diabetes: Using individualized prediction models to optimize selection of treatment. Diabetes *69*, 2075–2085. https://doi.org/10.2337/dbi20-0002.
7. Dennis, J.M., Shields, B.M., Hill, A.V., Knight, B.A., McDonald, T.J., Rodgers, L.R., Weedon, M.N., Henley, W.E., Sattar, N., Holman, R.R., et al. (2018). Precision Medicine in Type 2 Diabetes: Clinical Markers of Insulin Resistance Are Associated With Altered Short- and Long-term Glycemic Response to DPP-4 Inhibitor Therapy. Diabetes Care *41*, 705–712. https://doi.org/10.2337/dc17-1827.
8. Li, J., Albajrami, O., Zhuo, M., Hawley, C.E., and Paik, J.M. (2020). Decision algorithm for prescribing SGLT2 inhibitors and GLP-1 receptor agonists for diabetic kidney disease. Clin. J. Am. Soc. Nephrol. *15*, 1678–1688. https://doi.org/10.2215/CJN.02690320.
9. Brookes, S.T., Whitely, E., Egger, M., Smith, G.D., Mulheran, P.A., and Peters, T.J. (2004). Subgroup analyses in randomized trials: risks of subgroup-specific analyses: power and sample size for the interaction test. J. Clin. Epidemiol. *57*, 229–236.
10. Brookes, S.T., Whitley, E., Peters, T.J., Mulheran, P.A., Egger, M., and Davey Smith,

G. (2001). Subgroup Analysis in Randomised Controlled Trials: Quantifying the Risks of False-Positives and False-Negatives.

11. Basu, S., Raghavan, S., Wexler, D.J., and Berkowitz, S.A. (2018). Characteristics associated with decreased or increased mortality risk from glycemic therapy among patients with type 2 diabetes and high cardiovascular risk:Machine learning analysis of the ACCORD trial. Diabetes Care *41*, 604–612. https://doi.org/10.2337/dc17-2252.
12. Oikonomou, E.K., Suchard, M.A., McGuire, D.K., and Khera, R. (2022). Phenomapping-Derived Tool to Individualize the Effect of Canagliflozin on Cardiovascular Risk in Type 2 Diabetes. Diabetes Care *45*, 965–974. https://doi.org/10.2337/dc21-1765.
13. Tan, C.K., Zhuang, Y., and Wahli, W. (2017). Synthetic and natural Peroxisome Proliferator-Activated Receptor (PPAR) agonists as candidates for the therapy of the metabolic syndrome. Expert Opin. Ther. Targets *21*, 333–348. https://doi.org/10.1080/14728222.2017.1280467.
14. Ji, L., Song, W., Fang, H., Li, W., Geng, J., Wang, Y., Guo, L., Cai, H., Yang, T., Li, H., et al. (2021). Efficacy and safety of chiglitazar, a novel peroxisome proliferator-activated receptor pan-agonist, in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, phase 3 trial (CMAP). Sci. Bull. *66*, 1571–1580. https://doi.org/10.1016/j.scib.2021.03.019.
15. Xiaofeng, L., Yongyi, G., Lyuyun, Z., Gangyi, Y., Changjiang, W., and Zuojie, L. (2019). Efficacy and safety of chiglitazar in type 2 diabetes: a multi-center, randomized, double-blind, and parallel group clinical trial. Chinese Journal of Diabetes Mellitus *11*.
16. Xu, H.R., Zhang, J.W., Chen, W.L., Ning, Z.Q., and Li, X.N. (2019). Pharmacokinetics, Safety and Tolerability of Chiglitazar, A Novel Peroxisome Proliferator-Activated Receptor (PPAR) Pan-Agonist, in Healthy Chinese Volunteers: A Phase I Study. Clin. Drug Invest. *39*, 553–563. https://doi.org/10.1007/s40261-019-00779-4.
17. Jia, W., Ma, J., Miao, H., Wang, C., Wang, X., Li, Q., Lu, W., Yang, J., Zhang, L., Yang, J., et al. (2021). Chiglitazar monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomized, double-blind, phase 3 trial (CMAS). Sci. Bull. *66*, 1581–1590. https://doi.org/10.1016/j.scib.2021.02.027.
18. Kent, D.M., Steyerberg, E., and van Klaveren, D. (2018). Personalized evidence based medicine: predictive approaches to heterogeneous treatment effects. Bmj *363*, k4245.
19. Hayward, R.A., Kent, D.M., Vijan, S., and Hofer, T.P. (2006). Multivariable risk prediction can greatly enhance the statistical power of clinical trial subgroup analysis. BMC Med. Res. Methodol. *6*, 18.
20. Kent, D.M., Paulus, J.K., Van Klaveren, D., D'Agostino, R., Goodman, S., Hayward, R., Ioannidis, J.P.A., Patrick-Lake, B., Morton, S., Pencina, M., et al. (2020). The Predictive Approaches to Treatment effect Heterogeneity (PATH) statement. Ann. Intern. Med. *172*, 35–45. https://doi.org/10.7326/M18-3667.
21. Athey, S., and Imbens, G. (2016). Recursive partitioning for heterogeneous causal effects. Proc. Natl. Acad. Sci. USA *113*, 7353–7360.
22. Oikonomou, E.K., Spatz, E.S., Suchard, M.A., and Khera, R. (2022). Individualising intensive systolic blood pressure reduction in hypertension using computational trial phenomaps and machine learning: a post-hoc analysis of randomised clinical trials. Lancet. Digit. Health *4*, e796–e805. https://doi.org/10.1016/S2589-7500(22)00170-4.
23. Dennis, J.M., Henley, W.E., Weedon, M.N., Lonergan, M., Rodgers, L.R., Jones, A.G., Hamilton, W.T., Sattar, N., Janmohamed, S., Holman, R.R., et al. (2018). Sex and BMI alter the benefits and risks of sulfonylureas and thiazolidinediones in type 2 diabetes: a framework for evaluating stratification using routine clinical and individual trial data. Diabetes Care *41*, 1844–1853.
24. Yan, H., Wu, W., Chang, X., Xia, M., Ma, S., Wang, L., and Gao, J. (2021). Gender differences in the efficacy of pioglitazone treatment in nonalcoholic fatty liver disease patients with abnormal glucose metabolism. Biol. Sex Differ. *12*, 1–8. https://doi.org/10.1186/s13293-020-00344-1.
25. Osborn, O., Sears, D.D., and Olefsky, J.M. (2010). Fat-Induced Inflammation Unchecked. Cell Metabol. *12*, 553–554. https://doi.org/10.1016/j.cmet.2010.11.017.
26. Sugden, M.C., and Holness, M.J. (2006). Mechanisms underlying regulation of the expression and activities of the mammalian pyruvate dehydrogenase kinases. Arch. Physiol. Biochem. *112*, 139–149. https://doi.org/10.1080/13813450600935263.
27. Zhou, Y., Wang, H., Wang, Y., Xu, X., Li, F., Zhou, J., Shan, T., Huang, R., Cai, T., Liu, X., et al. (2022). Comparative Evaluation of Chiglitazar and Sitagliptin on the Levels of Retinol-Binding Protein 4 and Its Correlation With Insulin Resistance in Patients With Type 2 Diabetes. Front. Endocrinol. *13*, 801271. https://doi.org/10.3389/fendo.2022.801271.
28. Herman, G.A., Bergman, A., Stevens, C., Kotey, P., Yi, B., Zhao, P., Dietrich, B., Golor, G., Schrodter, A., Keymeulen, B., et al. (2006). Effect of Single Oral Doses of Sitagliptin, a Dipeptidyl Peptidase-4 Inhibitor, on Incretin and Plasma Glucose Levels after an Oral Glucose Tolerance Test in Patients with Type 2 Diabetes. J. Clin. Endocrinol. Metab. *91*, 4612–4619. https://doi.org/10.1210/jc.2006-1009.
29. Briaud, I., Kelpe, C.L., Johnson, L.M., Tran, P.O.T., and Poitout, V. (2002). Differential Effects of Hyperlipidemia on Insulin Secretion in Islets of Langerhans From Hyperglycemic Versus Normoglycemic Rats. Diabetes *51*, 662–668. https://doi.org/10.2337/diabetes.51.3.662.
30. Bae, J., Kim, G., Lee, Y.-H., Lee, B.-W., Kang, E.S., and Cha, B.-S. (2019). Differential Effects of Thiazolidinediones and Dipeptidyl Peptidase-4 Inhibitors on Insulin Resistance and β-Cell Function in Type 2 Diabetes Mellitus: A Propensity Score-Matched Analysis. Diabetes Ther. *10*, 149–158. https://doi.org/10.1007/s13300-018-0541-y.
31. Sato, H., Sugai, H., Kurosaki, H., Ishikawa, M., Funaki, A., Kimura, Y., and Ueno, K. (2013). The effect of sex hormones on peroxisome proliferator-activated receptor gamma expression and activity in mature adipocytes. Biol. Pharm. Bull. *36*, 564–573. https://doi.org/10.1248/bpb.b12-00868.
32. Mody, A., White, D., Kanwal, F., and Garcia, J.M. (2015). Relevance of low testosterone to non-alcoholic fatty liver disease. Cardiovasc. Endocrinol. *4*, 83–89. https://doi.org/10.1097/XCE.0000000000000057.
33. Naraharisetti, S.B., Lin, Y.S., Rieder, M.J., Marciante, K.D., Psaty, B.M., Thummel, K.E., and Totah, R.A. (2010). Human liver expression of CYP2C8: gender, age, and genotype effects. Drug Metab. Dispos. *38*, 889–893. https://doi.org/10.1124/dmd.109.031542.
34. Gower, J.C. (1971). A General Coefficient of Similarity and Some of Its Properties. Biometrics *27*, 857. https://doi.org/10.2307/2528823.
35. McInnes, L., Healy, J., and Melville, J. (2018). UMAP: Uniform Manifold Approximation and Projection for Dimension Reduction.
36. Lundberg, S.M., Erion, G., Chen, H., DeGrave, A., Prutkin, J.M., Nair, B., Katz, R., Himmelfarb, J., Bansal, N., and Lee, S.I. (2020). From local explanations to global understanding with explainable AI for trees. Nat. Mach. Intell. *2*, 56–67. https://doi.org/10.1038/s42256-019-0138-9.
37. Vickers, A.J., and Elkin, E.B. (2006). Decision Curve Analysis: A Novel Method for Evaluating Prediction Models. Med. Decis. Making *26*, 565–574. https://doi.org/10.1177/0272989X06295361.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
R software (version 4.2.2)	R Foundation for Statistical Computing	RRID: SCR_001905
JAVA software (version 8)	Oracle	https://www.java.com/
ML-PANPPAR	This paper	http://diabetesmodels.com:9001/index?type=3

RESOURCE AVAILABILITY

Lead contact

Further information regarding this manuscript and requests should be directed to the lead contact, Linong Ji, MD (jiln@bjmu.edu.cn).

Materials availability

This study did not generate any new materials.

Data and code availability

- Individual level of data from the study are obtained from Chipscreen Biosciences (Shenzhen, China) and availability of the data is subject to certain restrictions.
- This paper does not report original code, but the model reported in our paper is shared on the website (http://diabetesmodels.com:9001/index?type=3).
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

METHOD DETAILS

Study design and participants

ChiglitAzar Monotherapy with Placebo (CAMP) and ChiglitAzar Monotherapy with Sitagliptin (CAMS) study were two randomized, double-blinded, multicenter clinical trials of chiglitazar conducted in China. Both trials recruited Chinese participants of either gender. Patients with type 2 diabetes who were aged 18–70 years, with a BMI range of 18.5–35.0 kg/m^2, and had insufficient glycemic control (HbA_{1c} of 7.5–10.0% [58–86 mmol/mol]) in spite of the management of strict diet and exercise from 2014 to 2016. Eligible participants were randomly assigned in 1:1:1 to chiglitazar 32 mg, chiglitazar 48 mg or placebo in CAMP and chiglitazar 32 mg, chiglitazar 48 mg or sitagliptin 100 mg in CAMS for total 24 weeks. Trials were registered with ClinicalTrials.gov (identifiers: NCT02121717 for CAMP, NCT02173457 for CAMS) and the details of study design and sample size calculation have been published previously.[14,17]

In our study, we combined individual-level data from the intent-to-treat analysis of two trials. The eligibility criteria were patients allocated to chiglitazar or sitagliptin. No patients had prior medication for lipid-lowering or glucose-lowering drugs, and no patient received combined therapy during the trial. Patients without complete information on predictors, such as lipid profile or fasting insulin at baseline were excluded (N = 3, 2 from sitagliptin arm and 1 from chiglitazar), and consequently, a total of 1069 participants were included in the final analysis (Figure S6).

No informed consent was required for this post-hoc analysis and information were de-identified in advance. Ethical approvals were approved by Ethical Committees at each study center, and complied with the principles of Good Clinical Practice and the Declaration of Helsinki.

Candidate variables

Baseline variables including demographic information (such as age, sex, body mass index [BMI], and diabetes duration), and clinical laboratory assessments relevant to glucose metabolism (such as glycosylated hemoglobin [HbA_{1c}], fasting plasma glucose [FPG], and fasting insulin), lipid profile (total cholesterol [TC], high-density lipoprotein cholesterol [HDL], low-density lipoprotein cholesterol [LDL], triglycerides [TG], and free fatty acids [FFA]), and renal function (eGFR), were recorded as candidate predictors. Other baseline variables such as body weight, homoeostasis model assessment for insulin resistance and beta-cell function (HOMA-IR and HOMA-β, calculated using FPG and fasting insulin) were recorded for outcome analysis. During the follow-up period, HbA_{1c} was recollected at week 12 and 24 while other variables were only recollected at week 24. Missing data were imputed using the last observation carried forward (LOCF) method.

Outcomes

The primary outcome was the change in HbA_{1c} from baseline at week 24. Other glucose-lowering outcomes consisted of the change in HbA_{1c} from baseline to week 12, participants reaching HbA_{1c}<7% (53 mmol/mol) at week 24, and the change from baseline in FPG at week 24. Secondary endpoints included the changes in HOMA-IR, HDL, and TG from baseline at week 24. Safety endpoints included the incidence of hypoglycemia, edema and bone fracture, and changes in body weight and hematocrit at week 24.

Phenomap method

Approaches for estimation of individualized treatment effect in our article were referred from the article by Oikonomou et al.[12,22] Standardization of variables was performed, and phenotypic distances between individuals were quantified employing Gower's method, which takes into consideration both numerical and categorical baseline characteristics. This method yielded a measure of dissimilarity between any two sample points, with a lower distance signifying greater similarity between the individuals.[34] To visually represent the distribution of participant characteristics, we employed a two-dimensional projection technique and generated a color-coded phenomap using the Uniform Manifold Approximation and Projection (UMAP) method,[35] which best preserves the global data structure thereby allowing for the interpretation of the phenotypic distribution of patients within a topological space.

Treatment effect estimation

The individualized treatment effect was defined as the differences in HbA_{1c} change at week 24. We employed personalized weighted least-squares regression to estimate the relative treatment effect between chiglitazar and sitagliptin, with baseline HbA_{1c}, age, and sex as covariates. Weights were estimated based on the exponential function of (1 – Gower's distance), so higher weights were assigned to pairs of participants exhibiting closer similarity, while pairs displaying greater dissimilarity received penalized weights. To determine the optimal power metric for the exponential function, we conducted a comparison of the estimated treatment effect using unweighted regression against the nearest neighbors of each participant, considering various percentages (3%, 5%, 10%, and 20%) of the total sample size as references. The power coefficient that exhibited a robust estimation, characterized by both high correlation and low variation when compared to the references, was selected (Power = 20, Figure S7).

Two distinct subgroups were created based on the individualized treatment effect. The high-benefit group (HBG) consisted of individuals exhibiting a positive relative treatment effect (characterized by a greater decline in HbA_{1c} with chiglitazar compared to sitagliptin), while the low-benefit group (LBG) comprised individuals demonstrating the opposite effect.

Exploratory analysis

We also conducted an exploratory analysis to identify patients who exhibit greater glucose-lowering efficacy with different doses of chiglitazar. 412 patients with chiglitazar 32 mg and 410 patients with chiglitazar 48 mg were enrolled into analysis to calculate the relative treatment effect and divided into subgroups favoring the use of either 32 mg or 48 mg.

Construction of ML-PANPPAR

To facilitate the efficient identification of high-benefit group in clinical practice, we trained a model with extreme gradient-boosting (XGBoost). Data was randomly divided into the derivation cohort (N = 748) and the validation cohort (N = 321) in a 7:3 ratio. Hyperparameters were tuned using 10-fold cross-validation to maximize the average area under the receiver-operating characteristic curve (ROC-AUC). The preliminary model included variables such as age, sex, BMI, diabetes duration, HbA_{1c}, FPG, fasting insulin, TC, HDL, LDL, TG, FFA, and eGFR. The contributions of each variable to the model were then estimated using the SHAP (Shapley Additive Explanations) values, and the top 5 contributors were retrained to form the final model, ML-PANPPAR.[36] Details on hyperparameter calibration of ML-PANPPAR are listed in Table S6.

QUANTIFICATION AND STATISTICAL ANALYSIS

Data were presented as mean (SD) for continuous variables and as count (percentage) for category variables. Baseline characteristics were compared using Student's *t* test for continuous data and $\chi 2$ test for categorical data. The characteristics, estimated glucose-lowering trajectories, and relative outcomes were described within the subgroups derived from phenomap.

For all primary and continuous secondary endpoints, we applied analysis of covariance (ANCOVA) models with treatment and baseline HbA_{1c} stratum (<8.5% [69 mmol/mol] or $\geq$8.5% [69 mmol/mol]) as fixed effects, and baseline corresponding value (e.g., FPG, HOMA-IR, HDL, TG, weight) as covariate. The p value for interaction was obtained by assessing the interaction between treatment and subgroup. Secondary endpoints were controlled for multiple comparisons using the false discovery rate (FDR) method.

The performance of ML-PANPPAR was evaluated in the validation cohort using receiver operating characteristic curve-area under the curve for discrimination, calibration plot and Hosmer-Lemeshow test for calibration, and decision curve analysis to compare the net benefit of using the model versus treating all patients with chiglitazar or sitagliptin.[37]

To explore the influence of sex on the response to chiglitazar, we compared the relative treatment effect between males and females within the original study population. Additionally, we employed the inverse probability treatment weighting (IPTW) method to assess the association between sex and the efficacy of chiglitazar in lowering glucose levels.

Software packages

All statistical analysis was conducted using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). The method for Dimensionality reduction was conducted using package *UAMP*. The machine learning models were constructed using package *caret*. All statistical tests were two sided, with a p value of <0.05 was regarded as significance.