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PREDICTIVE ROLE OF BASELINE CLINICAL CHARACTERISTICS REGARDING THE TREATMENT EFFICACY OF LIRAGLUTIDE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

Background: Liraglutide is widely used in the treatment of type 2 diabetes mellitus (T2DM) because of its proven benefits in lowering blood glucose, reducing body weight, improving blood pressure, regulating blood lipids, and providing cardiovascular protection. However, liraglutide has been shown to be less effective in lowering glucose in some patients. The purpose of this study was to explore the factors affecting the glucose-lowering efficacy of liraglutide in patients with T2DM and to promote a rational basis for liraglutide application.

Methods: This was a retrospective cohort study involving patients with T2DM who were administered liraglutide once daily as a part of their diabetes care for at least 6 months. They were divided into two groups: responders (HbA1c decrease ≥1.0% or HbA1c <7.0% after 6 months of liraglutide treatment) and non-responders. The intergroup differences in the baseline data were analyzed, including basic profiles, test parameters, and comedications. The influencing factors of hypoglycemic efficacy were investigated using a binary logistic regression analysis.

Results: A total of 206 patients were included according to the inclusion criteria; 132 were responders and 74 were non-responders to liraglutide after 6 months of liraglutide therapy. According to the binary logistic regression analysis, age, baseline HbA1c, baseline postprandial plasma glucose (PPG), and duration of diabetes mellitus were found to be predictors of the hypoglycemic efficacy of liraglutide (P <0.05). A further linear regression analysis showed that patients with baseline HbA1c ≥7.31% had greater potential for response to liraglutide.

Conclusion: The identification of the abovementioned predictors for the hypoglycemic efficacy of liraglutide and the evaluation and prediction of the efficacy of liraglutide before its clinical application can facilitate individualized drug use.

Key words: liraglutide; hypoglycemic response; predictive factors; type 2 diabetes mellitus

Background

Type 2 diabetes mellitus (T2DM) is a public health issue that seriously threatens the health of many people, and according to the International Diabetes Federation (IDF), there are 537 million people with diabetes mellitus worldwide, of which more than 90% have T2DM [1]. China is the country with the highest number of T2DM patients, with a prevalence of 13% among adults, accompanied by the clinical dilemma that less than one-third of T2DM patients reach their glycemic control targets [2, 3]. Glucagon-like peptide-l (GLP-1) is an incretin hormone that promotes insulin release through a glucose concentration-dependent pattern, inhibiting glucagon release by acting on islet α cells and reducing islet β cells apoptosis while promoting proliferation, thereby improving insulin release and lowering blood glucose. However, the incretin effect is diminished or no longer present in patients with T2DM [4, 5]. However, the half-life of natural GLP-1 is very short, and it is degraded and inactivated by dipeptidyl peptidase IV within 2 minutes in vivo. Glucagon-like peptide-1 receptor agonists (GLP1RAs), such as liraglutide and beralutide, are structural modifications of GLP-1 that allow them to not only exert the effects of GLP-1 but also extend the duration of action, and are novel therapeutic agents for the treatment of T2DM [4]. In July 2009, liraglutide was approved in the EU for the treatment of patients with T2DM and also obtained approval for a weight loss indication in December 2014. According to the recommendations of several guidelines, including the European Association for the Study of Diabetes (EASD) consensus algorithm, the American Diabetes Association (ADA) guidelines, and the Chinese guidelines for prevention and care of T2DM (2021 edition), the combination regimen of GLP1RAs with metformin is preferred in clinical practice for the management of patients with T2DM, especially those who already have atherosclerotic cardiovascular disease or are obese [6-9].

Liraglutide is widely used clinically because of its proven benefits in lowering blood glucose, reducing body weight, improving blood pressure, regulating blood lipids, and providing cardiovascular protection [10-12]. However, several clinical trials have shown that liraglutide has poor efficacy in some patients as a hypoglycemic therapy, such as the LEAD-3 study, which found that 49% of patients did not achieve the American Diabetes Association's control goal of hemoglobin A1c (HbA1c) <7% after taking liraglutide for 3 months [13-15]. There were also significant individual differences in the efficacy of liraglutide for weight loss and the incidence of adverse drug reactions in patients with type 2 diabetes. It was found that, after 24 weeks of treatment with liraglutide, about 25% of the participants showed weight loss <5%, and some of them even presented weight gain, while about 50% of the patients were found to have adverse gastrointestinal reactions and were unable to continue the medication as a result [16, 17].

While the explanation for such variability is related to lifestyle changes and medication adherence, it may also be the result of specific genetic variants, patient characteristics, environmental factors, and drug interactions [18-19]. However, relevant indicators that can be used to predict responsiveness to liraglutide treatment need to be further explored. The previous studies, which suffered from small sample sizes, short observation periods, few clinical variables included in the studies, and a lack of comparisons across multiple time points, make it difficult to use the relevant research findings for clinical individualization and to promote the rational use of drugs [15, 20]. Therefore, this study aimed to identify the clinical characteristics associated with the response to liraglutide and to evaluate the predictive role of pivotal indicators.

Methods

Patients

We carried out a 6-month observational, retrospective study of 417 patients with T2DM treated with liraglutide and evaluated their responses to treatment. The participants were identified from the electronic medical record system between January 2021 and June 2022 at the Affiliated Hospital of Jiangnan University and the Affiliated Hospital of Xuzhou Medical University. Data were pooled from patients who met the following criteria: having a clinical diagnosis of T2DM, aged more than 18 years, estimated glomerular filtration rate $>$30 mL/min/1.73 m^2, and treatment with liraglutide as a part of their regular diabetes care at least 6 months before the data collection. Patients previously undergoing therapy with a GLP-1 analog or those with missing data were excluded from the current study. Ethics approval was granted by the institutional review board at our institution.

Study cohorts with definition of responders and non-responders

The clinical variables covered were sex; age; duration of diabetes; smoking history; drinking history; family history of diabetes; body mass index (BMI); waist-to-hip ratio (WHR); HbA1c; fasting plasma glucose (FPG); postprandial plasma glucose (PPG); fasting serum insulin (FINS); postprandial serum insulin (PINS); total cholesterol (TC); triglyceride (TG); high-density lipoprotein cholesterol (HDL-c); low-density lipoprotein cholesterol (LDL-c); and concurrent diabetic medications at baseline, 3 months, and 6 months following the initiation of liraglutide. Additionally, insulin resistance and beta-cell function were assessed as described previously [21]. On the basis of glycemic response to liraglutide administration, patients with T2DM were divided into responders and non-responders. In accordance with the National Institute for Health and Care Excellence (NICE) guidelines for the use of GLP-1 receptor agonists in treating T2DM, glycemic response was defined as a $\geq$ 1.0% reduction in HbA1c from baseline at 6 months of treatment with GLP-1 receptor agonists [22]. Therefore, in this study, responders were defined as achieving an HbA1c reduction of $\geq$ 1.0% or an reduction HbA1c of $<$7.0% after 6 months of liraglutide treatment, as against non-responders, i.e., patients who failed to achieve this decrease.

Statistical analysis

Statistical analyses were conducted using the SPSS software (version 16.0, SPSS Inc., Chicago, IL). The data are expressed as the mean ± standard deviation (SD) or percentages, depending on the situation. Baseline characteristics between responders and non-responders were assessed by an independent Student's t test for continuous data and the Chi-squared test or Fisher's exact test for categorical data. ANOVA for repeated measurements was used to assess the characteristics collected at different treatment time points for the responder and non-responder groups. Statistical power was calculated using power calculator software (http://www.ncss.com). Both linear regression and binary logistic regression analyses were used to estimate the best predictive model that could define the relationship between the baseline variables and reductions in HbA1c. Procedural linear regression and binary logistic regression analyses were performed to evaluate the best predictor variables that were able to determine the association between baseline variables and the decline in HbA1c. A value of $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of all the subjects

According to the inclusion and exclusion criteria, a total of 417 participants were included in the study (analysis of HbA1c at 3 months n = 292 and at 6 months n = 206) (Figure 1). Based on the definition of responders and non-responders, 206 patients with T2DM were divided into two groups, 132 of whom were responders and 74 of whom were non-responders to liraglutide treatment. The baseline characteristics of the participants are presented in Table 1. Compared with the responder group, the non-responder group showed a longer duration of T2DM ($P < 0.001$). There were no

significant differences between the responder and non-responder groups with respect to the other baseline characteristics.

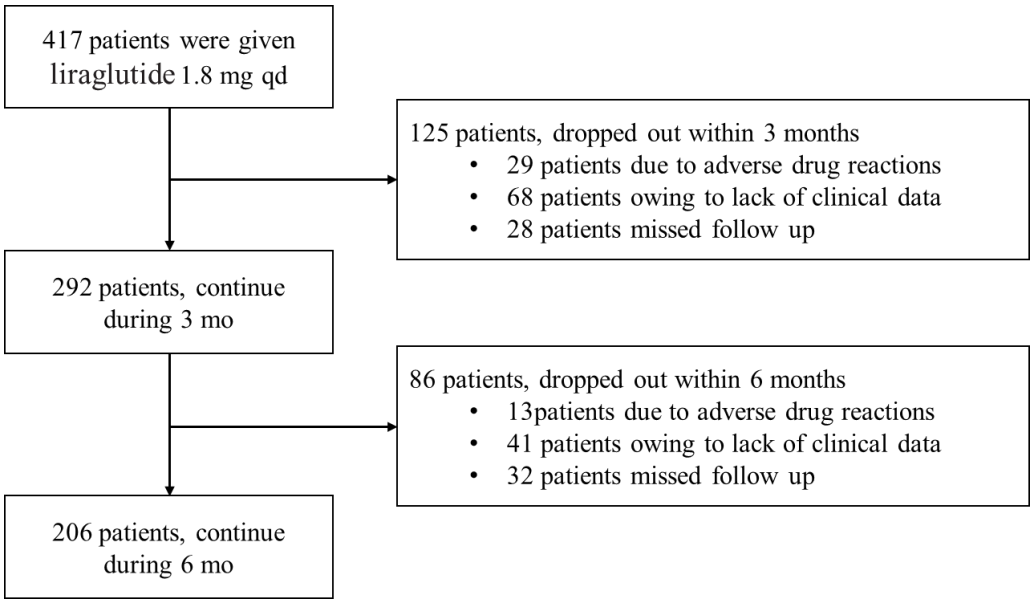

Figure 1 Flow chart of the eligibility of participants under liraglutide treatment

Table1 Baseline characteristics of type 2 diabetes mellitus (T2DM) patients who received liraglutide stratified by HbA1c response

Baseline characteristics	**Stratified groups**		***P* value**
Responders	**Non-responders**		
N(men/women)	132(86/46)	74(51/23)	0.600
Age (years)	45.62±12.81	44.86±9.74	0.659
BMI (kg/m^2)	26.46±4.15	27.22±3.03	0.166
WHR	0.93±0.07	0.94±0.07	0.129
Duration of diabetes (years)	5.30±2.33	9.28±4.80	0.000
Smoking history (%)	41(31.06)	26(35.14)	0.549
Drinking history (%)	23(17.42)	13(17.57)	0.979
Family history of diabetes (%)	28(21.21)	16(21.62)	0.945
Liraglutide only (%)	31(23.48)	15(20.27)	0.595
Liraglutide + OHAs (%)	42(31.82)	24(32.43)	0.928
Liraglutide + Insulin (%)	26(19.70)	17(22.97)	0.579
Liraglutide + OHAs +Insulin (%)	33(25.00)	18(24.32)	0.914

Abbreviations: BMI = body mass index; WHR = waist to hip ratio; OHAs = oral antihyperglycaemic agents.

Changes in clinical parameters at each time point after therapy with liraglutide

The changes in the clinical parameters from baseline to 3 months and then 6 months for the responder and non-responder groups are presented in Table 2 and Table 3. The results of the stratified analysis based on glycemic responses showed significant improvements in glucolipid metabolism in both the responder and non-responder groups after treatment with liraglutide, as evidenced by decreases in WHR, FPG, PPG, HbA1c, and TC and increases in HOMA-B. In addition, in the patients in the responder group, there was an elevation in FINS and PINS after 6 months of treatment with liraglutide, while a significant decrease in BMI, HOMA-IR, TG, and LDL-c was observed (Table 2). Regarding the patients in the non-responder group, no significant differences in BMI, FINS, PINS,

HOMA-IR, TG, HDL-c, and LDL-c were observed before and after treatment with liraglutide (Table 3).

Table 2 Clinical characteristics of patients with T2DM at baseline, 3 months and 6 months after liraglutide treatment within responders (n = 132)

Follow up points	**Adjusted *P* value**						
	Baseline	**3 months**	**6 months**	***P* value**	**Baseline to 3 months**	**3 to 6 months**	**Baseline to 6 months**
BMI (kg/m^2)	26.46±4.15	26.10±3.93	25.04±3.94	0.012	0.464	0.032	0.004
WHR	0.93±0.07	0.93±0.06	0.88±0.06	0.000	0.656	0.000	0.000
FPG (mmol/L)	10.70±2.48	7.58±1.70	6.85±1.45	0.000	0.000	0.002	0.000
PPG (mmol/L)	16.56±4.22	11.00±2.86	9.83±2.51	0.000	0.000	0.004	0.000
HbA1c (%)	10.08±1.60	7.66±1.33	7.18±1.13	0.000	0.000	0.004	0.000
FINS (mU/L)	11.07±7.06	12.21±7.21	13.65±7.54	0.016	0.203	0.109	0.004
PINS (mU/L)	31.34±19.06	40.38±24.18	46.73±28.87	0.000	0.003	0.035	0.000
HOMA-IR	5.17±3.44	4.08±2.68	4.16±2.42	0.003	0.002	0.823	0.005
HOMA-B	36.38±29.9	71.88±52.93	101.61±91.47	0.000	0.000	0.000	0.000
TC (mmol/L)	5.27±1.53	4.72±1.05	4.54±1.09	0.000	0.000	0.232	0.000
TG (mmol/L)	2.63±2.22	1.98±1.37	1.94±1.31	0.001	0.002	0.854	0.001
HDL-c (mmol/L)	1.25±0.44	1.24±0.37	1.22±0.35	0.770	0.828	0.626	0.481
LDL-c (mmol/L)	3.09±1.07	2.87±1.00	2.75±1.01	0.025	0.079	0.353	0.007

Parameters Overall

BMI = body mass index; WHR = waist to hip ratio; FPG = fasting plasma glucose; PPG = postprandial plasma glucose; HbA_{1c} = hemoglobin A_{1c}; FINS = fasting serum insulin; PINS = postprandial serum insulin; HOMA-IR = homeostasis model assessment for insulin resistance; HOMA-B = homeostasis model assessment for beta cell function; TC = total cholesterol; TG = triglyceride; HDL-c = high-density lipoprotein-cholesterol; and LDL-c = low-density lipoproteincholesterol.

Table 3 Clinical characteristics of patients with T2DM at baseline, 3 months and 6 months after liraglutide treatment within nonresponders (n = 74)

Follow up points	**Adjusted *P* value**						
Overall Parameters							
	Baseline	**3 months**	**6 months**	***P* value**	**Baseline to 3 months**	**3 to 6 months**	**Baseline to 6 months**
BMI (kg/m^2)	27.22±3.03	27.02±2.92	26.77±3.07	0.654	0.683	0.609	0.358
WHR	0.94±0.07	0.93±0.07	0.90±0.07	0.000	0.340	0.001	0.000
FPG (mmol/L)	9.21±2.37	7.42±1.58	7.38±1.66	0.000	0.000	0.902	0.000
PPG (mmol/L)	13.34±3.44	10.40±2.61	10.20±2.57	0.000	0.000	0.669	0.000
HbA1c (%)	8.63±0.94	8.07±0.94	8.06±1.01	0.000	0.001	0.910	0.000
FINS (mU/L)	12.30±6.46	13.47±7.45	14.19±7.08	0.256	0.309	0.535	0.102
PINS (mU/L)	39.54±25.41	44.18±28.73	48.08±32.84	0.206	0.335	0.417	0.076
HOMA-IR	5.02±2.95	4.36±2.53	4.65±2.47	0.318	0.131	0.506	0.398
HOMA-B	50.14±35.87	84.06±52.93	102.29±168.14	0.012	0.055	0.300	0.003
TC (mmol/L)	4.99±1.06	4.62±1.01	4.46±0.98	0.006	0.027	0.365	0.002
TG (mmol/L)	2.26±1.72	2.04±1.71	2.10±1.87	0.719	0.431	0.824	0.572
HDL-c (mmol/L)	1.24±0.35	1.20±0.34	1.16±0.33	0.345	0.477	0.455	0.145
LDL-c (mmol/L)	2.87±0.83	2.78±0.90	2.62±0.92	0.233	0.543	0.281	0.092

BMI = body mass index; WHR = waist to hip ratio; FPG = fasting plasma glucose; PPG = postprandial plasma glucose; HbA_{1c} = hemoglobin A_{1c}; FINS = fasting serum insulin; PINS = postprandial serum insulin; HOMA-IR = homeostasis model assessment for insulin resistance; HOMA-B = homeostasis

model assessment for beta cell function; TC = total cholesterol; TG = triglyceride; HDL-c = high-density lipoprotein-cholesterol; and LDL-c = low-density lipoprotein cholesterol.

Clinical parameter changes and HbA1c responses

There were no significant differences in FINS, PINS, HOMA-IR, and HOMA-B detected when comparing between the clinical indicators of the responders and non-responders at baseline, 3 months, and 6 months, respectively (Figure 2). However, compared to the responders, HbA1c levels were lower in the non-responders at baseline, but higher at 6 months ($P < 0.01$). However, compared to the responders, the non-responders had lower levels of HbA1c, FPG, and PPG at baseline ($P < 0.001$), but higher levels of HbA1c ($P < 0.001$) and FPG ($P < 0.05$) at 6 months. The analysis of the BMI levels of the responders and non-responders showed no significant differences at baseline, but they were lower in the responders at 6 months ($P < 0.01$).

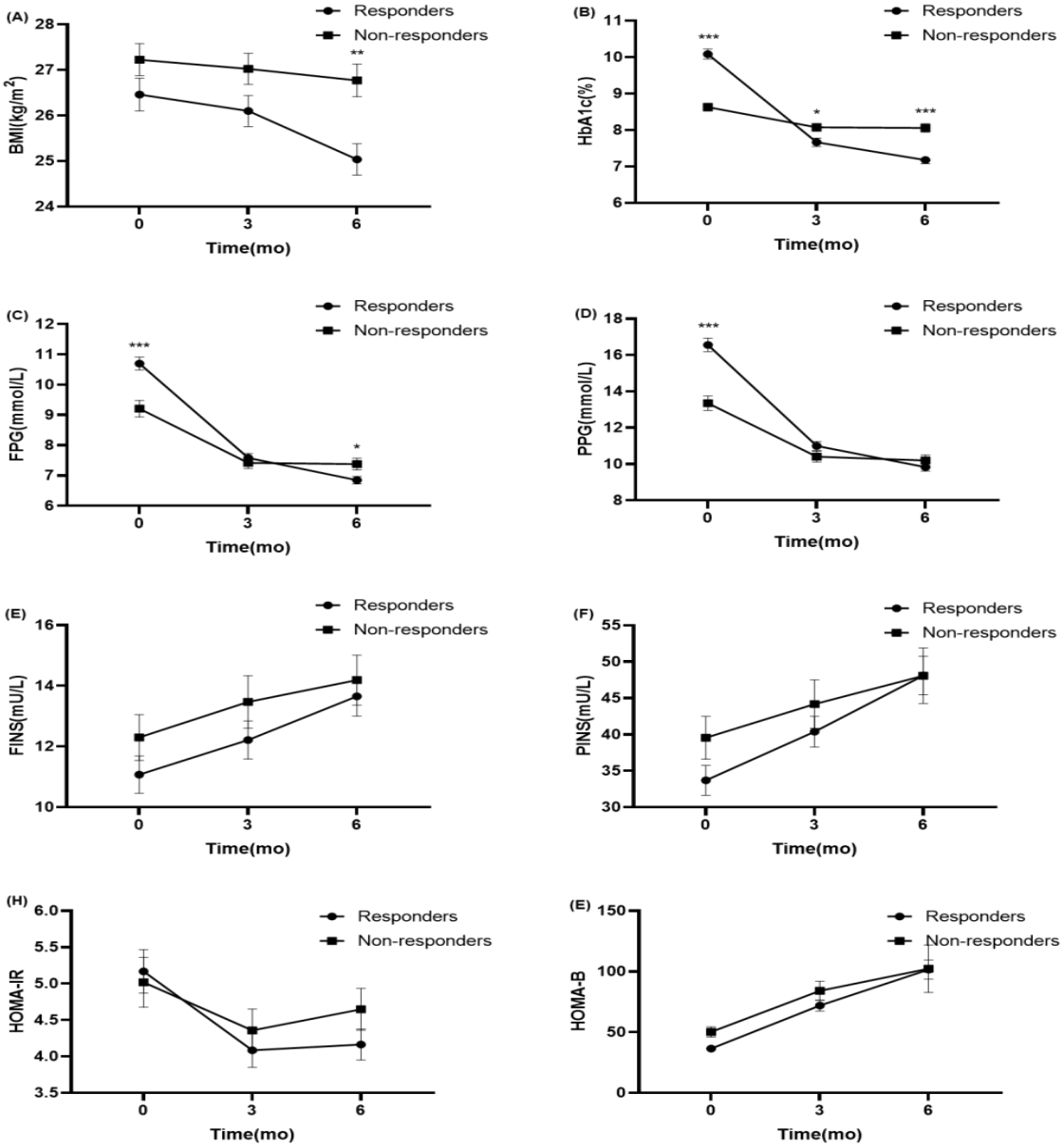

Figure 2 Comparison of BMI (A), HbA1c (B), FPG (C), PPG (D), FINS (E), PINS (F), HOMA-IR (G), HOMA-B (H) between responders (n = 132) and non-responders (n = 73) at baseline, 3 months and 6 months. $^{*}P < .005$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with nonresponders. Abbreviations: BMI = body mass index; HbA1c = haemoglobin A1c; FPG = fasting plasma glucose; PPG = postprandial plasma glucose; FINS = fasting serum insulin; PINS = postprandial serum insulin;

HOMA-IR = homeostasis model assessment for insulin resistance; HOMA-B = homeostasis model assessment for beta cell function

Predictive role of baseline characteristics associated with glycemic response in patients receiving liraglutide treatment

To evaluate the effects of the baseline characteristics and clinical indicators on the glycemic response of liraglutide, a binary logistic regression analysis was carried out to examine the key predictive role of the response to liraglutide in this study. In this study, age, sex, weight, personal history, medications, glucose, plasma insulin, and lipids were adjusted for a logistic regression analysis, and the results showed that age, baseline PPG, HbA1c, duration of diabetes, and family history of diabetes were predictive of the glycemic control effect of liraglutide treatment (Table 4 and Figure 3).

In addition, patients of an older age (OR = 1.080, CI: 1.030-1.133, P = 0.001), with higher baseline PPG (OR = 1.226, CI: 1.025-1.466, P = 0.026), with higher baseline HbA1c (OR = 3.151, CI: 1.890-5.241, P = 0.000), and with a shorter duration of diabetes (OR=0.549, CI: 0.440-0.684, P = 0.000) were more likely to be grouped as responders to liraglutide within 6 months. In order to evaluate the thresholds for age, baseline PPG, baseline HbA1c, and duration of diabetes, we performed a linear regression analysis to prove that there was a correlation between the baseline HbA1c (R^2=0.764, P < 0.001, Figure 4A), baseline PPG (R^2 = 0.423, P < 0.001, Figure 4B), and duration of diabetes (R^2 = 0.346, P = 0.004, Figure 4C) and the change in HbA1c from baseline to 6 months, with x-intercepts of 7.31 (95%CI: 7.09 to 7.51), 6.90 (95%CI: 5.13 to 8.21), and 19.63 (95%CI: 17.53 to 22.61), respectively, but no linear relationship was detected between age and the change in HbA1c. This suggests that patients presenting a baseline HbA1c ＞7.31%, a baseline PPG ＞6.9 mmol/L, and a duration of diabetes ＜ 19.63 years were more responsive to the hypoglycemic effects of liraglutide than other patients.

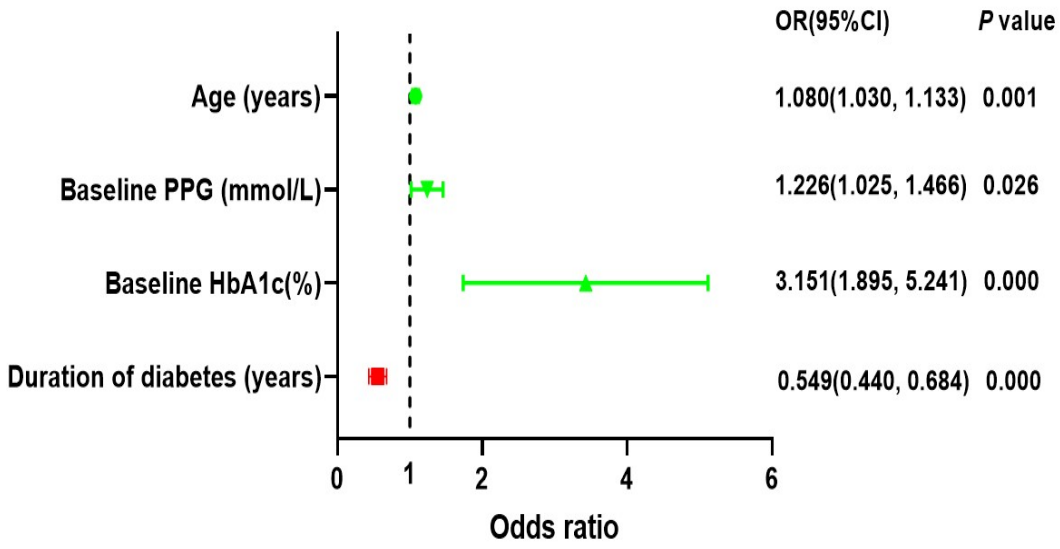

Figure 3 Binary logistic regression identified Age, baseline HbA1c, baseline PPG and duration of diabetes can predict response to liraglutide treatment.

Abbreviation: HbA1c = haemoglobin A1c; PPG = postprandial plasma glucose

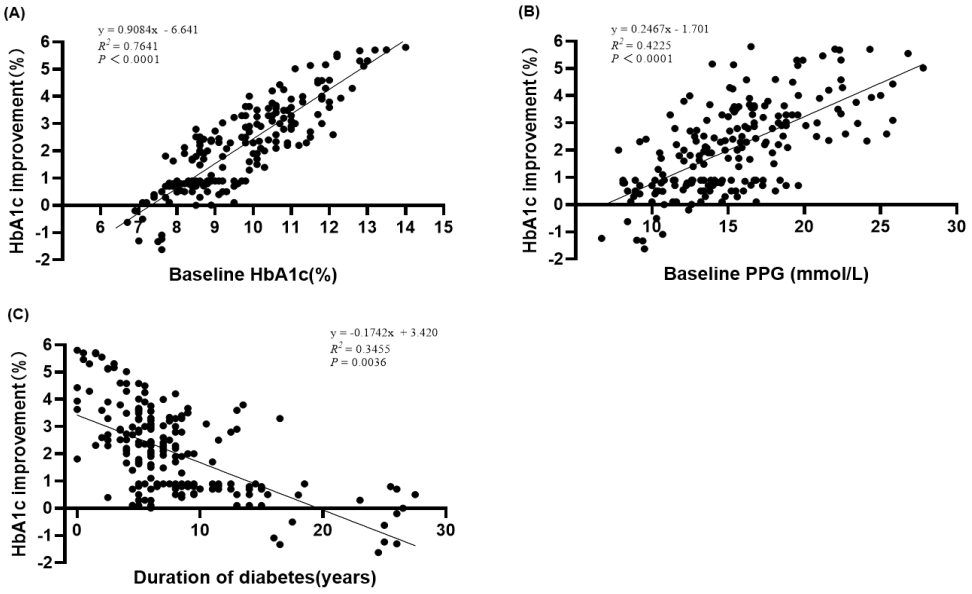

Figure 4 Linear relationship between the baseline HbA1c (A), baseline PPG (B), duration of diabetes (C) and changes in HbA1c after 6 months of liraglutide therapy. Results are shown with the equation for the line of best fit.

Abbreviation: HbA1c = haemoglobin A1c; PPG = postprandial plasma glucose

Table 4 Binary linear regression analysis variables that can predict response to liraglutide treatment

Variables	**OR**	**95% CI**	***P* value**
Age (years)	1.080	(1.030, 1.133)	0.001
Sex	0.856	(0.310, 2.363)	0.765
Smoking history (%)	0.709	(-3.477, 4.865)	0.736
Drinking history (%)	1.145	(0.331, 3.962)	0.830
Family history of diabetes (%)	1.838	(0.632, 5.346)	0.264
Duration of diabetes (years)	0.549	(0.440, 0.684)	0.000
Baseline BMI (kg/m^2)	0.998	(0.877, 1.135)	0.975
Baseline HbA1c(%)	3.151	(1.895, 5.241)	0.000
Baseline FPG (mmol/L)	0.880	(0.540, 1.435)	0.608
Baseline PPG (mmol/L)	1.226	(1.025, 1.466)	0.026
Baseline FINS (mU/L)	1.505	(0.870, 2.602)	0.143
Baseline PINS (mU/L)	1.001	(0.974, 1.029)	0.943
Baseline TC (mmol/L)	0.932	(0.419, 2.071)	0.862
Baseline TG (mmol/L)	1.194	(0.836, 1.705)	0.329
Baseline HDL-c (mmol/L)	1.469	(0.447, 4.831)	0.527
Baseline LDL-c (mmol/L)	1.123	(0.448, 2.814)	0.805
OHAs only	1.062	(0.245, 4.112)	0.698
Insulin only	0.732	(0.099, 4.631)	0.812
OHAs and Insulin	0.672	(0.201, 3.412)	0.524

Abbreviations: OR = odds ratio; CI = confidence interval; BMI = body mass index; HbA1c = haemoglobin A1c; FPG = fasting plasma glucose; PPG = postprandial plasma glucose; FINS = fasting serum insulin; PINS = postprandial serum insulin; PPG = postprandial plasma glucose; TC = total cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; OHAs = oral antihyperglycaemic agents.

Safety

Liraglutide was well tolerated in the responders and non-responders. Of the 206 patients ultimately included in the analysis, 164 (81.55%) did not show any symptoms of adverse gastrointestinal events (GIAEs), and 42 (18.45%) experienced GIAEs but were able to tolerate continued treatment.

During the observation period, no cases of severe hypoglycemic events were identified. The incidence of hypoglycemic events and GIAEs was balanced between both groups ($P > 0.05$). The numbers of ADR leading to withdrawal from the study drug were low (Figure 1).

Discussion

In this study, we explored potential predictors of HbA1c response to liraglutide in patients with T2DM. The findings suggest that age, baseline HbA1c, baseline PPG, and duration of diabetes are important factors influencing the HbA1c response to liraglutide, and that patients meeting the criteria of higher baseline HbA1c, higher baseline PPG, and a shorter duration of diabetes are more likely to have an HbA1c response to liraglutide. Therefore, the findings of our study are significant in guiding the clinical individualization of liraglutide application, and especially in allowing the pre-evaluation of patients who may be responders to liraglutide therapy.

In setting the responsiveness grouping criteria, HbA1c <7% was considered the criterion for glycemic response grouping according to the Guideline for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020 edition), but this criterion does not apply to elderly patients with a history of severe hypoglycemia, a short life expectancy, or significant microvascular or macrovascular complications since the HbA1c control target for these patients should be individualized and is frequently higher than 7%[23]. However, according to the National Institute for Health and Care Excellence (NICE) guidelines on the use of GLP-1 receptor agonists, a glycemic response is defined as a >1.0% reduction in HbA1c from baseline at 6 months of treatment with GLP-1 receptor agonists [22].It was found in the LEAD-3 study that the optimal glucose-lowering efficacy was achieved with liraglutide alone at a dose of 1.8 mg for 3 months, with a decrease in HbA1c of about 1% from baseline levels [24]. By considering the above criteria together, in this study, responders were defined as patients who achieved a decrease in HbA1c ≥1.0% or HbA1c <7.0% after 6 months of liraglutide treatment, while non-responders were patients who failed to achieve this decrease. There were significant individual differences in efficacy and adverse drug reactions when different patients were treated with an identical dose of GLP-1RAs [24, 25]. Differences in living environments, the genetic background of the patient, medication compliance, and pathophysiological status may contribute to such variations in treatment response. Our data showed that a total of 206 subjects were included in the analysis, 132 of whom responded to liraglutide treatment and 74 of whom were non-responders to liraglutide treatment; compared with the response group, the non-response group showed a longer duration of T2DM. These results correspond well with those found in a recent meta-analysis [26].

This study also revealed that age, baseline HbA1c, baseline PPG, and duration of diabetes were predictive of HbA1c improvement after 6 months of liraglutide treatment. Notably, there was a good linear correlation between baseline HbA1c and HbA1c improvement after liraglutide treatment (R^2 = 0.764), and for each 1% increase in HbA1c, the odds of being a responder increased to 3.15fold (95%CI: 1.85-5.24). The duration of diabetes as a predictor of response to liraglutide has been previously described, but the predictive roles of baseline HbA1c, age, and baseline PPG were not consistent with the findings identified in previous studies [25, 27]. Our data showed that the duration of diabetes was shorter in the responders than in the non-responders, but the predictive effect of the duration of diabetes on liraglutide efficacy needs to be determined in further large-scale studies. The

fact that the action of GLP1RAs and β-cell function are interdependent and that the level of GLP1 secretion and β-cell function are age-related may be a possible mechanism for the age-related hypoglycemic effect of liraglutide [28, 29]. Previous studies have found that patients with a long duration of diabetes have poorer pancreatic islet β-cell function and weaker responses to drug action, which suggests poorer glucose-lowering efficacy in patients with a long duration of diabetes treated with liraglutide and is consistent with our findings [25]. According to previous studies, BMI was considered to be a factor affecting the hypoglycemic efficacy of liraglutide based on the theory that liraglutide, as a long-acting GLP-1 agonist, has a strong effect on reducing FPG and body weight, and patients with an increased BMI tend to have a higher FPG, resulting in more pronounced glycemic control efficacy after liraglutide treatment. However, the effect of BMI and FPG on the glycemic control of liraglutide was not observed in this study, probably because the BMI range of the included subjects was 20-31 kg/m^2, which was different from the subjects reported in the literature [26].

To evaluate the predictive role of age, baseline HbA1c, baseline FPG, and diabetes duration on liraglutide responsiveness in a complex clinical context, we performed a correlation analysis and found that baseline HbA1c, baseline PPG, and diabetes duration were correlated with the changes in HbA1c values, respectively. Moreover, patients with lower baseline HbA1c (<7.31%), lower baseline FPG (<6.90), and a longer duration of diabetes (>19.63 years) were more likely to show non-response to liraglutide treatment, which is not entirely consistent with the observations of previous studies [25, 26, 30]. Studies with smaller cohorts showed that the proinsulin secretory effect of GLP-1RA was weaker in those with lower blood C-peptide levels and that a lower postprandial urinary C-peptide-to-creatinine ratio was associated with a reduced hypoglycemic response to liraglutide [31, 32]. Based on the abovementioned theory regarding the relationship between the exertion of incretin hormone and islet beta cells, and the fact that a long duration of diabetes is often accompanied by a decrease in beta cell mass and quantity, these factors may explain the better HbA1c response to liraglutide in patients with a limited duration of diabetes (≤19.63 years). This study thus provides useful insights into the real-world application of liraglutide. According to current advances in research, the influence of clinical factors on the HbA1c response to liraglutide should be fully considered in clinical practice. If more large-scale studies can be conducted, this will be beneficial to constructing individualized dosing models for liraglutide, allowing the development of precision medical tools for patients.

As for adverse reactions, 42 (18.45%) cases with GIAEs were detected in this study, which is consistent with the reports of studies conducted based on Asian populations, such as Chinese and Japanese populations, mostly occurring within 1-2 weeks of the first dose, mostly tolerable, and gradually decreasing as the treatment duration increased [12-13].

This study has several unanswered questions that require further research. First, our findings regarding age, baseline HbA1c, baseline FPG, and the duration of diabetes predicting the HbA1c response to liraglutide need replication because they are driven by marked differences in the responses of a relatively small number of participants. Second, as a retrospective analysis, the data regarding some of the influencing factors, such as lifestyle changes during the follow-up, were often lacking in the electronic medical record systems, so we were unable exclude the influence of other unrecorded influencing factors on weight reduction and glycemic control. Third, because the subjects were not newly diagnosed T2DM patients treated with liraglutide monotherapy, some were taking combined medications and their doses were adjusted up or down during the follow-up period, thus having confounding effects on the measurement of HbA1c changes. Finally, genetic factors may be important factors affecting drug efficacy; however, no pharmacogenomic study of liraglutide has been conducted. There is a need to further improve the evaluation criteria for the hypoglycemic efficacy of liraglutide and to enhance the rationality of clinical drug use.

Conclusion

In conclusion, this study identified predictors of HbA1c response to liraglutide in patients with T2DM through a retrospective analysis, which can provide a guiding basis for rational clinical use. It is recommended that clinical treatment with liraglutide should take full account of the effects of age,

baseline HbA1c, baseline PPG, and duration of diabetes on HbA1c response. In addition, further prospective studies are essential to lay the foundation for tailoring a more precise therapy for T2DM.

Abbreviations

T2DM: type 2 diabetes mellitus; GLP-1: Glucagon-like peptide-l; GLP1RAs: Glucagon-like peptide-1 receptor agonists; EASD: European Association for the Study of Diabetes; ADA: American Diabetes Association; BMI: body mass index; WHR; waist to hip ratio; FPG; fasting plasma glucose; PPG; postprandial plasma glucose; HbA_{1c}; hemoglobin A_{1c}; FINS; fasting serum insulin; PINS; postprandial serum insulin; HOMA-IR; homeostasis model assessment for insulin resistance; HOMA-B; homeostasis model assessment for beta cell function; TC; total cholesterol; TG; triglyceride; HDL-c; high-density lipoprotein-cholesterol; and LDL-c; low-density lipoproteincholesterol.

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Authors' contributions

JFS and XJP contributed equally. JFS and XJP wrote the main manuscript text and JN prepared figures. YJD and XL designed the experiments and revised the paper. JN and RNH contributed to data acquisition, and revised the paper. All authors reviewed the manuscript.

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Availability of data and materials

All datasets generated for this study are included in the article/Supplementary Material.

Declarations

Ethics approval and consent to participate

This study was carried out in accordance with the recommendations of the Ethics Committee of Affiliated Hospital of Jiangnan University (NO. LS2021091). All information obtained in the study was kept confidential.

Consent for publication Not applicable.

Competing interests

The authors declare that they have no competing interests.

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