

# Latent class trajectory modeling of glycated hemoglobin over a 13-year period in a large sample of outpatients with type 2 diabetes



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## ABSTRACT

**Background:** Glucose control depends on several factors such as social, economic, mental health, substance abuse, and eating behavior among other factors. The complexity of glucose control trajectories poses significant challenges especially when long-term care is required.

**Aim:** To identify different latent classes of glycated hemoglobin trend in order to better individualize therapy of diabetes.

**Methodology:** In this retrospective observational study 8989 adult patients with type 2 diabetes attending the diabetes clinic of Verona during the year 2007-2020 were analyzed. We applied LCMM with the goal of identifying patients belonging to subgroups with different trajectories of glycated hemoglobin. A multivariate logistic model was used to identify variables associated to class with worsening trend with respect to that with a stable trend.

**Results:** Class 1, with the improving trend, contained 630 (7.01%) of patients; class 2, the stable trend, 7975 (88.52%); and class 3, the worsening trend, 402 (4.47%) of patients. Subjects of class 3 were significantly younger, whereas those of class 1 were more frequently women, with a longer duration of diabetes and a worse glycemic control. The multivariate logistic model with the dependent variable worsening trend versus stable trend, showed that age was associated with a reduced probability of worsening trend, duration of diabetes increased the risk of a worsening trend as did women.

**Conclusion:** In conclusion, our study shows that most of the patients with type 2 diabetes followed a stable trend of glycated hemoglobin, and only less than 5% of patients follow a deteriorating trend.

## Introduction

Glycated hemoglobin is a fundamental biomarker for monitoring patients with diabetes [1]. It provides an estimate of glucose control over a previous period of three months [2]. Glucose control overtime depends on several factors, including not only therapy but even social, economic, mental health, substance abuse, and eating behavior among other factors [3,4]. Undoubtedly, the aim of diabetic therapy

is to reach the best glucose control in individual patient as suggested by clinical guidelines [5]. However, in real life the best glucose control is not easily obtainable in all, moreover some patients may worsen their glucose control overtime. Therefore, to individualize therapy is important to know the percentage of patients with type 2 diabetes that worsen their glucose control over time.

There are few data on the trend of glycated

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KEYWORDS

- type 2 diabetes
- glycated hemoglobin
- latent class model
- precision medicine

hemoglobin in ambulatory patients with type 2 diabetes under real life clinical practice. The acquisition of this notion may help to focus the attention on specific class of patients. The complexity and variability of glucose control trajectories pose significant challenges especially when long-term care is required [6].

Longitudinal analytic methods represent a potential for studying the trajectories of glucose control overtime in order to better characterize single patient with type 2 diabetes. An approach for subgroup discovery in longitudinal data is latent class mixed modeling (LCMM), a powerful method for unveiling meaningful and differing subgroups with a homogeneous pattern of change over time [7].

Therefore, the aim of the present study was to identify different latent classes of glycated hemoglobin overtime in an ambulatory setting in order to better characterize the trajectory of patients with type 2 diabetes and to quantify the impact of patients with a worsening trend. This notion may help to better individualize treatment of diabetes.

Methodology

In this retrospective observational study 8989 adult patients with type 2 diabetes were analyzed. All patients were regularly attending the diabetes clinic of Verona during the year 2007-2020. Patients were included if they have at least 5 or more glycated hemoglobin during the period of the study in order to model the trend. Age, sex, and duration of diabetes were also recovered. Hemoglobin A1c (HbA1c) was measured by high-performance liquid chromatography and standardized according to IFCC.

Since all analyses were carried out on routinely collected anonymized records, the study was deemed exempt from approval by the local ethics committee.

Statistical analysis

We applied LCMM with the goal of identifying patients with type 2 diabetes belonging to subgroups with different trajectories over time of glycated hemoglobin. We used the 'l cmm' function from R package l cmm [7]. The function estimates mixed-effect models and latent class mixed-effect models for different types of longitudinal outcomes. We built models for the entire cohort, using the available variables. A three class's quadratic model was selected. A multivariate logistic model was used to identify variables associated to class with worsening trend

with respect to that with a stable trend.

Results

In glucose trend we expected to encounter three types of patients: first, patients with stable trend overtime, second, patients with a worsening trend and third, patients with an ameliorating trend. Therefore, we select a three classes LCMM model that identified the expected three classes. FIGURE 1 shows the three classes as row data, while FIGURE 2 reported the three classes including the 95% confidence intervals. Class 1, with the improving trend, contained 630 (7.01%) of patients; class 2, the stable trend, 7975 (88.52%); and class 3, the worsening trend, 402 (4.47%) of patients. The posterior classification probability was 0.85 for class 1, 0.95 for class 2 and 0.84 for class 3 (TABLE 1).

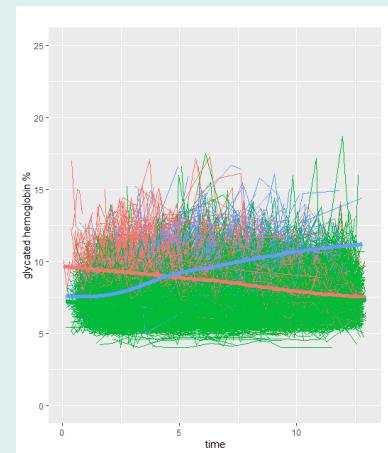


FIGURE 1: The trajectories of the three identified classes are shown with all the row data. Note: Latent Class (→) 1, (→) 2, (→) 3

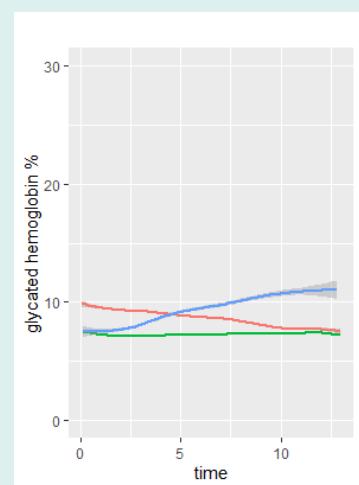


FIGURE 2: The trajectories of the three identified classes are shown with the 95% CI. Note: Latent Class (→) 1, (→) 2, (→) 3

**TABLE 1: Main characteristics of the subjects (n=8989).**

Age, years	67.9 ± 11.5
Sex, Women n(%)	3866 (43%)
Diabetes duration, years	9.2 [3.8, 19.7]
HbA1c, %	7.2 ± 1.2

**Note:** HbA1c: Glycated haemoglobin.

The 8989 patients with type 2 diabetes were about 68 years old, with an average duration of the disease of 9 years, and showed a quite good metabolic control as shown by mean glycated hemoglobin of 7.2%. Women were 43% of the sample. Subjects of class 3 were significantly younger, whereas those of class 1 were more frequently women, with a longer duration of diabetes and significantly higher glycated hemoglobin, as shown in TABLE 2. The multivariate logistic model with the dependent variable worsening trend (1) versus stable trend (0), showed that age was associated with a reduced probability of worsening trend, duration of diabetes increased the risk of a worsening trend as did women (TABLE 3).

**TABLE 2: Main characteristics of Latent classes of subjects (n=8989).**

Latent classes	1 n=630	2 n=7957	3 n=402	p
Age, years	65.7 ± 11.3	68.1 ± 11.3	62.8 ± 14.7	<0.001
Sex, Fn(%)	281 (49.7)	3512 (42.6)	73 (38.6)	0.002
Diabetes duration, years	22.1 ± 27.8	18.0 ± 26.9	17.4 ± 26.9	0.002
HbA1c, %	9.5 ± 1.5	7.0 ± 0.9	7.9 ± 1.2	<0.001

**Note:** HbA1c: Glycated haemoglobin.

**TABLE 3: Multivariate logistic analysis comparing the worse vs the stable trends.**

	OR (CI 95%)	p
Age, years	0.98 (0.97, 0.98)	<0.001
Sex, F	1.007 (1.004, 1.009)	<0.001
Duration of diabetes, years	1.38 (1.16, 1.64)	<0.001

In supplementary figures are reported the glycated hemoglobin trend divided in three periods of 4 years each. The stable class 2 maintained the same trend since the first four years period,

subjects with an ameliorating trend (class 1) kept improving overall the three periods, while class 3 worsen by the end of the first 4 years with a very slightly deterioration during the middle period and remained at the same level in the last 4 years (FIGURE S1).

### Discussion

The main result of the present study is that most (88.52%) of the ambulatory patients affected by type 2 diabetes maintained a stable trend of glycated hemoglobin over a long period of time. Only 4.47% of patients showed a worsening trend and, interestingly, the worse trend reach a steady state already during the first period of observation. Female sex and diabetes duration were significant predictors of a worse trend when compared with patients with stable trend, while age was inversely associated. It is important to remark that all patients were regularly attended the same diabetic clinic where the same clinical guidelines of treatment of type 2 diabetes were applied and shared by the entire team.

Therefore, less than 5% of patients showed a worsening trend. This figure is in line with previous studies. In 5423 patients with type 2 diabetes, 3.4% showed a worsening trend [8]. In a similar study, the percentage of patients with a worsening trend of glycated hemoglobin was 2.9% [9]. Moreover, the latter study has shown a correlation between longitudinal trends in glycated hemoglobin and outcomes [9].

The results of this study may have clinical implications as we identified a class of patients with type 2 diabetes that worse their glucose control over time. To identify these patients may lead to a more aggressive therapy in order to improve glucose control.

This study does allow us to infer the possible causes of the worse longitudinal trend; a dedicated study collecting multiple clinical data is needed. Nevertheless, a previous study has found a correlation between cognitive performance and worsening trend in elderly patients. However, other possible causes may be implicated [10].

The result of this study poses an important point; we can expect that about 5% of patients with type 2 diabetes exposed to the same clinical treatment will deteriorate their glycemic control over time. In the era of individualized medicine, our data emphasized the importance of selecting patients, even narrow subgroups of population, who may benefit from a different approach in treatment [11].

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**Conclusion**

Our study has limitations, we did not have clinical data to infer the possible causes of the deteriorating trend and it is a single center study, thus may be not generalize. In spite of these limitations, the strength of our study is that all patients were treated following the same clinical and therapeutic clinical guidelines.

In conclusion, our study shows that most of the patients with type 2 diabetes followed a stable trend overtime of glycated hemoglobin and only less than 5% of patients showed a deteriorating trend.

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**Disclosure Statement**

The authors have nothing to disclose.

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**Conflict of Interest**

Nothing to declare

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**Authors' Contributions**

G.Z. conceived, designed the study and performed the statistical analysis and drafted the initial article. M.S. prepared the database. B.A. revised the statistical analysis and the manuscript. All authors contributed to the interpretation of data, discussed the article, reviewed the article, revised it critically, and approved its final version to be published. G.Z. is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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