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CONFIDENCE INTERVALS ESTIMATION OF PREDICTED HBA1C DERIVED FROM TIME-IN-RANGE FOR LINEAR REGRESSION ANALYSIS

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Background

◆When an association between HbA1c and time-in-range (TIR) is assessed using univariate linear regression analysis, it is desirable that HbA1c values aren't biased in patients generally.

◆A general difference between HbA1c and TIR is whether patients with low HbA1c have hypoglycemia or not.

◆If HbA1c is distributed normally, whether patients with low HbA1c have hypoglycemia or not may affect whether TIR is distributed normally or not.

◆Moreover, in theory, abnormal distribution of TIR may be implied as the "center of curves for 95% confidence intervals estimation for predicted HbA1c derived from TIR" (C95%CIEcurvesA1c←TIR) which is off-center for distribution range of TIR.

◆Thus, we studied regarding confidence intervals estimation of predicted HbA1c derived from TIR for linear regression analysis.

Research design & Methods

One hundred one outpatients with type 2 diabetes underwent HbA1c testing, wore a FGM (FreeStyle Libre Pro), and did not change diabetic treatments, on a hospital visit.

TIR and mean glucose levels were calculated using FGM data over 24-h × 13 days.

We selected 2 patterns of 32 patients, each comprising 8 patients with HbA1c of 6% level, 8 patients with HbA1c of 7% level, 8 patients with HbA1c of 8% level, and 8 patients with HbA1c of 9% level.

Pattern 1 was selected to achieve the following: Patients with low HbA1c had low TIR; "The ratio of time-below-range (<70 mg/dL) to time-above-range (>180 mg/dL)" (TBR<70/TAR>180) negatively correlated to HbA1c.

Pattern 2 was selected to realize that "TBR<70/TAR>180 did not correlate to HbA1c.

◆Primary endpoints

☆Position of "C95%CIEcurvesA1c←TIR" in distribution range of TIR in patterns 1 and 2

◆Secondary endpoints

☆Position of "center of curves for 95% confidence intervals estimation for predicted mean glucose levels derived from HbA1c" (C95%CIEcurvesMean←A1c) in distribution range of HbA1c in patterns 1 and 2;

☆Distribution normality for HbA1c, TIR, and mean glucose levels in patterns 1 and 2; ☆Associations between TIR and HbA1c in patterns 1 and 2;

☆Associations between HbA1c and mean glucose levels in patterns 1 and 2; ☆Correlation between TBR<70/TAR>180 and HbA1c in patterns 1 and 2

☆"Curves for 95% confidence intervals prediction for predicted HbA1c derived from TIR" (95%CIPcurvesA1c←TIR) in patterns 1 and 2

☆"Curves for 95% confidence intervals prediction for predicted mean glucose levels derived from HbA1c" (95%CIPcurvesMean←A1c) in patterns 1 and 2

Result

Baseline characteristics

Characteristic	Overall	Pattern 1	Pattern 2
N (Male / Female)	101 (61 / 40)	32 (22 / 10)	32 (23 / 9)
Age, years	69.3 ± 13.6	72.2 ± 15.2	69.4 ± 14.7
BMI, kg/m^2	24.3 ± 4.1	23.7 ± 3.9	24.7 ± 5.2
HbA1c, %	8.0 ± 1.5	8.1 ± 1.1	8.0 ± 1.1
Mean glucose levels, mg/dL	168.0 ± 47.8	185.9 ± 39.0	168.9 ± 32.9
Time in range (70–180 mg/dL), %	61.0 ± 22.3	47.6 ± 21.9	61.5 ± 21.4
Time below range (<70 mg/dL), %	3.1 ± 7.2	2.6 ± 5.9	0.6 ± 0.9
Time above range (>180 mg/dL), %	35.9 ± 24.1	49.8 ± 23.4	37.9 ± 21.7
TBR<70/TAR>180	0.80 ± 3.18	0.11 ± 0.26	0.04 ± 0.09

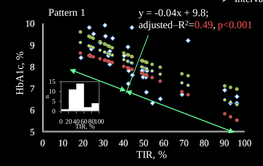
TBR<70/TAR>180: ratio of time below range (<70 mg/dL) to time above range (>180 mg/dL)

Data are shown as mean±SD.

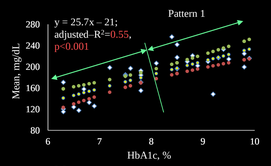
➢ The TIR in pattern 1 was lower than that in pattern 2 although the HbA1c was almost the same between patterns 1 and 2.

➢ The time below range (<70 mg/dL) in pattern 1 was higher than that in pattern 2.

➢ Interval estimation

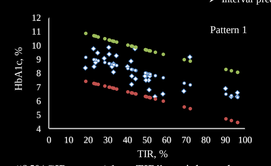


TIR was not distributed normally (p=0.01) while HbA1c was (p=0.65). (Kolmogorov–Smirnov test)
TIR was associated with HbA1c
The C95%CIEcurvesA1c←TIR was situated on the lower TIR side of the center of TIR distribution range.
TBR<70/TAR>180 correlated to HbA1c (r=–0.52, p<0.001).

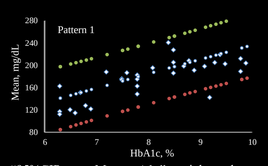


Mean glucose levels was distributed normally (p=0.12).
HbA1c was associated with mean glucose levels.
The "C95%CIEcurvesMean←A1c" was situated on center of distribution range of HbA1c.

➢ Interval prediction

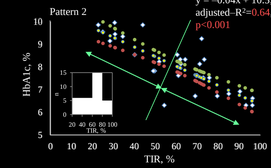


"95%CIPcurvesA1c←TIR" straightened more than "95%CIEcurvesA1c←TIR".
95%CI for prediction was wider than 95%CI for estimation

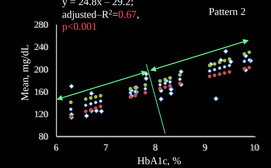


"95%CIPcurvesMean←A1c" straightened more than "95%CIEcurvesMean←A1c".
95%CI for prediction was wider than 95%CI for estimation

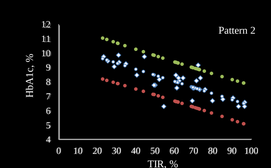
Univariate linear regression analysis and Spearman's rank correlation coefficient were used for the statistical analysis.



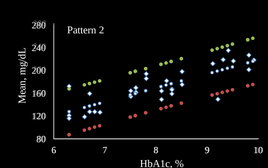
TIR and HbA1c were distributed normally (p=0.69, p=0.48).
TIR was associated with HbA1c.
The "C95%CIEcurvesA1c←TIR" was situated on center of distribution range of TIR.
TBR<70/TAR>180 did not correlate to HbA1c (r=–0.28, p=0.12).



Mean glucose levels was distributed normally (p=0.54)
HbA1c was associated with Mean.
The "C95%CIEcurvesMean←A1c" was situated on center of distribution range of HbA1c.



"95%CIPcurvesA1c←TIR" straightened more than "95%CIEcurvesA1c←TIR".
95%CI for prediction was wider than 95%CI for estimation



"95%CIPcurvesMean←A1c" straightened more than "95%CIEcurvesMean←A1c".
95%CI for prediction was wider than 95%CI for estimation

Discussion

95%CI for estimation is calculated using the following formula (x_m: mean of x; S_{xx}: sum of squares for x; V_E: residual variance; t: t-value of the Student's t-distribution)

$$y_0 \pm \sqrt{\left(\frac{1}{n} + \frac{(x_0 - x_m)^2}{S_{xx}}\right) V_E} \times t\,(n-2,\ 0.05)$$

When 95%CI for estimation are calculated using an identical formula analyzed using linear regression analysis, x_m, S_{xx}, V_E, and t (n – 2, 0.05) are constant, therefore, 95%CI for estimation depend on absolute differences between x_0 and x_m. Namely, x_0 being away more from x_m leads to wider 95%CI for estimation.

95%CI for prediction is calculated using the following formula (x_m: mean of x; S_{xx}: sum of squares for x; V_E: residual variance; t: t-value of the Student's t-distribution)

$$y_0 \pm \sqrt{\left(1 + \frac{1}{n} + \frac{(x_0 - x_m)^2}{S_{xx}}\right) V_E} \times t\,(n-2,\ 0.05)$$

$\frac{1}{n} + \frac{(x_0 - x_m)^2}{S_{xx}}$ is extremely smaller than 1 in general, therefore, 95%CI for prediction almost depend on V_E. In addition, V_E is constant when 95%CI for prediction are calculated using an identical formula analyzed using linear regression analysis. Thus, 95%CI for prediction are almost constant regardless of x.

➢ Interval estimation

When x is distributed normally, such as the TIR in pattern 2 in the present study, center of curves for 95% confidence intervals for estimation of y situates on center of distribution range of TIR, such as the C95%CIEcurves in pattern 2.

When x is not distributed normally, such as the TIR in pattern 1, center of curves for 95% confidence intervals for estimation of y is off-center for distribution range of TIR, such as the C95%CIEcurves in pattern 1. Specifically, in pattern 1, the mean of TIR was on lower TIR side from center of distribution range of TIR (47.6%) because of the distribution of TIR shown above, resulting in the C95%CIEcurves situated on lower TIR side from center of distribution range of TIR.

The difference of the distribution of TIR in pattern 1 from normal distribution is the small number of patients with TIR of 60–80%. The small number of patients with TIR of 60–80% despite normal distribution of HbA1c seems to be because patients with low HbA1c relatively have hypoglycemia, suggested by the negative correlation between TBR<70/TAR>180 and HbA1c in pattern 1. That is, increased patients with hypoglycemia and low HbA1c are likely to cause the smaller number of patients with TIR of 60–80%.

From the above, although it is the premise that HbA1c is distributed equally, the proportion of patients with hypoglycemia and low HbA1c may be sensed by identifying the C95%CIEcurves.

Simulation 1

In patients, if HbA1cs are normally distributed, and the out of range for TIR, including 20–40% for TIR of 60–80% (A1c of 6.5–7.5%), is mainly TAR>180,

Figure 1

TIRs are theoretically normally distributed.
TIR corresponding to A1c of 8% is 50%

From figure 1, in patients with TIR of 60–80% (A1c of 6.5–7.5%), if TBR<70 further increase,

Figure 2

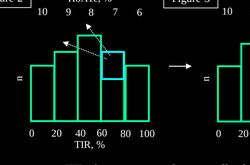
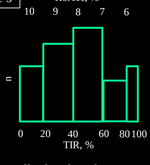


Figure 3



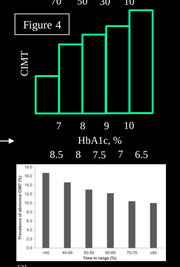
TIRs become not to be normally distributed.
TIR corresponding to A1c of 8% decreases and is projected to approximate 40%.

Not only increased hyperglycemia but also increased hypoglycemia has been previously reported to be associated with increased carotid intima-media thickness [1, 2]. Recently, it has been reported that decreased time in range is associated with increased carotid intima-media thickness (CIMT) in type 2 diabetes [3]. In this previous report, the prevalence of abnormal CIMT in patients whose HbA1c was 8–9% level was higher than that in patients whose HbA1c was 9–10% although the prevalence of abnormal CIMT gradually increased with decreasing TIR. This previous study results can be explained by considering that patients with HbA1c of 8–9% level have both hyperglycemia and hypoglycemia to some extent, that may lead to more increased CIMT compared to that in patients with HbA1c of 9–10%. Thus, the present study consideration may support the previous study results.

Simulation 2

In patients, if HbA1cs are normally distributed, and the out of range for TIR, including 30–50% for TIR of 50–70% (A1c of 7–8%), is mainly TAR>180,

Figure 4



From figure 4, in patients with TIR of 50–70% (A1c of 7–8%), if TBR<70 further increase,

Figure 5

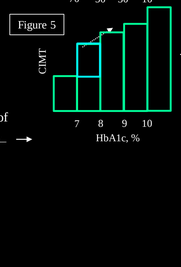
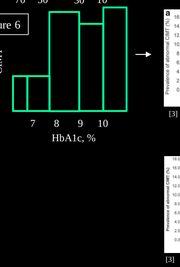
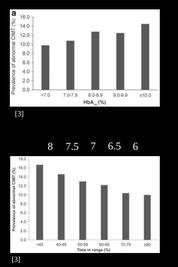


Figure 6





1. Yamasaki Y, et al. Diabetes Care. 2000; 23:1310-5. 2. Giménez M, et al. Diabetes Care. 2011; 34:198-203. 3. Lu J, et al. Diabetes Technol Ther. 2020; 22:72-8.

➢ Interval prediction

The present study results regarding 95%CI for prediction are reasonable. When patients want to know reliability of prediction safely, 95%CI for prediction are useful.

Conclusion

➢ For linear regression analysis, the confidence interval estimation of predicted HbA1c derived from TIR may imply the degree of hypoglycemia occurrence for patients with low HbA1c.

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