Association Between Triglyceride Level and Glycemic Control Among Insulin-Treated Patients With Type 2 Diabetes

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Context: Elevated blood triglyceride levels are known to increase the risks of diabetes and pre-diabetes. However, it is still unclear whether elevated triglyceride levels are associated with inadequate glycemic control in patients with type 2 diabetes mellitus.

Objective: To investigate the association between elevated triglyceride levels and inadequate glycemic control among insulin-treated patients with type 2 diabetes mellitus.

Design, Setting, and Patients: We recruited 20,108 patients with type 2 diabetes mellitus who were treated with a sufficient dose of insulin. These patients were from the 2013 China National HbA_{1c} Surveillance System study conducted in Mainland China. Multivariate logistic regressions were used

patients with type 2 diabetes mellitus can prevent the development or slow the progression of macrovascular and microvascular complications (4–10). The International Diabetes Mellitus Practices Study, which comprised 17 less affluent countries in Eastern Europe, Asia, Latin America, and Africa, revealed that only 20% to 30% of patients with diabetes achieved the goal of HbA_{1c} <7.0% (11). In the Hong Kong Diabetes Registry study of 7549 Chinese patients with type 2 diabetes mellitus, 39.7% of patients undergoing therapy were able to attain the glycemic target of HbA_{1c} <7.0% (12).

It has been accepted that some patients with type 2 diabetes mellitus eventually require insulin therapy to achieve more satisfactory glycemic control. Nevertheless, some patients receiving insulin therapy still cannot attain adequate glycemic control. Results from a large-scale survey in Mainland China demonstrated that only 26% to 31% of patients receiving insulin therapy achieved the targeted HbA_{1c} level of <7.0% (13). A Johns Hopkins Hospital study of Americans showed that approximately half (51%) of patients with type 2 diabetes mellitus receiving insulin therapy, with a total daily dose >0.4 U/kg of body weight, remained hyperglycemic (14). This begs the question as to what accounts for the failure of insulin therapy. Several prospective studies have demonstrated that elevated blood triglyceride (TG) levels increased the risk of diabetes (15–21), impaired fasting glucose level (15, 22), and impaired glucose tolerance (21). However, the relationship between TG levels and glucose metabolism is more complex in the pathological status of diabetes and its complications and may be influenced by the actions of antidiabetic drugs, such as insulin and metformin, on glucose and lipid metabolism. Therefore, the simple inference that elevated TG levels in patients with diabetes necessarily account for the deterioration of glucose metabolism and resulting inadequate glycemic control is insufficient. Currently, the assessment of dyslipidemia in patients with diabetes has focused mainly on its "chronic" actions, which lead to cardiovascular complications (23, 24), whereas the association of TG level with glucose metabolism is more "acute" than its association with heart disease (25). To our knowledge, no study has assessed whether elevated blood TG levels are associated with unfavorable glycemic control in patients with type 2 diabetes mellitus.

Using the very large, multicenter, cross-sectional Mainland China National HbA_{1c} Surveillance System (CNHSS) study, we extracted a population of patients with type 2 diabetes mellitus without diabetes complications who were treated with sufficient insulin and assessed the association of elevated TG levels with inadequate glycemic control.

Materials and Methods

Study subjects

The CNHSS study, which was launched by the Chinese Diabetes Society, was conducted between 2011 and 2013 in Mainland China. The CNHSS was established to monitor glycemic control among adult patients with type 2 diabetes mellitus. The survey was conducted from April to June in 2013, and recruited 238,639 outpatients with type 2 diabetes mellitus from 602 hospitals located in 90 cities in 29 provincial and administrative regions of Mainland China. The inclusion criteria were outpatients who had type 2 diabetes mellitus, were 18 years or older, and were treated with insulin, oral antidiabetic drugs (OADs), and other drugs (26, 27). The exclusion criteria included (i) diabetes secondary to other diseases; (ii) treatment with Chinese herbal medicines only; (iii) being pregnant or breastfeeding an infant; and (iv) unconsciousness or inability to communicate. During this survey period, on each workday the first seven consecutive outpatients who entered each hospital's endocrinology outpatient department and met the eligibility criteria were invited to participate in the survey until 400 patients were recruited from

the use of OADs and insulin. The date of diabetes diagnosis and medical history of NCDs and dates of their diagnosis were retrieved; these NCDs included hypertension, coronary heart disease, cerebrovascular disease, dyslipidemia, diabetic retinopathy, and diabetes-related foot ulcers. Standing height, body weight, and blood pressure levels were recorded during the interviews. Briefly, heights and weights were measured in light clothing with the use of standardized stadiometers and scales. Blood pressure level was measured on the right arm using a standard mercury sphygmomanometer or an electronic sphygmomanometer with the subjects resting for at least 5 minutes in a sitting position. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. All laboratory examinations, including total cholesterol (TC), TGs, low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose, and HbA_{1c}, were performed in the local hospitals where the interviews were conducted. The venous blood sample was taken on the next morning after at least 8 hours of overnight fasting. Blood glucose level was measured by the hexokinase/glucose oxidation method. HbA_{1c} was measured by HPLC. TGs and TC were determined by the oxidase method, and low density lipoprotein by the homogeneous method (29, 30). High-density lipoprotein cholesterol (HDL-C) was calculated using the Friedewald equation (31), where HDL-C = TC − LDL-C − TG/2.2, with all four quantities measured in mmol/L. One trained staff member entered all the data and uploaded the entered data into the central database.

Assessment of covariates

TG levels were categorized into four groups according to the guidelines on prevention and treatment of dyslipidemia (32) and quantiles of the sampling distribution. In addition, elevated TC and LDL-C profiles were classified in accordance with published criteria (32). BMI was assessed as either normal weight (BMI <24.0 kg/m^2) or overweight (BMI ≥ 24.0 kg/m^2). Elevated blood pressure level was considered to be a systolic blood pressure level ≥ 130 mm Hg and/or a diastolic blood pressure level ≥ 80 mm Hg.

Definition of inadequate glycemic control

The main outcome variable was inadequate glycemic control. On the basis of the HbA_{1c} target recommended in published guidelines (33, 34), two types of inadequate glycemic control were defined: $HbA_{1c} \geq 7.0\%$ (53 mmol/mol) and $HbA_{1c} \geq 6.5\%$ (48 mmol/mol).

Statistical analysis

Continuous data were expressed as mean plus SD. Frequencies and percentages were used to express categorical variables. Continuous variables in each of the groups were compared using the Kruskal-Wallis H test. Homoscedasticity of continuous variables among different TG groups were compared by performing the Bartlett test and Levene test. The χ^2 test was used to compare proportions for categorical variables. Logistic regressions were used to calculate ORs and 95% CIs for inadequate glycemic control. Subgroup analyses were conducted to further explore the association between TG levels and the risk of inadequate glycemic control by predefined stratifications of sex, age, BMI, blood pressure, and duration of diabetes. In addition, the presence of nonlinearity between continuous TG levels and ORs of individual glycemic control outcome was assessed by dose-response analyses using restricted cubic spline regression. For all analyses, a two-tailed value <0.05 was considered statistically significant. All statistical analyses were performed using version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute, Cary, NC).

Results

Among the 20,108 patients included in the study, the mean age was 56.6 ± 11.6 years. The characteristics of the study population categorized along the different blood TG levels are summarized in Table 1. Results of the homoscedasticity test for continuous variables among the different TG groups are provided in Table 2. Overall, 56% of insulin-treated patients with diabetes had elevated TG levels (≥ 1.70 mmol/L). The prevalence of HbA_{1c} values $\geq 7.0\%$ and $\geq 6.5\%$ was 67.2% and 83.4%, respectively. Individuals with higher TG levels less frequently self-monitored their blood glucose level and generally had higher blood pressure levels and TC and LDL-C values. These individuals with higher TG levels also had a higher prevalence of inadequate glycemic control. There were statistically significant increasing trends in the proportion of patients with $HbA_{1c} \geq 7.0\%$ and $HbA_{1c} \geq 6.5\%$ with respect to the different categories of TG levels.

After step-forward adjustments for sex, age (model 1), BMI (model 2), blood pressure, TC, LDL-C, and HDL-C (model 3), duration of diabetes, diabetes education, and the frequency of SMBG (model 4) in the multivariable-adjusted models, graded positive ORs of inadequate glycemic control for those with step-elevated TG levels were similar across the different models. In the analyses of the final model adjusted simultaneously for all potential confounding factors, the ORs (95% CI) of $HbA_{1c} \geq 7.0\%$ for those with TG levels in the ranges of 1.70 to 2.29, 2.30 to 3.39, and ≥ 3.40 mmol/L were 1.06 (0.98, 1.15), 1.35 (1.23, 1.48), and 3.12 (2.76, 3.53), respectively, compared with patients with TG levels <1.70 mmol/L (Table 3). There were statistically significant trends with increased odds of inadequate glycemic control in the four categories of TG levels (< 0.001 for trend for all comparisons). For inadequate glycemic control of $HbA_{1c} \geq 6.5\%$, the results were similar to those of $HbA_{1c} \geq 7.0\%$ (Table 3). When all patients with TG levels ≥ 1.70 mmol/L were combined as one group, this group was associated with 35% (OR: 1.35; 95% CI: 1.26, 1.44) and 36% (OR: 1.36; 95% CI: 1.25, 1.48) increased odds of having $HbA_{1c} \geq 7.0\%$ and $HbA_{1c} \geq 6.5\%$, respectively, compared with the group

Table 1. Characteristics of Study Patients According to TG Level

Characteristic	Subclass of TG Level (mmol/L)				P
	<1.70 (n = 8853)	1.70–2.29 (n = 4392)	2.30–3.39 (n = 3367)	≥3.40 (n = 3496)	
Male sex, n (%)[a]	4631 (52.3)	2352 (53.6)	1833 (54.4)	1702 (48.7)	<0.001
Age, y	56.0 (11.3)	56.0 (11.1)	56.6 (10.7)	59.3 (13.1)	<0.001
BMI, kg/m^2	23.4 (2.7)	23.9 (2.7)	24.2 (2.8)	24.3 (2.6)	<0.001
SBP, mm Hg	126.2 (13.0)	129.1 (11.2)	130.7 (11.2)	130.9 (11.6)	<0.001
DBP, mm Hg	79.1 (8.8)	80.7 (8.4)	82.0 (8.9)	88.0 (10.4)	<0.001
Times of SMBG per wk, n (%)					<0.001
0	4777 (54.0)	2497 (56.8)	2026 (60.2)	2780 (79.5)	
1–2	2109 (23.8)	1070 (24.4)	756 (22.4)	413 (11.8)	
≥3	1967 (22.2)	825 (18.8)	585 (17.4)	303 (8.7)	
Diabetes education, n (%)	4814 (54.4)	2423 (55.2)	1667 (49.5)	1097 (31.4)	<0.001
Duration, y	5.5 (4.8)	5.1 (4.7)	5.0 (4.5)	5.0 (3.7)	<0.001
TC, mmol/L	4.3 (1.3)	4.6 (1.2)	5.2 (2.3)	5.6 (2.8)	<0.001
LDL-C, mmol/L	2.3 (0.8)	2.6 (0.8)	2.8 (0.9)	3.5 (1.6)	<0.001
HDL-C (<1 mmol/L), n (%)	3258 (36.8)	1976 (45.0)	1718 (51.0)	3059 (87.5)	<0.001
TG/HDL-C, n (%)					<0.001
<1.70	6632 (74.9)	1995 (45.4)	942 (28.0)	99 (2.8)	
1.70–2.29	631 (7.1)	717 (16.3)	497 (14.7)	87 (2.5)	
≥2.30	1590 (18.0)	1680 (38.3)	1928 (57.3)	3310 (94.7)	
FPG, mmol/L	7.4 (1.9)	7.6 (1.8)	8.0 (2.0)	8.1 (1.7)	<0.001
HbA_{1c}, %, n (%)					<0.001
<6.50	1845 (20.8)	746 (17.0)	509 (15.1)	231 (6.6)	
6.50–6.99	1719 (19.4)	860 (19.6)	469 (13.9)	217 (6.2)	
≥7.00	5289 (59.8)	2786 (63.4)	2389 (71.0)	3048 (87.2)	

Abbreviations: DBP, diastolic blood pressure; FPG, fasting plasma glucose; SBP, systolic blood pressure.

[a] *P* values for sex differences in TG levels are 0.485, 0.276, 0.857, and 0.016 among four groups with TG levels <1.70, 1.70–2.29, 2.30–3.39, and ≥3.40 mmol, respectively.

with TG level <1.70 mmol/L (Table 3). When all patients with TG levels ≥2.30 mmol/L were combined as one group, this group was associated with 77% (OR: 1.77; 95% CI: 1.64, 1.91) and 53% (OR: 1.53; 95% CI: 1.39, 1.69) increased odds of having HbA_{1c} ≥7.0% and HbA_{1c} ≥6.5%, respectively, compared with the group with TG level <2.30 mmol/L (Table 3).

Table 2. Homoscedasticity Test of Continuous Variables Among Four TG Groups

Characteristic	Bartlett Test		Levene Test	
	χ^2 Statistic	P	F Statistic	P
Age, y	183.6	<0.001	65.1	<0.001
BMI, kg/m^2	27.1	<0.001	10.9	<0.001
SBP, mm Hg	200.5	<0.001	74.8	<0.001
DBP, mm Hg	211.9	<0.001	49.2	<0.001
TC, mmol/L	4875.7	<0.001	86.1	<0.001
LDL-C, mmol/L	2914.3	<0.001	550.8	<0.001
HDL-C, mmol/L	5443.0	<0.001	128.9	<0.001
Duration, y	329.7	<0.001	31.7	<0.001
FPG, mmol/L	77.6	<0.001	17.8	<0.001
HbA_{1c}, %	313.7	<0.001	48.2	<0.001

Abbreviations: DBP, diastolic blood pressure; FPG, fasting plasmas glucose; SBP, systolic blood pressure.

Using multivariate logistic regression, we also analyzed other factors associated with inadequate glycemic control. We found that elevated blood pressure level, high TC level, and high LDL-C level were each positively associated with inadequate glycemic control, which is either HbA_{1c} ≥7.0% or HbA_{1c} ≥6.5%, whereas diabetes education and frequency of SMBG were negatively associated with inadequate glycemic control. Notably, elevated TG level is the strongest of these associated factors (Table 4). Furthermore, the independent association between TG/HDL-C ratio and glycemic control was also assessed. The adjusted ORs and 95% CIs for HbA_{lc} ≥7.0% comparing TG/HDL-C ratios in the range of 1.70 to 2.29, 2.30 to 3.39, and ≥3.40 with the lowest group were 1.45 (1.31, 1.62), 1.43 (1.27, 1.61), and 1.66 (1.54, 1.80), respectively (Table 5). Our analysis also showed a similar positive association between TG/HDL-C ratios and HbA_{lc} ≥6.5% (Table 5).

To examine the consistency of the association between elevated TG levels and inadequate glycemic control, we performed subgroup analyses among the different subpopulations defined by the multiple characteristics of these patients. The positive association of TG levels and inadequate glycemic control were generally similar across

Table 3. ORs (95% CI) for Inadequate HbA_{1c} Control by TG Groups Among 20,108 Patients With Type 2 Diabetes Mellitus Treated With Insulin

	Subclass of TG Level (mmol/L)			Combined Category (mmol/L)
Model	**<1.70**	**1.70–2.29**	**2.30**	

these subgroups stratified by sex, age, BMI, blood pressure, and duration of diabetes (Figs. 1 and 2). Nonlinear positive association between elevated TG level and inadequate glycemic control was observed by performing a restricted cubic spline logistic regression. Restricted cubic spline curves showed a J-shaped association between continuous TG level and inadequate HbA_{1c} control (Fig. 3). ORs and 95% CIs were calculated for continuous TG levels with respect to the reference value of 1.70 mmol/L after simultaneous adjustment for all potential confounding factors (Fig. 3). Based on the TG-outcome association trajectory, we found significant nonlinear dose-response relationships between glycemic control outcomes and change in continuous TG levels (all values <0.001 for linearity of TG level in the logistic regression analysis). The odds of HbA_{1c} $\geq 7.0\%$ and

Table 5. Multivariate Logistic Regression Analysis of Inadequate Glycemic Controls With Ratios of TG/HDL and Other Variables

	HbA_{1c} ≥7.0%		HbA_{1c} ≥6.5%	
Characteristic	**OR**	**95% CI**	**OR**	**95% CI**
Sex (ref. female)	0.86	0.81–0.92	0.84	0.78–0.91
Age, y (ref. <50)				
50–59	1.00	0.92–1.08	1.02	0.92–1.12
		–1.08	1.02	0.921

HbA_{1c} ≥6.5% were significantly higher in those with higher TG levels compared with reference levels of 1.70 mmol/L and 2.30 mmol/L, respectively.

Discussion

Inadequate glycemic control remains a major problem despite the many diabetes treatments. HbA_{1c} is the recommended indicator of glycemic control in patients with type 2 diabetes mellitus (33). The criteria for optimal glycemic control in these patients is HbA_{1c} <7.0%, whereas for patients without complication, the criteria is stricter at HbA_{1c} <6.5% (33, 34). In this large population-based multicenter study, we found that 67.2% and 83.4% of patients without diabetic complications who were treated with a sufficient dose of insulin did not reach the HbA_{1c} <7.0% and HbA_{1c} <6.5% targets, respectively. We showed in this patient population that elevated TG levels were strongly associated with inadequate glycemic control, defined by the criteria of HbA_{1c} ≥7.0% and HbA_{1c} ≥6.5%. This association was further confirmed by consistency in subgroup analyses across subgroups categorized by sex, age, BMI, blood pressure, and duration of diabetes. Notably, the strength of the association between TG level and glycemic control was the strongest among all factors associated with inadequate glycemic control. To the best of our knowledge, this is the only large population–based study that has examined the association between elevated TG levels and inadequate glycemic control in patients with type 2 diabetes mellitus who were receiving sufficient insulin treatment.

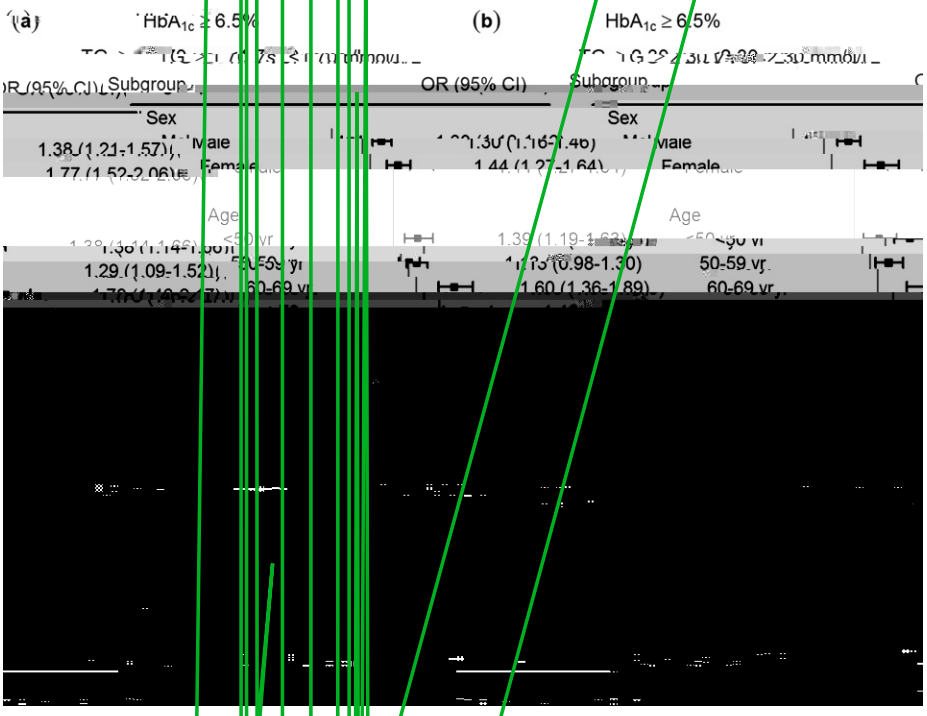

Figure 2. Subgroup analysis of the association between TG level and inadequate glycemic control, HbA_{1c} ≥6.5%. Horizontal lines represent 95% CIs. ORs and 95% CIs are for comparisons of a combined group of hypertriglyceridemia (TG levels ≥1.70 mmol/L or ≥2.30 mmol/L) with patients with normal TG levels (<1.70 mmol/L or <2.30 mmol/L). The multivariable model was adjusted for sex, age, BMI, blood pressure, TC, LDL-C, HDL-C, duration of diabetes, diabetes education, and frequency of SMBG. (a) TG levels ≥1.70 mmol/L vs <1.70 mmol/L. (b) TG levels ≥2.30 mmol/L vs <2.30 mmol/L.

Several studies have examined the determinants for inadequate glycemic control in patients with type 2 diabetes mellitus and demonstrated a positive association between long disease duration and complications with inadequate glycemic control (*i.e.*, HbA_{1c} ≥7.0%) (11–13). However, only one study has examined whether elevated TG levels were associated with inadequate glycemic control in patients with type 2 diabetes mellitus. Findings from this study showed only that elevated TG levels were associated with increased odds of inadequate glycemic control, defined as HbA_{1c} ≥6.5% in Chinese patients with diabetes treated with OADs (35). That study was relatively small, including only 455 patients with type 2 diabetes mellitus treated with OADs, and did not consider the possible confounding role of diabetic complications and their related treatment, which could

have contributed to glycemic control; thus, that study may have biased the strength of the association between TG levels and glycemic control (35).

We attempted to reduce these deficiencies of the previous study, as our study subjects were from a well-defined patient population treated with sufficient insulin and without other NCDs. In this population, less than half of patients attained the glycemic target, which enabled us to identify the determinant factors for inadequate glycemic control and assess whether elevated TG levels were associated with risk of inadequate glycemic control. In this study, hypertriglyceridemia was stratified into three groups of borderline elevation (1.70 to 2.29 mmol/L), elevation (2.30 to 3.39 mmol/L), and high elevation (≥3.40 mmol/L) levels, which showed respective increases of 35% (95% CI: 25%, 48%) and 212% (95% CI: 176%, 253%) in the odds of having HbA_{1c} ≥7.0% for the elevated and high elevation levels of TG; all three levels of hypertriglyceridemia were associated with the lower HbA_{1c} ≥6.5%. When all groups (≥1.70 mmol/L or ≥2.30 mmol/L) with hypertriglyceridemia were combined, this group was associated with 35% (77%) and 36% (53%) increased risks of HbA_{1c} ≥7.0% and ≥6.5%, respectively, compared with TG levels <1.70 mmol/L (or <2.30 mmol/L). This positive association was confirmed by its consistency in the different subgroups, including patients with different sex, age, BMI, blood pressure level, and duration of diabetes (Figs. 1 and 2). These results indicated that the association of TG with glycemic metabolism in insulin-treated patients with type 2 diabetes mellitus was similar to that in nondiabetic patients with developing type 2 diabetes mellitus (15–21), impaired fasting glucose level (15, 22), and impaired glucose tolerance (21).

In addition, we found that high TG levels had the strongest association with inadequate glycemic control among those factors (Table 4). This led us to conclude that elevated TG levels were strongly and positively associated with inadequate glycemic control in patients with type 2 diabetes mellitus treated with sufficient doses of insulin. Because TG is usually concomitantly increased with the glucose level in individuals with obesity, we tried to reduce the confounding interference of obesity on the association by adjustment of BMI, which only slightly affected the association (OR: 1.81; 95% CI: 1.71, 1.92 and OR: 1.82; 95% CI: 1.72, 1.94 before and after adjustment of BMI for HbA_{1c} ≥7.0%, respectively) (Table 3). In fact, we found that elevated TG levels were also significantly associated with inadequate glycemic control even in patients with diabetes and normal BMI (OR: 1.67; 95% CI: 1.49, 1.87 for HbA_{1c} ≥7.0%) [Fig. 1(b)]. We also demonstrated that the association is specific, as evidenced by the dose-response relationship between elevated TG levels and inadequate glycemic control and the much weaker association of inadequate glycemic control with total cholesterol (OR: 1.15; 95% CI: 1.06, 1.26 for HbA_{1c} ≥7.0%) (Table 4). These results all indicate that the association is not simply a con-

bias that an insufficient dose of insulin was a confounding cause of inadequate glycemic control (which would influence the strength of the association with elevated TG levels). Excluding patients with diabetic complications further reduced bias from the influence of these complications and their treatments (*i.e.*, lipid-lowering drugs) on metabolism. Furthermore, this study benefited from detailed information in the clinical medical records of each research center, allowing us to adjust for potential confounding factors. Lastly, it is noteworthy that the results are largely robust because of the

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