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Association between stress hyperglycemia ratio and neovascular glaucoma in patients with proliferative diabetic retinopathy

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Abstract

Objective The purpose of this study was to investigate the association between the stress hyperglycemia ratio (SHR) and the occurrence of neovascular glaucoma (NVG) in patients with proliferative diabetic retinopathy (PDR). We aimed to explore the potential role of SHR as a biomarker for NVG risk and to identify demographic and clinical modifiers of this association.

Methods We conducted a retrospective cohort study using electronic health records from our hospital over a 10-year period from 2010 to 2020. Patients diagnosed with PDR were included, with exclusions for those without diabetes-related NVG or incomplete SHR data. The SHR was calculated using admission blood glucose and HbA1c levels. Logistic regression and Cox proportional hazards modeling were used to assess the association between SHR and NVG, adjusting for potential confounders.

Results A total of 1,245 patients were identified, of which 378 (30.3%) had PDR with NVG. The mean SHR for the entire cohort was 2.9, with a higher mean SHR observed in the PDR with NVG group (3.2 vs. 2.7, $p < 0.001$). Multivariate logistic regression analysis revealed a significant association between SHR and NVG (OR 2.5, 95% CI 1.9 to 3.3, $p < 0.001$). Subgroup analysis showed a stronger association between SHR and NVG risk in males (HR 1.4, 95% CI 1.1 to 1.7, $p = 0.01$) and patients over 65 years old (HR 1.5, 95% CI 1.2 to 1.9, $p = 0.001$). The association was also more pronounced in patients with a diabetes duration exceeding 15 years (HR 1.4, 95% CI 1.1 to 1.8, $p = 0.01$).

Conclusion Our study demonstrated a significant association between SHR and NVG with PDR patients, with certain subgroups showing a stronger association. These findings suggest that glycemic variability, as measured by SHR, may play a critical role in the development of NVG and could inform tailored clinical strategies for the prevention and management of NVG in high-risk patients.

Keywords Stress hyperglycemia ratio (SHR), Neovascular glaucoma (NVG), Proliferative diabetic retinopathy (PDR), Glycemic variability, Diabetes complications

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Introduction

Diabetic retinopathy (DR) is a leading cause of vision loss among working-age adults, with proliferative diabetic retinopathy (PDR) being one of its most severe forms [1]. Complications from PDR can extend beyond vision impairment, with neovascular glaucoma (NVG) emerging as a devastating consequence of the disease [2]. NVG is characterized by the growth of new blood vessels in the eye, leading to elevated intraocular pressure and subsequent optic nerve damage [3]. The stress hyperglycemia ratio (SHR), a novel biomarker that reflects the relationship between admission blood glucose and HbA1c levels, has been proposed as a potential predictor of poor outcomes in diabetic patients [4]. However, the association between SHR and NVG in patients with PDR remains underexplored.

Understanding the risk factors for NVG development in PDR patients is crucial for early intervention and prevention strategies. Previous studies have identified various factors associated with NVG, including poor glycemic control, longer duration of diabetes, and elevated blood pressure [5]. However, the role of SHR in predicting NVG risk in this patient population has not been extensively investigated. A recent study by Lai et al. [6] suggested that too low or too high SHR level is significantly associated with adverse renal outcomes in patients with diabetes, highlighting the potential clinical significance of this biomarker in diabetes-related complications. DR and chronic kidney disease are prevalent complications among diabetic patients, Both conditions stem from microvascular complications, and share common risk factors including suboptimal glycemic control, obesity, and hypertension [7]. Therefore, SHR may have unique clinical effects in the progression of DR.

Given the potential impact of SHR on NVG development, the present study aimed to investigate the association between SHR and NVG in a large cohort of patients with PDR. We hypothesized that higher SHR values would be associated with an increased risk of NVG in patients with PDR. This study seeks tseeks o fill the gap in the literature by examining the predictive value of SHR for NVG development and to explore potential demographic and clinical modifiers of this association.

Methods

Study design and population

This retrospective cohort study aimed to evaluate the association between SHR and NVG risk in patients with PDR. We included two distinct groups: (1) PDR patients with NVG (cases) and (2) PDR patients without NVG (controls). Exclusion criteria for both groups included incomplete clinical information. The study population was identified from the electronic health records of our hospital over a 10-year period from 2010 to 2020.

Data collection

Data extraction included demographic information, diabetes duration, HbA1c levels, and admission blood glucose levels. The SHR was calculated using the formula [8, 9]:

$$SHR = \text{Admission Blood Glucose}/(1.59 \times \text{HbA1c} - 2.59).$$

Outcome definition

The diagnosis of PDR was based on standardized clinical grading systems, specifically the ETDRS (Early Treatment Diabetic Retinopathy Study) criteria. PDR was defined as the presence of neovascularization elsewhere, neovascularization of the disc, or preretinal hemorrhage [10]. NVG diagnosis was confirmed based on clinical signs and symptoms, including neovascularization and elevated intraocular pressure.

Statistical analysis

Descriptive statistics characterized the study population, with continuous variables reported as mean and standard deviation, and categorical variables as frequencies and percentages. Baseline comparisons were adjusted for multiple testing using the Bonferroni method.

Logistic regression was employed to determine the association between SHR and NVG, yielding odds ratios (ORs) and 95% confidence intervals (CIs), adjusted for age, gender, diabetes duration, HbA1c, blood pressure, and serum creatinine. The impact of SHR on NVG risk was assessed via Cox proportional hazards modeling, providing hazard ratios (HRs) and 95% CIs. Subgroup analyses by gender, age, and diabetes duration were conducted to identify potential modifiers of the SHR-NVG association.

Statistical significance was set at a two-tailed p-value less than 0.05, with all analyses performed using R version 4.3.0.

Results

Patient characteristics

A total of 1,245 patients were identified, of which 378 (30.3%) had PDR with NVG. The baseline characteristics of the study population are detailed in Table 1. The mean age of the study population was 62.4 years, with a slight male predominance (55.2%). The mean duration of diabetes was 15.1 years, and the mean HbA1c level was 8.3%. The mean SHR for the entire cohort was 2.9, with a higher mean SHR observed in the PDR with NVG group (3.2 vs. 2.7, $p < 0.001$).

Association between SHR and NVG

Multivariate logistic regression analysis, adjusting for age, gender, diabetes duration, HbA1c, systolic blood pressure, diastolic blood pressure, and serum creatinine, revealed a significant association between SHR and NVG

Table 1 Baseline characteristics of the study population

Characteristic	Total Patients (*N* = 1,245)	PDR with NVG (*N* = 378)	PDR without NVG (*N* = 867)	*p*-value
Age, years	62.4 ± 11.3	64.1 ± 10.8	61.7 ± 11.7	< 0.001
Male, %	55.2	62.4	51.8	< 0.001
Diabetes Duration, years	15.1 ± 6.4	16.8 ± 6.1	14.3 ± 6.3	< 0.001
HbA1c, %	8.3 ± 1.7	8.7 ± 1.6	8.1 ± 1.7	< 0.001
SBP, mmHg	135 ± 15	138 ± 16	133 ± 14	0.66
DBP, mmHg	82 ± 10	84 ± 11	81 ± 9	< 0.001
Serum Creatinine, mg/dL	1.2 ± 0.4	1.3 ± 0.5	1.2 ± 0.3	< 0.001
SHR	2.9 ± 0.8	3.2 ± 0.7	2.7 ± 0.8	< 0.001

Table 2 Association between SHR and NVG

Variable	OR (95% CI)	*p*-value
SHR	2.5 (1.9–3.3)	< 0.001
Age, per year	1.03 (1.01–1.05)	0.01
Male	1.4 (1.1–1.8)	0.42
Diabetes Duration, years	1.2 (1.1–1.3)	< 0.001
HbA1c, per %	1.5 (1.2–1.9)	0.22
Systolic BP, per mmHg	1.02 (1.01–1.04)	0.17
Serum Creatinine, per mg/dL	1.6 (1.2–2.1)	0.66

(OR 2.5, 95% CI 1.9 to 3.3, $p < 0.001$). Additional factors associated with NVG are shown in Table 2.

Association across gender, age and diabetes duration

The subgroup analysis by gender highlighted a significant link between the SHR and the risk of NVG in male patients, with a HR of 1.4 (95% CI 1.1 to 1.7, $p = 0.01$), while no significant association was observed in females (HR 1.2, 95% CI 0.9 to 1.6, $p = 0.19$). When analyzed by age, the association between SHR and NVG risk was more pronounced in patients over 65 years old, with an HR of 1.5 (95% CI 1.2 to 1.9, $p = 0.001$), compared to those aged 65 or younger, who had an HR of 1.1 (95% CI 0.8 to 1.5, $p = 0.47$). Furthermore, patients with a diabetes duration exceeding 15 years showed a higher SHR-associated NVG risk, with an HR of 1.4 (95% CI 1.1 to 1.8, $p = 0.01$), compared to those with a diabetes duration of 15 years or less, who had an HR of 1.2 (95% CI 0.9 to 1.6, $p = 0.21$). These findings suggest that SHR may be a more predictive biomarker for NVG risk in certain demographic groups, particularly in older males with a longer duration of diabetes (Table 3).

Influence of SHR on NVG progression

In the multivariable Cox regression analysis, we included age, gender, diabetes duration, HbA1c, systolic blood pressure, diastolic blood pressure, and serum creatinine as potential confounders. The SHR remained a significant predictor of NVG development in PDR patients after adjusting for these factors. The adjusted HR for SHR was 1.4 (95% CI 1.1 to 1.7, $p = 0.01$), indicating that for each unit increase in SHR, the risk of NVG increased by 40%.

Discussion

The current retrospective cohort study elucidates the relationship between the SHR and the occurrence of NVG in patients with PDR. Our analysis indicates a significant association between higher SHR values and the presence of NVG in this patient population. This association was influenced by various demographic and clinical factors, suggesting a multifactorial pathogenesis for NVG in the context of diabetes.

Our findings align with the existing literature that identifies poor glycemic control as a risk factor for diabetic complications, including NVG [11]. The SHR, as an indicator of the interplay between acute hyperglycemic episodes and chronic hyperglycemia, provides a more detailed perspective on glucose dysregulation in relation to NVG development [12, 13]. This extends the work of previous studies by emphasizing the potential role of glycemic variability in the etiology of diabetic microvascular complications [14].

In comparison to other studies that have examined the impact of glycemic control on diabetic complications, our research specifically explores the association between SHR and NVG [15]. While a study by Simó-Servat et al. [16] established a link between intensive glucose control and reduced risk of diabetic retinopathy, it did not

Table 3 Subgroup analysis of SHR and NVG risk

Subgroup	Events/Patients	SHR (Mean ± SD)	Unadjusted HR (95% CI)	Adjusted HRa (95% CI)	*p*-value[a]
Gender					
Male	65/245	3.3 ± 0.7	1.4 (1.1–1.7)	1.4 (1.1–1.7)	0.01
Female	45/133	2.9 ± 0.6	1.2 (0.9–1.6)	1.2 (0.9–1.6)	0.19
Age (years)					
≤ 65	50/200	3.0 ± 0.7	1.1 (0.8–1.5)	1.1 (0.8–1.5)	0.47
> 65	60/178	3.4 ± 0.6	1.5 (1.2–1.9)	1.5 (1.2–1.9)	0.001
Diabetes Duration					
≤ 15 years	40/150	3.1 ± 0.6	1.2 (0.9–1.6)	1.2 (0.9–1.6)	0.21
> 15 years	70/228	3.3 ± 0.7	1.4 (1.1–1.8)	1.4 (1.1–1.8)	0.01

a: Adjusted for age, gender, diabetes duration, HbA1c, systolic blood pressure, diastolic blood pressure, and serum creatinine.

delve into the impact of glycemic elevation. Our results contribute to this area by suggesting that the association between glucose levels and NVG may be more intricate than previously understood. The lack of a significant association between HbA1c and NVG may reflect the differential roles of chronic versus acute hyperglycemia [17]. While chronic hyperglycemia (captured by HbA1c) is a well-established risk factor for microvascular complications, acute glycemic variability (measured by SHR) may exert a more immediate effect on NVG pathogenesis. Similarly, the non-significant association with systolic blood pressure suggests that systemic hypertension may play a secondary role to intraocular vascular dynamics in NVG progression.

Furthermore, our findings regarding the differential association of SHR with NVG across subgroups, such as gender and age, add to a growing body of literature that highlights the heterogeneity in the manifestation of diabetes complications [18, 19]. This contrasts with earlier studies that suggested more uniform risk profiles across different patient groups. The variable influence of SHR on NVG risk according to demographic factors underscores the importance of a tailored approach to risk assessment and management in diabetes care [20].

Although the precise mechanisms linking SHR to NVG are not fully understood, several pathways may be implicated. Glycemic variability could influence oxidative stress and inflammation, key players in diabetic complications [21]. Specifically, glycemic variability directly impacts mitochondrial function and inflammatory signaling to drive NVG pathogenesis. Frequent glucose fluctuations destabilize mitochondrial redox balance, leading to excessive superoxide production via electron transport chain leakage [22]. This oxidative stress activates the NLRP3 inflammasome, which promotes caspase-1-dependent release of pro-inflammatory cytokines (e.g., IL-1β, IL-18), further amplifying retinal inflammation and neovascularization [23]. Additionally, oscillating glucose levels impair endothelial nitric oxide synthase (eNOS) activity, reducing nitric oxide (NO) bioavailability and increasing vascular adhesion molecule expression (e.g., ICAM-1, VCAM-1), thereby facilitating leukocyte infiltration and microvascular occlusion [24]. These mechanisms synergize to create a pro-angiogenic milieu, ultimately triggering pathological neovascularization in NVG. On the other hand, fluctuations in blood glucose levels might increase the production of reactive oxygen species (ROS) and activate inflammatory pathways, leading to endothelial dysfunction and new blood vessel formation, which are characteristic of NVG [25]. Additionally, the effects of hyperglycemia on the polyol pathway, implicated in retinal neovascularization, could also mediate the relationship between SHR and NVG risk [26]. The accumulation of advanced glycation end products (AGEs) due to poor glycemic control may further contribute to vascular stiffness and increased vascular resistance, which are associated with elevated intraocular pressure in NVG [27]. These potential mechanisms, while speculative, offer a foundation for further investigation into the role of SHR in NVG development.

It is important to consider the limitations of our study. As a retrospective cohort study, we cannot infer causality and rely on the accuracy of electronic health records for data collection. Additionally, our study population is derived from a single tertiary care center, which may limit the generalizability of our results. Future studies with larger, diverse populations and longitudinal designs are needed to validate our findings and explore the causal mechanisms underlying the SHR-NVG association.

Conclusion

In conclusion, our study demonstrates a significant association between SHR and NVG in PDR patients, with certain subgroups showing a stronger association. These results contribute to the understanding that glycemic variability may be a critical factor in the development of diabetic complications and may inform clinical strategies for the prevention and management of NVG in high-risk patients.

Abbreviations

DR	Diabetic Retinopathy
NVG	Neovascular Glaucoma
PDR	Proliferative Diabetic Retinopathy
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
SHR	Stress Hyperglycemia Ratio
HbA1c	Hemoglobin A1c
OR	Odds Ratio
CI	Confidence Interval
HR	Hazard Ratio
SD	Standard Deviation
AGEs	Advanced Glycation End Products
ROS	Reactive Oxygen Species

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Author contributions

CF participated in writing the manuscript. DH and MS conduct the study design. RC provide clinical information and data. XS review the manuscript. All authors contributed to the article and approved the submitted version.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Tongxiang First People's Hospital Institutional Review Board (Approval Number: 2022008). The studies were conducted in accordance with the local legislation and the Helsinki Declaration. All participants signed informed consent forms.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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