

Clinical Characteristics, Serum Uric Acid and Bullosis Diabeticorum Outcomes in Patients With Diabetes Mellitus

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Research

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Abstract

Background: Bullosis diabeticorum (BD) is a spontaneous, non-inflammatory vesicular disease of diabetes, with the observed risk of infection, including diabetic skin ulcers, osteomyelitis and even leading to amputation. However, the exact cause of BD is not well understood. So the aim of this study is to explore the high-risk factors of BD for preventing its occurrence.

Methods: A retrospective study was conducted, including baseline characteristics, laboratory data, and bullosis diabeticorum outcomes of 602 patients with bullosis diabeticorum. Besides, 904 diabetic patients without bullosis diabeticorum in the same period were randomly selected as the control group. The indicators of the two groups were compared. Multivariable logistic regression analysis was performed to investigate which indicator was most associated with bullosis diabeticorum outcomes.

Results: SCr[145.00(69.00-195.00) $\mu\text{mol/L}$, n = 602 vs. 81.00(27.40-35.60) $\mu\text{mol/L}$, n= 904, p=0.032], BUA [674.00(372.50-758.50) $\mu\text{mol/L}$, n = 602 vs. 318.50(241.75-415.25) $\mu\text{mol/L}$, n= 904, p = 0.003] and Cys-C[1.96(1.10-2.95) mg/L, n = 602 vs. 1.49(1.10-1.62) mg/L, n = 904, p=0.004] was significantly higher in BD-positive patients than that in BD-negative patients, whereas eGFR [67.38(45.33-87.53) ml/min, n = 602 vs. 75.86(56.80-95.69) ml/min, n = 904, p=0.038] of patients with BD was significantly lower than that of patients without BD. Multiple logistic regression analysis showed that BUA, but not SCr, Cys-C and eGFR, was independently and significantly associated in a positive manner with BD (odds ratio: 8.569, 95% confidence interval: 1.136-55.250, p=0.004).

Conclusion: We found a positive and independent association of BUA with BD, which provides a great clinical predictive factor for BD and helps to prevent the appearance of diabetic foot.

Background

Bullosis diabeticorum (BD) is a sort of rare skin disease, characterized by spontaneous non-inflammatory manifestation, which is mainly observed in patients with diabetes mellitus. It most often occurs in the lower extremities, in which there is an observed risk of developing secondary infections, including diabetic skin ulcers, osteomyelitis or wet gangrene, and even leading to amputation. However, the exact cause and related risk factors of BD is not well understood. Several studies revealed that its occurrence is closely related to diabetes with complications of microangiopathy, neuropathy, and poor regulation of blood glucose^[1, 2]. And some researchers also believe that long-term microvascular disease in patients with diabetes will cause tissue hypoxia and microcirculation ischemia to form blisters^[3, 4]. To our knowledge, there is no clinical practice guidance for this disease. In this retrospective observational study, to further analyze the risk factors of BD, we examined the association between clinical indicators and BD in patients with diabetes.

Materials And Methods

Study subjects

A retrospective observational study was conducted in 602 patients with bullosis diabeticorum and 904 patients without bullosis diabeticorum from 2017–2020 in Nanfang Hospital, Guangzhou. The diagnosis of BD depends on the patient's clinical manifestations and immunological examination. Clinical manifestations included: 1) the patients with diabetes had no history of dermatologic disorders and related medical treatment, recent trauma or acute edema. 2) Lesions appear rapidly, primarily in an acral distribution in areas of normal-appearing skin, and diameter ranges from a few centimeters to very large. Immunological examination included histological examination showed

that C3, IgM, IgA and IgG were negative by direct immunofluorescence (DIF) staining. Patients were included if BD was diagnosed. Patients were excluded if bullae due to burns or edema, friction bullae, bullous pemphigoid, bullous fixed drug reaction, epidermolysis bullosa acquisita, porphyria cutanea tarda and erythema multiforme were diagnosed. Furthermore, patients with stress due to wearing shoes or excessive use, or a clinical course of new bullae that regularly indicate other skin diseases are not included in the study. Each patient provided written informed consent before being enrolled in the study. The study received ethical approval from the ethics committee of Nanfang Hospital, Southern Medical University (NFEC-2017-013).

Laboratory test indicators and bullosis diabeticorum outcome

Blood indicators were determined using a full-automatic biochemical analyzer. Glycated hemoglobin (HbA1c) was measured via high-performance liquid chromatography (batch number: 64191330).

Statistical analysis

Data are expressed as mean \pm standard deviation, or median (25th-75th percentile).

The normality of variables was assessed. Differences in mean and median values were evaluated by using Student's t-test and the Mann–Whitney U test, respectively. Multiple logistic regression analysis was performed to examine the influence of all variables. The odds ratios with 95% CIs, were calculated.

Results

Clinical characteristics of patients with diabetes, and comparisons between patients with and without BD

Table 1 showed the characteristics of 904 patients with diabetes, among whom 602 (25.3%) were positive for BD. The serum level of BUA was 674.00(372.50-758.50) $\mu\text{mol/L}$ in patients with BD, which was significantly higher than the value of 318.50(241.75-415.25) $\mu\text{mol/L}$ in subjects without BD ($p = 0.003$). Various clinical parameters in patients with diabetes were compared between those with and without BD. BD-positive patients had significantly higher SCr[145.00(69.00-195.00) $\mu\text{mol/L}$, $n = 602$ vs. 81.00(27.40–35.60) $\mu\text{mol/L}$, $n = 302$, $p = 0.032$] and Cys-C[1.96(1.10–2.95) mg/L , $n = 602$ vs. 1.49(1.10–1.62) mg/L , $n = 302$, $p = 0.004$] than those BD-negative patients. Furthermore, BD-positive patients showed a significantly lower eGFR ($p = 0.038$) than BD-negative patients. As for eGFR, it was significantly lower in BD-positive patients than that of BD-negative patients [67.38(45.33–87.53) ml/min , $n = 602$ vs. 75.86(56.80-95.69) ml/min , $n = 302$, $p = 0.038$].

Serum BUA levels were significantly higher in patients with BD than in those without, whereas eGFR levels were significantly lower in patients with BD than in those without.

Table 1
Clinical and biochemical characteristics of the study patients

	Total	without DB	with DB	P-value
Patients (n[%])	1506	904(60.03%)	602(39.97%)	-
Gender (male/female)	945/561	524/380	421/181	0.056
Age (years)	63.83 ± 11.33	64.17 ± 11.34	62.83 ± 11.32	0.391
Duration of DM (years)	9.00(4.00–14.00)	10.00(56.80-95.69)	7.00(2.50–13.50)	0.082
SP (mmHg)	137.00(125.00-155.00)	136.00(125.00-153.00)	139.00(126.00-159.50)	0.455
DP (mmHg)	80.00(71.00–86.00)	79.00(70.00–86.00)	80.00(73.00–86.00)	0.164
RBG (mmol/L)	13.60(9.10–17.20)	13.85(9.18–17.33)	12.80(8.65–16.75)	0.269
HbA1c,% (mmol/mol)	8.8(7.30–10.80) [72.66(56.26–94.51)]	8.70(7.10–10.70) [71.56(54.08–93.42)]	9.10(7.60–11.00) [75.93(59.54–96.70)]	0.314
Hb (g/L)	113.00(99.00-124.00)	114.00(99.00-125.00)	113.00(94.00-124.00)	0.472
WBC (×10 ⁹)	8.98(7.09–12.07)	9.00(7.19–11.95)	8.93(6.59–12.36)	0.452
N (×10 ⁹ /L)	6.33(4.29–9.30)	6.43(4.41–9.26)	6.02(3.94–9.81)	0.513
PCT (mg/L)	0.109(0.050–0.372)	0.102(0.047–0.418)	0.169(0.056–0.372)	0.389
CRP (mg/L)	29.37(4.60-72.51)	10.20(5.02–72.51)	28.40(4.19–66.39)	0.382
K (mmol/L)	4.16(3.82–4.55)	1.09(3.80–4.54)	4.21(3.90–4.57)	0.204
Na (mmol/L)	139.00(136.00-141.20)	137.00(136.00-141.03)	140.00(136.00-141.65)	0.314
Ca (mmol/L)	2.17(2.09–2.27)	2.17(2.09–2.27)	2.19(2.09–2.26)	0.984
Mg (mmol/L)	0.82(0.76–0.87)	0.82(0.76–0.87)	0.81(0.77–0.88)	0.975
BUN (mmol/L)	5.90(4.50–8.07)	5.90(4.44–7.73)	6.50(4.90–9.10)	0.062
SCr (μmol/L)	104.00(65.00-159.00)	81.00(27.40–35.60)	145.00(69.00-195.00)	0.032
BUA (μmol/L)	427.00(241.00-559.00)	318.50(241.75-415.25)	674.00(372.50- 758.50)	0.003
Cys-C (mg/L)	1.63(1.10–2.42)	1.49(1.10–1.62)	1.96(1.10–2.95)	0.004

SP: Systolic pressure; DP: Diastolic pressure; RBG: random blood glucose; Hb: hemoglobin; WBC: white blood cell; N: neutrophil; PCT: procalcitonin; CRP: C-reactive protein; BUN: blood urea nitrogen; SCr: serum creatinine; BUA: blood uric acid; Cys-C: Cystatin C; eGFR: estimated glomerular filtration rate; ALB: albumin; DBIL: direct bilirubin; IBIL: indirect bilirubin; TG: Triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein. Values are expressed as mean ± standard deviation, number, or median (Q1–Q3).

SP: Systolic pressure; DP: Diastolic pressure; RBG: random blood glucose; Hb: hemoglobin; WBC: white blood cell; N: neutrophil; PCT: procalcitonin; CRP: C-reactive protein; BUN: blood urea nitrogen; SCr: serum creatinine; BUA: blood uric acid; Cys-C: Cystatin C; eGFR: estimated glomerular filtration rate; ALB: albumin; DBIL: direct bilirubin; IBIL: indirect bilirubin; TG: Triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein. Values are expressed as mean ± standard deviation, number, or median (Q1–Q3).

	Total	without DB	with DB	P-value
eGFR (ml/min)	73.99(53.78-95.00)	75.86(56.80-95.69)	67.38(45.33–87.53)	0.038
ALB (g/L)	32.90(28.10–36.40)	32.90(28.00-36.93)	32.30(28.55–35.25)	0.276
DBIL (μmol/L)	2.70(1.90-4.00)	2.85(2.00-4.10)	2.40(1.55–3.75)	0.010
IBIL (μmol/L)	3.70(2.30–5.50)	3.70(2.50–5.50)	3.70(2.05–5.70)	0.435
TG (mmol/L)	1.22(0.87–1.71)	1.24(0.88–1.74)	1.21(0.84–1.67)	0.863
TC (mmol/L)	4.20(3.46–4.89)	4.23(3.46–4.87)	4.20(3.44–5.07)	0.775
HDL (mmol/L)	0.90(0.73–1.06)	0.91(0.73–1.05)	0.90(0.70–1.07)	0.947
LDL (mmol/L)	2.65(2.07–3.15)	2.69(2.07–3.18)	2.53(2.06–3.08)	0.229
VLDL (mmol/L)	0.65(0.41–0.84)	0.64(0.41–0.81)	0.67(0.43–0.91)	0.279
<p>SP: Systolic pressure; DP: Diastolic pressure; RBG: random blood glucose; Hb: hemoglobin; WBC: white blood cell; N: neutrophil; PCT: procalcitonin; CRP: C-reactive protein; BUN: blood urea nitrogen; SCr: serum creatinine; BUA: blood uric acid; Cys-C: Cystatin C; eGFR: estimated glomerular filtration rate; ALB: albumin; DBIL: direct bilirubin; IBIL: indirect bilirubin; TG: Triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein. Values are expressed as mean ± standard deviation, number, or median (Q1–Q3).</p>				
<p>SP: Systolic pressure; DP: Diastolic pressure; RBG: random blood glucose; Hb: hemoglobin; WBC: white blood cell; N: neutrophil; PCT: procalcitonin; CRP: C-reactive protein; BUN: blood urea nitrogen; SCr: serum creatinine; BUA: blood uric acid; Cys-C: Cystatin C; eGFR: estimated glomerular filtration rate; ALB: albumin; DBIL: direct bilirubin; IBIL: indirect bilirubin; TG: Triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein. Values are expressed as mean ± standard deviation, number, or median (Q1–Q3).</p>				

Multiple logistic regression analysis of factors associated with BD

Multiple logistic regression analysis was employed to examine whether BUA and eGFR were independently and significantly associated with the presence of BD. Model 1, which excluded eGFR, showed that duration of DM, N and BUA emerged as a significant and independent factor associated with the presence of BD (odds ratio: 8.569, 95% confidence interval [CI]: 1.136–55.250, $p = 0.004$). Model 2, in which eGFR was replaced with BUA, demonstrated that eGFR was not significantly associated with the presence of BD (odds ratio: 0.994, 95% CI: 0.981–1.007, $p = 0.387$). Furthermore, even when eGFR and BUA levels were simultaneously included as independent variables in model 3, the addition of eGFR did not affect the significant association of BUA, as well as the duration of DM (odds ratio: 15.224, 95% CI: 1.658–80.215, $p = 0.006$) (Table 2).

Table 2
Multiple logistic regression analysis of factors associated with BD

	Model1			Model2			Model3		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Gender(male/female)	1.456	0.788–2.691	0.230	1.755	0.965–3.191	0.065	1.46	0.790–2.700	0.228
Age(years)	1.004	0.978–1.031	0.758	1.002	0.975–1.030	0.886	1.003	0.976–1.032	0.815
Duration of DM(years)	0.956	0.918–0.995	0.029	0.958	0.921–0.997	0.034	0.956	0.918–0.995	0.029
SP(mmHg)	1.008	0.993–1.022	0.298	1.008	0.994–1.023	0.248	1.008	0.993–1.022	0.305
DP(mmHg)	0.992	0.967–1.018	0.561	0.995	0.970–1.021	0.724	0.992	0.966–1.018	0.547
RBG(mmol/L)	0.973	0.932–1.016	0.215	0.968	0.927–1.010	0.133	0.973	0.932–1.016	0.222
HbA1c,(mmol/mol)	0.997	0.983–1.010	0.620	0.997	0.984–1.010	0.646	0.997	0.984–1.010	0.619
Hb (g/L)	0.993	0.977–1.009	0.391	0.994	0.977–1.010	0.444	0.993	0.977–1.010	0.434
WBC($\times 10^9$)	0.828	0.570–1.204	0.323	0.902	0.628–1.295	0.577	0.829	0.570–1.203	0.323
N($\times 10^9$ /L)	1.230	0.826–1.831	0.09	1.21	0.762–1.649	0.562	1.230	0.826–1.831	0.308
PCT(mg/L)	0.979	0.803–1.195	0.838	0.984	0.809–1.196	0.868	0.978	0.801–1.195	0.830
CRP (mg/L)	0.999	0.995–1.004	0.756	0.999	0.995–1.004	0.817	0.999	0.995–1.004	0.747
K(mmol/L)	0.988	0.609–1.603	0.961	1.056	0.647–1.724	0.827	0.982	0.603–1.597	0.941
Na(mmol/L)	1.004	0.939–1.073	0.908	1.022	0.956–1.092	0.521	1.004	0.939–1.073	0.910
Ca(mmol/L)	8.200	0.533–126.09	0.131	9.454	0.629–142.114	0.104	8.038	0.521–124.012	0.135
Mg(mmol/L)	1.686	0.146–19.48	0.676	1.575	0.140–17.665	0.712	1.738	0.148–20.333	0.660
BUN(mmol/L)	0.914	0.827–1.010	0.079	0.956	0.868–1.051	0.351	0.912	0.823–1.010	0.078
SCr(μ mol/L)	1.002	0.998–1.006	0.351	1.001	0.997–1.005	0.568	1.002	0.998–1.006	0.379

OR: odds ratio, 95% CI: 95% confidence intervals.

	Model1			Model2			Model3		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
BUA(umol/L)	8.569	1.136–55.250	0.004				15.224	1.658–80.215	0.006
Cys-C(mg/L)	1.215	0.820–1.800	0.332	1.144	0.766–1.707	0.511	1.209	0.816–1.792	0.345
eGFR(ml/min)				0.994	0.981–1.007	0.387	0.998	0.985–1.012	0.824
ALB(g/L)	0.946	0.880–1.017	0.131	0.949	0.884–1.018	0.146	0.946	0.881–1.017	0.133
DBIL(mg/dl)	0.872	0.740–1.029	0.105	0.869	0.738–1.025	0.095	0.872	0.739–1.028	0.103
IBIL(mg/dl)	1.048	0.925–1.186	0.463	1.054	0.932–1.191	0.406	1.047	0.925–1.186	0.464
TG(mmol/L)	0.779	0.525–1.156	0.215	0.815	0.552–1.204	0.304	0.778	0.524–1.155	0.214
TC(mmol/L)	0.670	0.247–1.819	0.432	0.602	0.222–1.637	0.320	0.674	0.248–1.832	0.439
HDL(mmol/L)	1.634	0.512–5.220	0.407	1.602	0.501–5.119	0.427	1.623	0.507–5.198	0.415
LDL(mmol/L)	1.125	0.385–3.285	0.830	1.252	0.428–3.660	0.681	1.115	0.380–3.269	0.842
VLDL(mmol/L)	3.286	0.731–14.86	0.121	3.833	0.861–17.071	0.078	3.266	0.725–14.715	0.123

OR: odds ratio, 95% CI: 95% confidence intervals.

Discussion

Bullosis diabeticorum(BD) is a cutaneous complication in patients with diabetes mellitus, which even could precede the diagnosis of diabetes mellitus and be suggested to be probable cutaneous markers for early detection of overt diabetes or prediabetes. The first case of bullosis diabeticorum was reported by Kramer in 1930. Cantwell and Martz further first coined the term “Bullosis Diabeticorum” in 1967, and this remains the common nomenclature today^[3, 5]. BD is characterized by spontaneously formed bullae, without pain, trauma or any signs of inflammation. The blisters of BD often suddenly appear overnight, sometimes within 1 hour without any obvious cause, no recent trauma, and rarely cause slight discomfort. Sometimes the blisters are large, with irregular borders and looseness, very similar to burn lesions. And the bulla are full of serum and rarely bleed^[6, 7]. Typical blisters are superficial and contain transparent sterile liquids^[8]. Blisters usually heal within 2–6 weeks, without scarring. And three-year follow-up survey of 25 patients with BD showed that the median healing time was 2.5 months^[6]. But there is a high chance of recurrence in the same or different body parts. Although bullous lesions are usually cured without scarring, they often turn into ulcers^[3]. BD of the feet may turn into severe chronic ulcers, accompanied by skin necrosis and infection. It is reported that skin manifestations are associated with a significant incidence of diabetic foot ulcers^[9, 10]. The

association between osteomyelitis and BD also has been reported, leading to a high rate of amputation [11, 12]. Special attention should be paid to the prevention of high-risk patients.

BD is often described in adults from 34 to 91 years of age, mostly in males (male to female ratio: 2 to 1), with acute onset and bullous formation, which is similar to our findings. In our research, BD shows a higher frequency in males, also with a male-to-female ratio of 2:1. Studies have estimated that the prevalence among patients with diabetes is between 0.16% and 2%^[6]. One of the reasons for the underestimated situation is that patients with BD lack the awareness of seeking medical attention and healing automatically. Some researchers suspect that this situation is more common than people generally believed^[11]. In our clinical experience and observation, BD is not uncommon, especially in patients with diabetic foot (DF). The exact incidence of BD has not yet been calculated. Among the 1506 patients with diabetes included in this study, 602 had BD. Thus, there was a BD incidence rate of 39.97% in patients with diabetes. Many cases of BD are described as patients with diabetes exposed to ultraviolet light without any trauma, or diabetic patients with kidney disease, microangiopathy and long-term uncontrolled diabetes^[11]. And BD can occur in patients with pre-diabetes, even in patients with good glycemic control (type 1 or type 2 diabetes)^[13, 14]. Some researchs have noticed that their patients have neuropathy, but this is not universal^[6, 15].

Calcium and magnesium imbalances, adverse reactions of modern diabetes drugs or immune vasculitis are also considered important factors^[6-8]^[16, 17]. There is no literature describing the correlation between the occurrence of BD and the clinical indicators of diabetic patients. And no formal diagnosis and treatment guidelines exist now. Understanding the risk factors for BD can help clinicians take prompt action and take preventive measures in a timely manner, and prevents the formation of chronic ulcers. In this observational study, we examined the association between clinical parameters and BD. The present observational study demonstrated that higher BUA but not eGFR, was significantly and positively associated with the prevalence of BD in patients with diabetes, suggesting higher BUA as a definite risk for BD, independent of other risk factors for BD, such as age, HbA1c, SCr, Cys-C, eGFR, etc. Eunsung Kim and his colleagues found that elevated SUA levels are independently associated with the presence of ulcers, thereby suggesting the potential role of hyperuricemia in the pathogenesis of vasculopathy^[18]. Another research indicates SUA as a marker of microvascular damage^[19]. Therefore, elevated SUA may lead to the occurrence of DB by affecting microvascular lesions, but further research is needed to confirm that. Glucose control does not seem to be directly related to the formation of bullae. Bernstein and his colleagues concluded that cation imbalance caused by renal failure may be a possible cause of BD^[8]. But these were not be found in our research. Vesicular fluid usually contains protein and may contain eosinophils or a small number of polymorphonuclear cells^[17, 20]. M. Derighetti reported that histopathological examination of BD showed microvascular disease with degeneration of the vessel wall^[21].

It is thought BD is related to insufficient blood vessel supply and increased vascular pressure, resulting in the epidermal-dermal junction dividing at the level of the hyaluronic membrane. Some authors speculate that its etiology may be related to local connective tissue changes in the subbasement membrane area. Some patients have a skin separation level within the epidermis, while others have a skin separation level below the epidermis^[15]. Histological examination showed that C₃, IgM, IgA and IgG were negative by direct immunofluorescence (DIF) staining^[17]. This is different from hemorrhagic bullae, which show atrophy and scarring after healing; these manifest as the destruction of the cleavage surface and anchored fibrils below the junction of the dermal epidermis. Histopathological examination of BD showed inconsistent degrees of skin separation. In most published cases, there is cleavage in the epidermis without lysis of spinous cells^[22]. Some studies on BD have reported mild or thickened skin papillary blood vessels and focal deposition of capillary walls. Electron microscopy showed that the cell membrane and the

basement membrane were separated, and before that, fixed filaments and hemi-desmosomes were lost. One study found no evidence that complement or immunoglobulin deposition, direct immunofluorescence and surrounding skin is normal^[23]. We recommend that extensive BD should be considered a limb-threatening condition. These patients require timely admission, the involvement of diabetes and foot care teams ^[24].

Recognition depends on the clinician's familiarity with this situation. There is no firm consensus on how to deal with these lesions^[25]. It is recommended to treat non-infectious bullae with suction blisters to prevent spontaneous rupture, and use blistering skin as the wound cover^[26]. If the bullous fluid has appeared cloudy, it may indicate that an infection has occurred, and it needs to be treated according to the DF treatment process. BD of feet require standard assessment and standard wound care procedures. The clinical manifestations of the lesions in these patients are similar to those reported previously. Our research reminds clinicians that BD is a skin disease that is not so rare and has a direct correlation with BUA. Our medical center saw more cases in a relatively short period of time. Little is known about the causes of BD. We observed that almost all of these blisters occurred on the skin parts without calluses, which indicates that these parts are not affected by high pressure. This typical skin disease is much more common than we know now. Any damage to the skin of the feet of diabetic patients may be the first step in amputation. Therefore, it is important to recognize this disease to ensure that appropriate treatment is provided to help avoid ulcers and infections ^[27-29]. Although there are some reports about BD, whether it is from the perspective of etiology or pathology, it is still poorly understood.

Conclusion

High BUA is associated with BD in patients with diabetes. This association remains significant even after adjustment for other clinical indicators. The present study indicated that BUA is an independent factor that is positively associated with the prevalence of BD in patients with diabetes.

Declarations

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Authors' contributions

All the authors contributed significantly to the manuscript. Yulan Cai was primarily responsible for the data analysis and writing of the manuscript. Shili Zhang significantly revised the draft, interpreted the data, and involved in data analyses.

Ying Cao and Fang Gao collected the information and participated in data interpretation. Mengchen Zou was responsible for designing the study and critically revising the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data is available upon reasonable request to the corresponding author.

Ethics approval and consent to participate

This study protocol was approved by the Ethics Committee of Nanfang Hospital, Southern Medical University (Permit Number: NFEC-2017-013). Written informed consent was obtained from all participants. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration.

Competing interests

The authors declare that they have no competing interests

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