European Review for Medical and Pharmacological Sciences 2022; 26: 5353-5361

# Risk factors and psychological condition of pruritus in type 2 diabetes mellitus: a retrospective, propensity score-matched study

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**Abstract. – OBJECTIVE: Our aim is to characterize patients with pruritus in type 2 diabetes, determine independent risk factors and explore the impact of the psychological condition of these patients.**

**MATERIALS AND METHODS: This is a retrospective study. From October 1, 2020, to September 30, 2021, 944 individuals with T2DM who had medical treatment were identified from the database. Electronic medical record information including patient characteristics, complications, laboratory data, and medication usage was obtained from the database. Propensity score matching, univariate analysis and a multivariable logistic regression model were used in this study. Based on observation, we discussed the psychological impact of pruritus on these patients.**

**RESULTS: There were 97 patients with T2DM who suffered from pruritus. After propensity score matching based on age, gender, and family history of diabetes etc., 97 pairs of subjects were matched. 97 patients were categorized as the Pruritus group and 97 patients as the Non-pruritus group. In univariate analysis, there were 5 variables significantly related to pruritus, including BMI, absolute eosinophils, percentage of eosinophils, diabetic kidney disease, diabetic retinopathy. After multivariable logistic regression, BMI (OR 1.094, 95%CI 1.010-1.185) and diabetic retinopathy (OR 2.440, 95%CI 1.229-4.847) were considered significant. Patients with pruritus in T2DM suffer greatly in psychological condition in many ways.**

**CONCLUSIONS: For patients with pruritus complicated by T2DM, BMI and diabetic retinopathy may be independent risk factors. Mental health problems such as anxiety and depression might exacerbate by pruritus. The intimate partner relationship was also challenged due to the restless sleep caused by their partner. Frequent monitoring of BMI and diabetic retinopathy and psychological assessment may be warranted in these patients.**

*Key Words:*
Type 2 diabetes, Pruritus, Risk factors, Psychological condition, Retrospective, Propensity score matched study, BMI, Diabetic retinopathy.

## Introduction

Diabetes Mellitus is a global epidemic. The International Diabetes Federation (IDF) estimates that about 537 million people had diabetes globally in 2021. China is the top epicenter of the global epidemic of diabetes mellitus. The total number of patients with diabetes in China is estimated to be 14.09 million according to the IDF Atlas 10th edition[1]. Pruritus, an unpleasant sensation that provokes the desire to scratch, is prevalent in patients with type 2 diabetes mellitus (T2DM). The prevalence of pruritus in patients with diabetes ranges from 15.6% to 60.2%[2]. Patients with pruritus suffer a lot, they do not only scratch repeatedly, but also pinch or damage their skin with devices, which will lead to severe complications, such as excoriations, ulcerations, severe infection, necrosis, crusts, nodules, atrophy and scars, as well as hyper- and hypo-pigmentation of the skin[3,4]. In addition, pruritus affects quality of life significantly. The intensity of pruritus has been found to be associated with sleep disturbance, fatigue, social isolation, deficits in attention, memory and cognitive speed; some patients have mental health problems, such as depression, in response to pruritus, and are at significantly higher risk of suicide[5-7]. Nevertheless, specific independent predictors of pruritus in type 2 diabetes have not yet been identified. Thus, getting a better understanding of the risk factors of pruritus in T2DM patients may raise awareness

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on prevention and management, and improve their quality of life. Propensity score matching (PSM) is a statistical procedure for reducing bias by assembling a sample in which confounding factors are balanced between treatment groups[8]. Therefore, the aim of this study is to determine independent risk factors for patients with pruritus in T2DM.

## Materials and Methods

### Study Designs and Population

This is a retrospective, propensity score-matched study. Patients with type 2 diabetes who had medical treatment at Shen Zhen Traditional Chinese Medicine Hospital between October 1, 2020, and September 30, 2021, were enrolled. Electronic medical records of patients were collected from the hospital's clinical database (iMesical HIS 8.4). According to the diagnosis of pruritus, we classified the patients into the pruritus (Pru) group and the non-pruritus group (Non-pru). After PSM, the associations between multiple potential factors and the outcomes were explored in univariable logistic analyses, including laboratory data, complications, and medicine usage. Multivariable logistic regression models were used to analyze the impact of risk factors on pruritus, with the adjustment for other variables that were statistically significant in the univariable logistic analyses. The flowchart for objects of selection is shown in Figure 1.

### Inclusion Criteria

(1) aged≥18 years; (2) have been diagnosed with type 2 diabetes mellitus; (3) had medical treatment in hospital.

### Exclusion Criteria

(1) pruritus in kidney disease; (2) pruritus in hepatobiliary diseases (cholestatic pruritus); (3) pruritus in malignancy; (4) pruritus in infectious diseases; (5) pruritus in neurological diseases; (6) pruritus in psychiatric diseases; (7) drug-induced chronic pruritus.

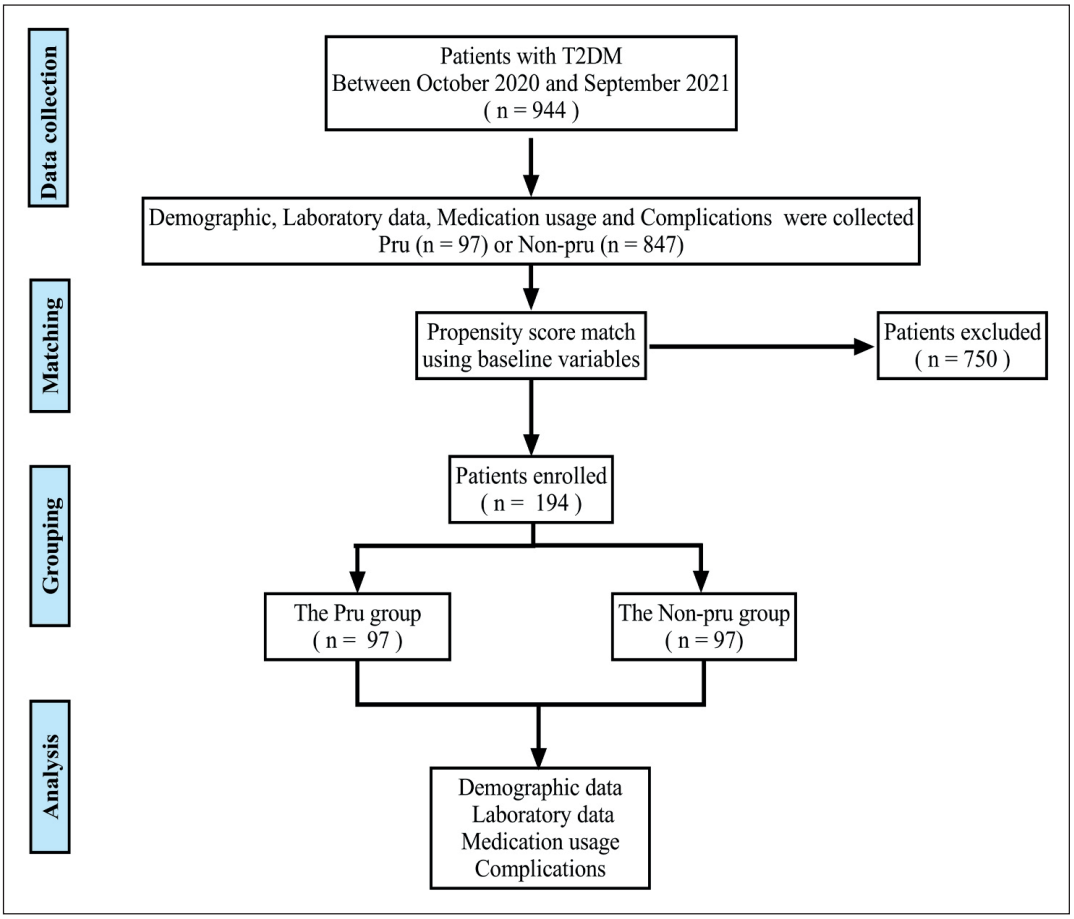


**Figure 1.** Flowchart for cohort selection. Pru: pruritus, Non-pru: Non-pruritus.

### Data Collection

Patients' data of demographic, laboratory, complications, and medication usage were collected from an electronic medical records database by researchers. All data were checked by two researchers and a third researcher adjudicated any difference in interpretation between the two primary reviewers. This study was approved by the Institutional Review Board of Shenzhen Traditional Chinese Medicine Hospital, and the requirement for informed consent was waived because non-identifiable data for patients' personal information were used. All clinical investigations were conducted in accordance with the Declaration of Helsinki.

### Statistical Analysis

To control the nonrandom assignment of patients, One-to-one matching was undertaken by the propensity score matching (PSM) method; a logistic regression model was constructed and used to estimate all patients' propensity scores. Variables used in the model included age, gender, heart rates, blood pressure, duration of T2DM, and family history of diabetes. The propensity score-matching tolerance was 0.2. No replacement was allowed. Matching was performed by the minimal adjacent method. We evaluated the balances of matched covariates with standardized differences and considered differences of less than 10% to be matched sufficiently.

All statistical analyses were performed with the SPSS 25.0 statistical packages (IBM, Armonk, NY, USA). Continuous data of missing were interpolated by mean imputation. Values are presented as the mean±standard (SD) deviation for data that were normally distributed or median and inter-quartile range for data that were not normally distributed for continuous variables and number (%) for categorical variables. The Kolmogorov-Smirnov test was used to inspect the normality and homogeneity of variance of all the data. For the two-group comparison, $p$-values were derived from the one-way Student's $t$-test to determine differences between groups with normally distributed data and Mann-Whitney non-parametric test with other data. For multi-group comparison, $p$-values were derived from one-way ANOVA (continuous variables) or Chi-square test (categorical variables). For all comparisons, $p<0.05$ was considered statistically significant. After PSM, Paired $t$-test was used for continuous data and the McNemar test was used for categorical data.

## Results

### Baseline Characteristics

In the end, we identified 944 individuals within electronic records from the clinical database. There were 97 patients with pruritus and 847 patients without pruritus. In the unmatched cohort, the proportion of male patients was 59.2% (559/385), and patients' mean age was 58.13±13.58 years. The proportion of patients with pruritus was 10.28% (97/944), and the proportion of patients without pruritus was 89.72% (847/944). Table I shows the baseline of patients in unmatched. After propensity score matching, 97 pairs of subjects were fuzzy matched. 97 patients were categorized as the Pru group and 97 patients as the Non-pru group. In the propensity score-matched cohort, the proportion of male patients was 56.7% (110/194). Patients with pruritus were older (59.32±12.88 *vs.* 58.82±14.11) and had a longer duration of T2DM (median [InterQuartile Range, IQR]) 10 years [5 to 19] *vs.* 10 years [4 to 16]. The baseline characteristics of the matched group are presented in Table II. As Figure 2 shows, all confounding variables are considered properly adjusted by propensity score matching.

**Table I.** The demographic of patients with pruritus in T2DM before matching.

| | Pru (n=97) | Non-pru (n=847) | t/z/$\chi^2$ | p | Std.Diff |
|---|---|---|---|---|---|
| Gender | | | 2.05 | 0.15 | |
| Male | 64 (66.0%) | 495 (58.4%) | | | 0.16 |
| Female | 33 (34.0%) | 352 (41.6%) | | | -0.16 |
| Heart rate (bpm) | 84 (76, 92) | 84 (76, 94) | -0.20 | 0.84 | 0.01 |
| SBP (mmHg) | 136 (122,144) | 132 (120,145) | -1.38 | 0.17 | 0.02 |
| DBP (mmHg) | 81 (74, 89) | 81 (73, 88) | -0.72 | 0.47 | 0.06 |
| Duration of T2DM (years) | 10 (5, 19) | 10 (4, 16) | -1.27 | 0.21 | 0.12 |
| Family history of T2DM (years) | 39 (40.2%) | 329 (38.8%) | 0.07 | 0.79 | -0.03 |

**Table II.** The demographic of patients with pruritus in T2DM after matching.

| | Pru (n=97) | Non-pru (n=847) | t/z/$\chi^2$ | *p* | Std.Diff |
|---|---|---|---|---|---|
| Age (years) | 59.32±12.88 | 58.82±14.11 | 0.26 | 0.80 | 0.16 |
| Gender | | | 6.80 | 0.01* | |
| Male | 64 (66.0%) | 46 (47.4%) | | | -0.09 |
| Female | 33 (34.0%) | 51 (52.6%) | | | 0.09 |
| Heart rate (bpm) | 84 (76, 92) | 84 (75, 92) | -0.25 | 0.81 | -0.09 |
| SBP (mmHg) | 136 (122,144) | 133 (122.5,145.5) | -0.50 | 0.62 | -0.03 |
| DBP (mmHg) | 81.65±10.18 | 79.04±9.31 | -1.86 | 0.06 | -0.07 |
| Duration of T2DM (years) | 10 (5, 19) | 9 (3, 16) | 0.94 | 0.35 | 0.05 |

Note: *: $p<0.05$

### Univariate Analysis Results

Among the included 194 patients, univariable analyses showed 5 variables were significantly related to pruritus, including BMI ($t$=2.64, $p$=0.01), absolute eosinophils ($z$=-3.11, $p$=0.00), percentage of eosinophils ($z$=-2.80, $p$=0.01), diabetic kidney disease ($\chi^2$=5.26, $p$=0.02), diabetic retinopathy ($\chi^2$=7.04, $p$=0.01). The detailed information is shown in Table III.

### Multivariable Logistic Regression Model Results

After adjusting for BMI, absolute eosinophils, percentage of eosinophils, diabetic kidney disease, diabetic retinopathy in multivariable logistic regression analyses, BMI (OR 1.094, 95%CI 1.010-1.185) and DR (OR 2.440, 95%CI 1.229-4.847) were independent risk factors for pruritus in patients with T2DM ($p<0.05$). All other model covariates were not statistically significant ($p>0.05$). The detailed information was shown in Figure 3.

## Discussion

This study provided comprehensive data on the demographic, laboratory, and complications as well as drug usage of patients with pruritus in T2DM. According to a previous study[9], pruritus in T2DM is associated with age, diabetes mellitus duration, FPG levels, HbA1c levels, combined hyperlipidemia, combined diabetic retinopathy, and

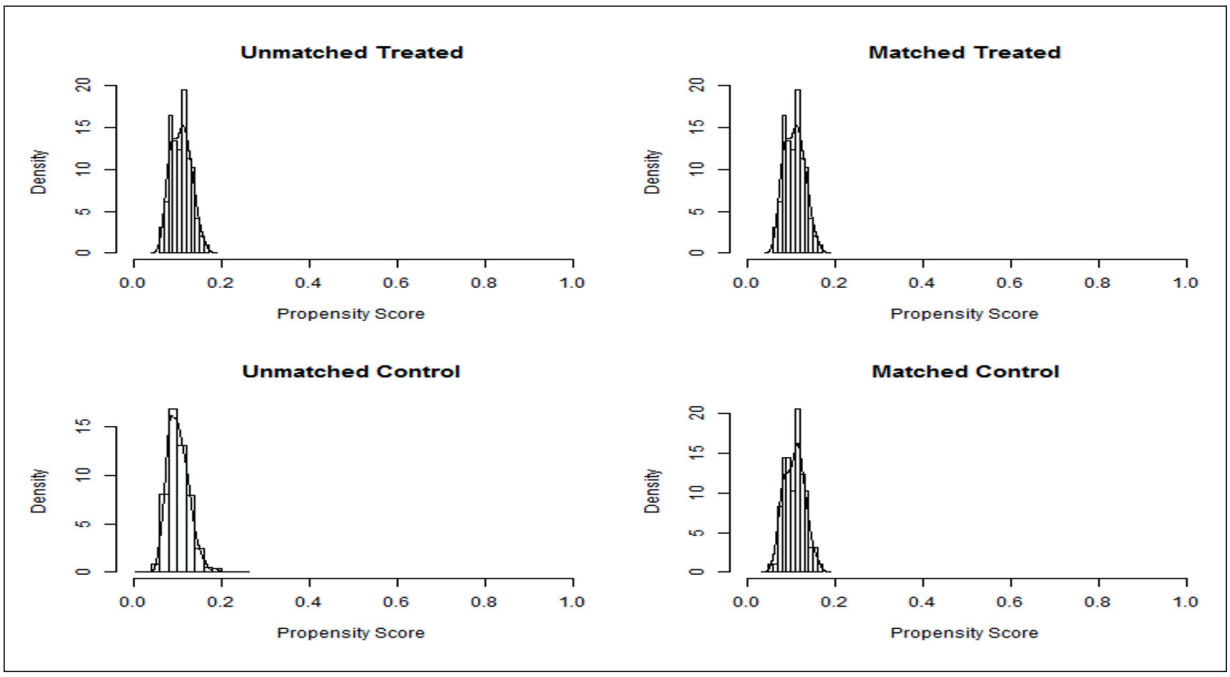


**Figure 2.** Histogram of propensity value distribution.

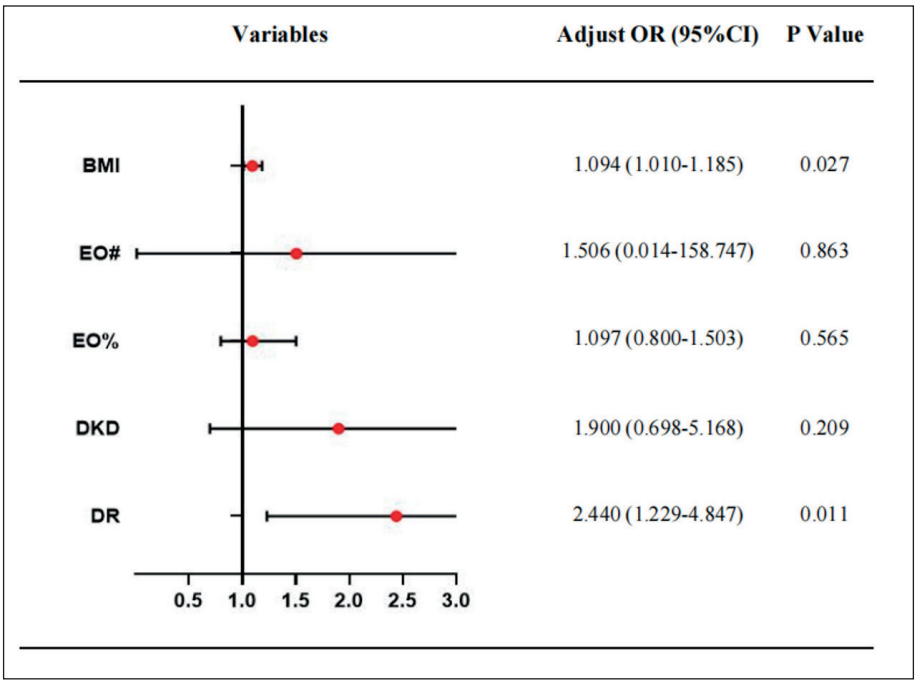


**Figure 3.** Multivariable logistic regression for patients with pruritus in T2DM.

combined diabetic peripheral neuropathy. Different from their findings, ours showed that the prevalence of pruritus in T2DM was 10.28%, lower than previous study[2]; we also observed BMI and DR may be the potential risk factors associated with pruritus in patients with T2DM. This difference might be related to that our study had a larger sample size and we used PSM. It suggests that more studies are needed in the real-world study to explore the risk factors for patients with skin pruritus in T2DM.

Few studies[10,11] reported the role of BMI in patients with pruritus in T2DM predictions, and in this study, we showed that the mean BMI of type 2 diabetes mellitus complicated with skin pruritus was 25.45±3.92 kg/m$^2$ and for every 1 kg/m$^2$ increase in BMI, the risk of pruritus in patients with T2DM will be increased by 0.09% (OR=1.094, $p$<0.05). Higher BMIs had been shown to negatively influence the skin, as it increases the risk of infectious diseases, including candidiasis, intertrigo, cellulitis, folliculitis, and gas gangrene[12-14]. In addition, obesity is considered to be a risk of intractable dermatosis, the barrier and moisturizing functions decreased with obesity, and the skin was markedly dried and rough, leading to xerosis and altered transepidermal water loss (TEWL)[15,16]. Obese-diabetes patients have dry skin due to the disrupted skin barrier function[10,17]. In diabetic patients, sudomotor failure is an important manifestation; there was a significant reduction of nerve fibers innervating sweat glands and indices for parasympathetic nervous activity were lower compared with the non-diabetic group, leading to impaired cutaneous microcirculatory function that affects skin barrier homeostasis such as dry skin and frequent skin wounds[18,19]. The high BMI of patients with T2DM might be linked to stratum corneum (SC) hydration changes and exacerbates the skin dryness as well as severer cutaneous manifestations. The severities of the initial confirmed cases were mostly mild. Thus, timely diagnosis and early weight loss support can alleviate severe cases. It is reported that about 70% of patients with diabetes mellitus were overweight and obese in China in 2021[20]. Therefore, careful monitoring of long-term trends in BMI is essential. In 2019, with a focus on disease prevention and health promotion, the State Council of China's cabinet issued a new guideline-Healthy China initiative[21]. The guideline highlights that we have to strengthen the health management of patients with diabetes mellitus, not only focusing on glucose control but also providing professional advice on weight management.

In the present study, we observed DR may face more risk of pruritus with T2DM. The results of our logistic regression analysis revealed that individuals with DR were nearly 2.5 times more likely to have pruritus compared with those without retinopathy. DR can be a powerful predictor of the progression of pruritus in diabetic patients. It was

**Table III.** Univariate analysis for patients with pruritus in T2DM.

| | Non-pru(n=97) | Pru (n=97) | t/z/$\chi^2$ | *p* |
|---|---|---|---|---|
| ***BMI (kg/m²)*** | 24.19±3.57 | 25.45±3.92 | 2.64 | 0.01* |
| ***Laboratory data*** | | | | |
| EO# | 0.13 (0.09,0.23) | 0.20 (0.13,0.33) | -3.11 | 0.00* |
| EO% | 2.10 (1.50,3.10) | 2.90 (1.75,4.75) | -2.80 | 0.01* |
| BASO# | 0.01 (0.00,0.01) | 0.01 (0.00,0.01) | -0.18 | 0.86 |
| BASO% | 0.10 (0.00,0.20) | 0.10 (0.00,0.20) | -0.09 | 0.93 |
| HbA1c (%) | 8.20 (6.80,10.60) | 8.60 (7.15,9.75) | -0.25 | 0.80 |
| FPG (mmol/L) | 7.35 (5.65,9.64) | 7.35 (6.13,10.13) | 0.66 | 0.51 |
| SCr (μmol/L) | 69.00 (56.50,89.00) | 73.00 (60.00,91.00) | -1.40 | 0.16 |
| TG (mmol/L) | 1.42 (1.00,2.37) | 1.56 (1.06,2.79) | -1.22 | 0.22 |
| TC (mmol/L) | 4.44 (3.73,4.95) | 4.40 (3.31,5.26) | -0.03 | 0.98 |
| HDL-C (mmol/L) | 1.04 (0.89,1.21) | 1.03 (0.85,1.18) | -0.58 | 0.56 |
| LDL-C (mmol/L) | 2.52±0.85 | 2.58±1.13 | 0.42 | 0.68 |
| FC-P (mmol/L) | 1.70±0.90 | 1.79±1.03 | -0.66 | 0.51 |
| P2BG (mmol/L) | 11.66 (9.33,15.46) | 11.32 (9.47,15.62) | -0.24 | 0.81 |
| P2C-P (mmol/L) | 4.41 (2.42,7.28) | 3.70 (2.04,6.06) | -1.04 | 0.30 |
| ***Complications*** | | | | |
| DKD | 18 (18.6%) | 7 (7.2%) | 5.26 | 0.02* |
| DR | 36 (37.1%) | 18 (18.6%) | 7.04 | 0.01* |
| DPN | 73 (75.3%) | 67 (69.1%) | 0.66 | 0.42 |
| ***Medication usage*** | | | | |
| CSII | 14 (14.4%) | 12 (12.4%) | 0.05 | 0.83 |
| CGM | 13 (13.4%) | 0 (0%) | —— | —— |
| ***Medication usage*** | | | | |
| Metformin | 57 (58.8) | 48 (49.5%) | 1.72 | 0.24 |
| SUs | 10 (10.3%) | 17 (17.5%) | 1.57 | 0.21 |
| Glinide | 8 (8.2%) | 2 (2.1%) | 3.13 | 0.07 |
| Glycosidase inhibitors | 12 (12.4%) | 13 (13.4%) | 0.00 | 1.00 |
| DPP-4 inhibitors | 48 (49.5%) | 47 (48.5%) | 0.02 | 1.00 |
| SGLT-2 inhibitors | 51 (52.6%) | 48 (49.5%) | 0.20 | 0.77 |
| Insulin therapy | 64 (66.0%) | 56 (57.7%) | 5.94 | 0.29 |

Note. EO#: absolute eosinophils; EO%: percentage of eosinophils; BASO#: absolute basophilic granulocyte; BASO%: percentage of basophilic granulocyte; HbA1c: glycated hemoglobin; FPG: fasting blood glucose; SCr: Serum creatinine; TG: triglycerides; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; FCP: fasting C-peptide; P2BG: postprandial 2-hour blood glucose; P2C-P: postprandial 2-hour C-peptide; DKD: Diabetic Kidney Disease; DR: diabetic retinopathy; DPN: diabetic peripheral neuropathy; CSII: continuous subcutaneous insulin infusion; CGM: Continuous Glucose Monitoring; SUs: sulfonylurea; DPP-4: dipeptidyl peptidase-4; SGLT-2: Sodium-glucose cotransporter protein-2. *: $p<0.05$

found that diabetic patients with retinopathy and neuropathy also more frequently have dermatologic disease[22]. Diabetic retinopathy is classified as a microvascular disease, which can be considered a reliable marker of the deleterious effects of diabetes in an individual because the presence of diabetic retinopathy means that microcirculation has already been damaged by the diabetic milieu[23]. DR may be a predicted risk factor in pruritic diabetic patients. The reasons might be linked with the pathophysiology of DR. Chronic hyperglycaemia, advanced glycation end products (AGEs) and oxidative stress are the major pathogenetic determinant of diabetic retinopathy and are implicated in several cutaneous pathologies. First, hyperglycaemia damages cells directly or indirectly. Hyperglycemia directly affects the vascular endothelial cells and disrupts the proliferation of keratinocytes and fibroblasts, leading to skin barrier hardened and reduced TEWL[24-26]. Second, AGEs, which are linked to hyperglycemia, cause marked functional and structural alterations in human skin[27]. In the epidermis, glycated keratin leads ischaemia, hypoxia, yellowish change in skin color, and a decrease in water content of the stratum corneum (SC), resulting in the reduction of the antioxidant

defence system and skin dryness[27,28]. Third, oxidative stress does not only induce structural and functional alterations in the retina[29] but also accelerates the process of skin aging, aggravating skin dryness[30]. Therefore, we need more approaches, such as screening and combination therapy, to decrease the damage caused by DR and reduce the risk of pruritus complicating type 2 diabetes.

In daily observations and care, pruritus has a substantial impact on psychological conditions. Much of the research on pruritus has examined the correlation between pruritus and mental health problems[6,30,31]. In order to seek temporary relief from itching, patients will ignore medical advice, repeatedly scratch, stimulate with hot water or ice, or even use sharp instruments such as knives to scrape the skin. However, these actions may alleviate the pruritus the first time but will trigger severer pruritus as the further destruction of the skin barrier leads to a release of pro-inflammatory mediators and neurotrophic mediators and thus to more pruritus[32]. Severer pruritus can provoke anxiety and depression, increasing the risk of self-injury and committing suicide. Some afflicted patients had a tendency to conceal symptoms during the consultation, they believed they would be stigmatized, and others might look down on them because of their pruritus, even if the person was a professional physician or nurse. When the lesion was in the scrotum or vulva, some patients were too ashamed to tell the truth, only when the other person was someone they trusted or a professional of the same sex as themselves, they would boldly speak out about their skin troubles. As a result, there is underdiagnosis. In addition, they faced various problems in social interaction. Some patients attempted to hide scratch lesions and try hard not to scratch when itching attacks in special settings such as meetings, dating, and swimming. These experiences can reduce self-esteem and self-efficacy, aggravating upset, anxiety, and depression. The intimate partner relationship was also challenged. In fact, not only the patients with pruritus in T2DM suffer greatly from sleep disturbance, but also their intimate partners. Some people complained the restless sleep due to their partner with pruritus being tossed and turned in bed all night. In order to sleep well, some of them even chose to sleep in separate rooms. This can easily lead to quarrels in the long run, especially in the current COVID-19 epidemic period when travel is restricted. Therefore, in addition to treating pruritus and T2DM, efforts to decrease the impact of negative psychological conditions are of vital importance in order to improve the quality of life.

## Conclusions

Our findings demonstrate that BMI and DR may be the risk factors for pruritus in patients with T2DM, which may also be linked to the development and persistence of pruritic diabetes. Apart from that, negative psychological conditions also have a significant effect on the impact of quality of life. These results point out that pruritus management is urgent. Early prevention, treatment, and management are needed to improve the quality of life of these patients. There are some limitations of our work. In the first place, our study was retrospective with many confounding factors even though the PSM was used to balance the nonrandom assignment of patients. There is one more point: we used mean imputation to estimate the missing values of continuous variables, which may reduce the effective value of the data. Last but not least, we fail to use quantitative research to explore patients' psychological conditions. More multicenter cross-sectional studies and prospective studies are both highly promising and urgently needed to explore the effect of more risk factors on pruritus in patients with T2DM. In order to explain the causes and symptoms of psychological problems in these patients and explore the relationship between the severity of mental health problems and the degree of pruritus, we also need to use a combination of qualitative and quantitative research in the future.

### Conflict of Interests

The authors declare that they have no conflict of interests.

### Authors' Contribution

Mingming Xu and Yuanyuan Chen contributed to the conception and design of the study. Qiuping Yang, Siping Peng and Haiyan Yang collected the data. Zhenzhen Li, Xiangge Fan analyzed the data, and all authors interpreted the data. Qiuping Yang drafted the manuscript, and all authors were involved in critical revision and approval of the final manuscript. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

### Funding

None.

### Ethical Approval

This study was approved by the Ethics Committee of Shenzhen Traditional Chinese Medicine Hospital. We certify that the study was performed in accordance with the 1964 Declaration of Helsinki and later amendments.

### Acknowledgements

This work was not supported by any project.

### Availability of Data and Materials

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

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## References

1) IDF, IDF Diabetes Atlas 2021. (2021) https://diabetesatlas.org/atlas/tenth-edition/.
2) Welz-Kubiak K, Reszke R, Szepietowski JC. Pruritus as a sign of systemic disease. Clin Dermatol 2019; 37: 644-656.
3) Weisshaar E, Szepietowski JC, Dalgard F, Garcovich S, Gieler U, Gimenez-Arnau A, Lambert J, Leslie T, Mettang T, Misery L, Savk E, Streit M, Tschachler E, Wallengren J, Stander S. European S2k Guideline on Chronic Pruritus. Acta Derm Venereol 2019; 99: 469-506.
4) Deleuran M, Georgescu V, Jean-Decoster C. An Emollient Containing Aquaphilus dolomiae Extract is Effective in the Management of Xerosis and Pruritus: An International, Real-World Study. Dermatol Ther (Heidelb) 2020; 10: 1013-1029.
5) Kwatra SG. Breaking the Itch-Scratch Cycle in Prurigo Nodularis. N Engl J Med 2020; 382: 757-758.
6) Zeidler C, Pereira MP, Dugas M, Augustin M, Storck M, Weyer-Elberich V, Schneider G, Stander S. The burden in chronic prurigo: patients with chronic prurigo suffer more than patients with chronic pruritus on non-lesional skin: A comparative, retrospective, explorative statistical analysis of 4,484 patients in a real-world cohort. J Eur Acad Dermatol Venereol 2021; 35: 738-743.
7) Yosipovitch G, Rosen JD, Hashimoto T. Itch: From mechanism to (novel) therapeutic approaches. J Allergy Clin Immunol 2018; 142: 1375-1390.
8) Morgan CJ. Reducing bias using propensity score matching. J Nucl Cardiol 2018; 25: 404-406.
9) Lei Q, Wei JY, Yu RP, Guo HL. Clinical features and related factors of type 2 diabetes mellitus complicated with skin pruritus. Chin J Diabetes Mellitus 2018; 10: 280-284.
10) Ibuki A, Kuriyama S, Toyosaki Y, Aiba M, Hidaka M, Horie Y, Fujimoto C, Isami F, Shibata E, Terauchi Y, Akase T. Aging-like physiological changes in the skin of Japanese obese diabetic patients. SAGE Open Med 2018; 6: 2050312118756662.
11) [11].Darlenski R, Mihaylova V, Handjieva-Darlenska T. The Link Between Obesity and the Skin. Front Nutr 2022; 9: 855573.
12) Metin A, Dilek N, Bilgili SG. Recurrent candidal intertrigo: challenges and solutions. Clin Cosmet Investig Dermatol 2018; 11: 175-185.
13) Cheong HS, Chang Y, Joo EJ, Cho A, Ryu S. Metabolic Obesity Phenotypes and Risk of Cellulitis: A Cohort Study. J Clin Med 2019; 8: 953.
14) Wipperman J, Bragg DA, Litzner B. Hidradenitis Suppurativa: Rapid Evidence Review. Am Fam Physician 2019; 100: 562-569.
15) Hirt PA, Castillo DE, Yosipovitch G, Keri JE. Skin changes in the obese patient. J Am Acad Dermatol 2019; 81: 1037-1057.
16) Mori S, Shiraishi A, Epplen K, Butcher D, Murase D, Yasuda Y, Murase T. Characterization of skin function associated with obesity and specific correlation to local/systemic parameters in American women. Lipids Health Dis 2017; 16: 214.
17) Ozlu E, Uzuncakmak TK, Takir M, Akdeniz N, Karadag AS. Comparison of cutaneous manifestations in diabetic and nondiabetic obese patients: A prospective, controlled study. North Clin Istanb 2018; 5: 114-119.
18) Luo KR, Chao CC, Hsieh PC, Lue JH, Hsieh ST. Effect of glycemic control on sudomotor denervation in type 2 diabetes. Diabetes Care 2012; 35: 612-616.
19) Nomura T, Yoshida-Amano Y, Yoshida K, Fujii A, Tanahashi M, Sugiyama Y, Iwata K, Murase T. Relationships between transepidermal water loss, cutaneous microcirculatory function and autonomic nervous activity. Int J Cosmet Sci 2017; 39: 275-283.
20) Overweight and obese people account for over 70% of diabetes patients in China. (2021) Available at: https://new.qq.com/omn/20211127/20211127V02FNB00.html
21) Healthy China initiative. (2021) Available at: http://www.gov.cn/xinwen/2019-07/15/content_5409694.htm
22) Demirseren DD, Emre S, Akoglu G, Arpaci D, Arman A, Metin A, Cakir B. Relationship between skin diseases and extracutaneous complications of diabetes mellitus: clinical analysis of 750 patients. Am J Clin Dermatol 2014; 15: 65-70.
23) Vujosevic S, Aldington SJ, Silva P, Hernandez C, Scanlon P, Peto T, Simo R. Screening for diabetic retinopathy: new perspectives and challenges. Lancet Diabetes Endocrinol 2020; 8: 337-347.
24) Burgess JL, Wyant WA, Abujamra BA, Kirsner RS, Jozic I. Diabetic Wound-Healing Science. Medicina (Kaunas, Lithuania) 2021; 57: 1072.
25) Lima AL, Illing T, Schliemann S, Elsner P. Cutaneous Manifestations of Diabetes Mellitus: A Review. American journal of clinical dermatology 2017; 18: 541-553.
26) Lai CCK, Nor NM, Kamaruddin NA, Jamil A, Safian N. Comparison of transepidermal water loss and skin hydration in diabetics and nondiabetics. Clin Exp Dermatol 2021; 46: 58-64.
27) Yokota M, Tokudome Y. The Effect of Glycation on Epidermal Lipid Content, Its Metabolism

and Change in Barrier Function. Skin Pharmacol Physiol 2016; 29: 231-242.

28) Yokota M, Masaki H , Okano Y, Tokudome Y. Effect of glycation focusing on the process of epidermal lipid synthesis in a reconstructed skin model and membrane fluidity of stratum corneum lipids. Dermatoendocrinol 2017; 9: e1338992.

29) Kang QZ, Yang CX. Oxidative stress and diabetic retinopathy: Molecular mechanisms, pathogenetic role and therapeutic implications. Redox Biol 2020; 37: 101799.

30) Li YF, Ouyang SH, Tu LF, Wang X, Yuan WL, Wang GE, Wu YP, Duan WJ, Yu HM, Fang ZZ, Kurihara H, Zhang YW, He RR. Caffeine Protects Skin from Oxidative Stress-Induced Senescence through the Activation of Autophagy. Theranostics 2018; 8: 5713-5730.

31) Dalgard FJ, Svensson A, Halvorsen JA, Gieler U, Schut C, Tomas-Aragones L, Lien L, Poot F, Jemec GBE, Misery L, Szabo C, Linder D, Sampogna F, Spillekom-van Koulil S, Balieva F, Szepietowski JC, Lvov A, Marron SE, Altunay IK, Finlay AY, Salek S, Kupfer J. Itch and Mental Health in Dermatological Patients across Europe: A Cross-Sectional Study in 13 Countries. J Invest Dermatol 2020; 140: 568-573.

32) Zeidler C, Pereira MP, Dugas M, Augustin M, Storck M, Weyer-Elberich V, Schneider G, Ständer S. The burden in chronic prurigo: patients with chronic prurigo suffer more than patients with chronic pruritus on non-lesional skin. Journal of the European Academy of Dermatology and Venereology: JEADV 2021; 35: 738-743.