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Association of non-insulin-based insulin resistance indices, mean platelet volume and prostate cancer: a cross-sectional study

Jinru Wang[1], Hengqing An[2*] and Ning Tao[1*]

Abstract

Purpose Insulin resistance and prostate cancer (PCa) association results remain controversial. However, few studies have compared the role of various non-insulin-based insulin resistance (NI-IR) indices and mean platelet volume (MPV) in PCa.

Methods We conducted a cross-sectional study, the case group included 354 patients with PCa, and the control group included 1,498 non-PCa participants. We performed inverse probability weighting to reduce the impact of differences in baseline information between the case and control groups on results. Weighted logistic regression analysis for assessing the relationship between NI-IR indices and PCa risk. Fitting 4-point restricted cubic spline (RCS) plots to show the trend of NI-IR indices with PCa risk. The interaction between insulin resistance and platelet volume based on generalized additive model (GAM) to reveal the impact of the interaction between insulin resistance and cardiovascular risk on PCa. In the end, we performed three sensitivity analyses to verify the stability of results.

Results Weighted logistic regression analysis revealed that all NI-IR indices were associated with PCa. When NI-IR indices were evaluated as continuous variables, in the all variables adjusted model (model 3), the adjusted OR of ZJU index was 1.337 (95%CI: 1.296–1.379), the adjusted OR of TyG index was 5.300 (95%CI:4.208–6.675), the adjusted OR of TG/HDL-c was 1.431 (95%CI:1.335–1.534), and the adjusted OR of METS-IR was 1.129 (95%CI:1.110–1.149). When NI-IR indices were analyzed as categorical variables, also in model 3, using Q1 as reference, the adjusted OR of ZJU index in Q5 was 15.592 (95%CI:10.809–22.492), the adjusted OR of TyG index in Q5 was 7.306 (95%CI:5.182–10.301), the adjusted OR of TG/HDL-c in Q5 was 4.790 (95%CI:3.459–6.632), and the adjusted OR of METS-IR in Q5 was 9.844 (95%CI:6.862–14.121). RCS displayed that PCa risk tended to increase as the ZJU index, TyG index, TG/HDL-c, and METS-IR increased. The interaction test based on the GAM indicated that the value of the interaction between TG/HDL-c and MPV on the PCa risk was $\chi^2 = 6.924$($P = 0.009$). With the increase in TG/HDL-c and the decrease in MPV, the PCa risk progressively increases. The sensitivity analysis further confirmed the robustness of the results.

Conclusions NI-IR indices were associated with an increased PCa risk. The interaction between MPV and insulin resistance may further contribute to the PCa risk.

Keywords Prostate cancer (PCa), Insulin resistance, Non-insulin-based insulin resistance (NI-IR) indices, Mean platelet volume (MPV), Cardiovascular risk

*Correspondence:
Hengqing An
9269735@qq.com
Ning Tao
38518412@qq.com

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Introduction

Prostate cancer (PCa) is the second leading cause of cancer death in men [1]. The prevalence of obesity has been increasing around the world. Obesity-induced insulin resistance, cardiovascular diseases and malignant tumors are gradually becoming a global public health problem. In the meantime, obesity has been demonstrated to play a role in the development of PCa [2]. A number of studies have attributed the link between obesity and cancer to insulin resistance [3, 4]. Previous studies have shown that there is a complex interaction between metabolically unhealthy, metabolic syndrome and the risk of PCa [5, 6]. A critical component of the metabolic syndrome is insulin resistance, insulin resistance may play an essential role in the pathogenesis of metabolic syndrome [7]. However, it is unclear whether the positive association between metabolic syndrome and the risk of PCa is driven by insulin resistance or other aspects of the metabolic syndrome. This study aims to investigate the association between non-insulin-based insulin resistance (NI-IR) indices, mean platelet volume (MPV), and PCa risk.

Insulin is a polypeptide hormone that regulates carbohydrate and fat metabolism by improving glucose uptake. In diabetes, insulin loses that ability to enhance cellular glucose uptake and utilization, which is clinically defined as insulin resistance [8]. Insulin and insulin-like growth factor (IGF) are synthetic metabolic endocrine hormones, has an important physiological role in glucose metabolism, cell proliferation, cell death, and angiogenesis, overstimulation of these biomarkers and their relevant combining proteins has been related to an increased risk of several malignant tumors, including PCa [9]. There is still controversy surrounding the association between insulin resistance and PCa [10–13]. A Meta-analysis suggests that PCa patients have higher fasting serum insulin and HOMA-IR levels [12]. A study analyzing 259,884 men from eight European cohorts demonstrated that insulin resistance was negatively associated with the incidence of PCa [14]. The results of a meta-analysis involving 11,796 participants revealed a non-significant correlation between plasma insulin concentrations and PCa [15]. The assessment of four Swedish cohorts also indicated there was no significant correlation between insulin resistance markers and PCa risk [10]. Hyperinsulinemic euglycemic glucose clamp is invasive and time-consuming, homeostatic measure of insulin resistance is costly and complex, they have limited clinical utility and feasibility in large-scale epidemiologic investigations [16]. There are several NI-IR indices for example Zhejiang University (ZJU) index, triglyceride-glucose (TyG) index, ratio of triglycerides to high-density lipoprotein cholesterol (TG/HDL-C) and metabolic score of insulin resistance (METS-IR), has well correlated with homeostatic model assessment of insulin resistance (HOMA-IR), and are better than HOMA-IR as metabolic syndrome indicators [17–20]. In particular, the ZJU index is a new metabolic index that integrates changes in aspartate aminotransferase (AST), alanine aminotransferase (ALT), triglycerides (TG), body mass index (BMI), includes blood glucose, blood lipids, and liver function, is a powerful indicator for recognizing insulin resistance [21]. Concurrently, we found that there is a scarcity of research on the relationship between the ZJU index and PCa.

MPV is the estimation of average platelet size, used to evaluate the size and number of platelets, is recognized as a biomarker of platelet activity and function. MPV is a prospective simplified and easy biomarker for early diagnosis and prognosis of insulin resistance [22]. It was demonstrated that increased MPV measured in metabolic disordered patients [23, 24]. Insulin resistance is significantly related to adverse cardiovascular events, therefore MPV can be used as a biomarker for early identification of microvascular complications and cardiovascular risk in diabetes mellitus [25–27].Platelet count increase and platelet count decrease are both considered risk factors for tumor development [28]. MPV has value as a diagnostic indicator of PCa [29]. Platelets involved in virtually all processes of tumor metastasis. Platelet-tumor cell interactions are critical for hematological tumor metastasis: (1) tumor cells enter the circulation and become circulating tumor cells, causing platelets to activate, aggregate, and wrap around tumor cells to form tumor microthrombus, creating a favorable tumor microenvironment for tumor metastasis; (2) platelets wrap tumor cells in thrombosis, preventing them from being attacked by natural killer (NK) cells, important for the survival of tumor cells in the bloodstream [30]; (3) platelets promote tumor metastasis by accelerating epithelial-mesenchymal transition (EMT), endothelial adhesion, angiogenesis, tumor proliferative processes, and platelet-derived microvesicle (PMV) formation [31, 32].

On the basis of previous evidence, we evaluated the association of NI-IR indices with the development of PCa. We also revealed the mutual effect of insulin resistance and platelets on PCa through the interaction between NI-IR indices and MPV.

Methods

Study population

This study was a cross-sectional design. The study population was from the First Affiliated Hospital of Xinjiang Medical University from January 2020 to August 2024. The case group included 354 patients diagnosed with PCa by performing prostate biopsy and puncture in the urology department, and the control group consisted

of a total of 1,498 individuals who were diagnosed with benign prostatic hyperplasia (BPH) by prostate biopsy and puncture, as well as men who underwent a physical examination at the physical examination center during the same period. Inclusion criteria for case and control groups: (1) In the case group, patients diagnosed with PCa on first prostate biopsy puncture. In the control group, individuals diagnosed with BPH by prostate biopsy, or men with physical examination during the same period. (2) The data are complete. (3) Can read, understand and sign informed consent forms. Exclusion criteria for case and control groups: (1) In the case group, PCa patients with other types of cancer or cancer history. In the control group, participants with any type of cancer or cancer history; (2) Participants with a history of lipid metabolism disorders or the use of triglyceride lowering medications. This protocol was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (Grant number: 20220 308–166). All participants signed an informed consent form after clearly understanding the purpose of this study protocol.

Physical and biochemical indicator measurements

The basic information, physical examination and laboratory samples of the participants were collected by specialized doctors or nurses in hospital. All participants take off shoes and measure height, accurate to 0.1 cm. Weight is measured by body composition analyzer, accurate to 0.1 kg. Participants fasted for 10–12 h on the first night of admission, the following morning, venous blood specimens were collected from the anterior elbow vein at 8:00–9:00 a.m. and sent to the hematology department, to detect fasting blood glucose (FG), triglycerides (TG), alanine aminotransferase (ALT), glutamine aminotransferase (AST), high-density lipoprotein cholesterol (HDL-c), etc.

Insulin resistance index calculation

The ZJU index was defined as BMI + FG (mg/dL) *0.0555 + TG (mg/dL)*0.011 + 3 × ALT (U/L) /AST(U/L) [17]. The formula of TyG index, was calculated as ln[TG (mg/dL) × FG (mg/dL) /2] [33]. The TG/HDL-C ratio, was defined by TG (mg/dL) divided by HDL-C (mg/dL) [34]. The METS-IR formula was defined as ln[(2 × FG (mg/dL) + total cholesterol(mg/dL)] × BMI/ ln[HDL-C(mg/dL)] [35].

Statistical analysis

The continuous variables with normal distribution are shown by $\bar{\chi} \pm s$, The non-normally distributed continuous variables are expressed as M (P_{25}, P_{75}). We implemented multiple interpolation for missing secondary variables. The basic information in the case and control groups were compared by t-test or Mann–Whitney U-test, and χ^2 test. Age as a matching variable to perform inverse probability weighting and reduce the interference of confounders. The association between NI-IR indices and the development of PCa was evaluated by univariate and multivariate weighted logistic regression. Four-point restricted cubic spline were constructed to fit the correlation between NI-IR indices and the risk of developing PCa. Interaction test based on generalized additive model (GAM) to assess the effects of the interaction of NI-IR indices with MPV on the risk of developing PCa. Finally, sensitivity analysis were performed to evaluate the robustness of results. $P < 0.05$ considered as statistically significant difference. SPSS and R (version 4.2.0) were used to carry out all analyses.

Results

Clinical characteristics of the study population

This study included 354 PCa patients in the case group, the control group included 1498 participants without PCa (included BPH and healthy individuals). The median ages of the case and control groups were 71 and 49 years, respectively. There was statistical difference in age between the case and control groups ($P < 0.05$), see Table 1. There was a significant difference in age between the case group and the control group. To address this issue, we applied inverse probability weighting to balance age between the case and control groups. Inverse probability weighting was applied to equalize the age difference between the two groups by assigning a weight to each participant. We performed inverse probability weighting with age as the matching variable. The mean age of the case and control groups was 61.56 years and 58.91 years, the difference in age between the two groups was not statistically significant ($P > 0.05$), see Table 2.

The correlation of NI-IR indices and the risk of developing PCa

Weighted logistic regression analysis

After inverse probability weighting, we explored the factors influencing the development of PCa by employing weighted logistic regression analyses. Model 1 was not adjusted for any variables. Model 2 was adjusted for statistically significant differences in the univariate weighted logistic regression analyses, decreased the influence of confounding factors on study results. Model 3 was adjusted for MPV based on Model 2. The results showed that a higher NI-IR index was associated with a higher risk of PCa. When NI-IR indices were evaluated as continuous variables, in the all variables adjusted model (model 3), the adjusted OR of ZJU index was 1.337 (95%CI: 1.296–1.379), the adjusted OR of TyG index was 5.300 (95%CI:4.208–6.675), the adjusted OR of TG/

Table 1 Basic information of study population before inverse probability weighting

Variables	Case group ($n=354$)	Control group ($n=1498$)	Z	P
Age (years)/(M(P_{25},P_{75}))	71.00(65.00,77.00)	49.00(47.00,54.00)	−25.757	< 0.001
Body mass index (Kg/m^2)/(M(P_{25},P_{75}))	25.50(23.12,26.86)	24.62(22.86,26.42)	−2.812	0.005
Red blood cell (× 10^{12}/L)/(M(P_{25},P_{75}))	4.470(4.06,4.89)	4.82(4.58,5.05)	−10.836	< 0.001
Hemoglobin (g/L)/(M(P_{25},P_{75}))	133.00(117.00,145.25)	150.00(144.00,156.00)	−17.139	< 0.001
Mean corpuscular volume (fl)/ (M(P_{25},P_{75}))	92.20(89.60,95.00)	93.40(91.28,95.00)	−7.615	< 0.001
Mean corpuscular hemoglobin (pg)/ (M(P_{25},P_{75}))	30.40(29.40,31.20)	30.60(29.70,31.30)	−2.761	0.006
Mean corpuscular hemoglobin concentration (g/L)/(M(P_{25},P_{75}))	333.00(326.00,341.00)	334.00(327.00,341.00)	−1.592	0.111
Red cell distribution width (%)/ (M(P_{25},P_{75}))	12.70(12.20,13.30)	12.50(12.10,12.90)	−5.010	< 0.001
Platelet count (× 10^9/L)/(M(P_{25},P_{75}))	220.00(181.75,254.25)	218.00(185.00,255.00)	−0.117	0.907
Mean platelet volume (MPV) (f1)/ (M(P_{25},P_{75}))	9.50(8.70,10.20)	8.90(8.30,9.60)	−8.025	< 0.001
Plateletocrit (%)/(M(P_{25},P_{75}))	0.20(0.18,0.24)	0.20(0.17,0.22)	−3.306	0.001
Platelet distribution width (%)/ (M(P_{25},P_{75}))	15.80(11.30,16.30)	16.10(15.80,16.50)	−8.711	< 0.001
Aspartate aminotransferase (AST) (U/L)/(M(P_{25},P_{75}))	23.33(18.48,29.74)	20.30(17.30,23.90)	−7.366	< 0.001
Alanine aminotransferase (ALT) (U/L)/(M(P_{25},P_{75}))	24.13(18.10,35.51)	21.90(16.70,29.57)	−4.240	< 0.001
Lactate dehydrogenase (U/L)/(M(P_{25},P_{75}))	181.00(153.68,217.86)	170.00(155.70,183.60)	−6.446	< 0.001
γ-glutamyl transpeptidase (U/L)/(M(P_{25},P_{75}))	28.63(18.98,52.63)	26.55(19.56,39.00)	−2.581	0.010
Alkaline phosphatase (U/L)/(M(P_{25},P_{75}))	90.30(63.42,170.50)	74.75(63.80,88.50)	−7.672	< 0.001
Fasting glucose (FG) (mmol)/(M(P_{25},P_{75}))	5.48(4.83,6.71)	5.22(4.83,5.70)	−5.093	< 0.001
Fasting triglycerides (TG) (mmol)/(M(P_{25},P_{75}))	1.25(1.00,1.70)	1.25(0.91,1.63)	−1.905	0.057
Total cholesterol (mmol)/(M(P_{25},P_{75}))	3.98(3.38,4.69)	4.75(4.17,5.35)	−12.788	< 0.001
High-density lipoprotein cholesterol (mmol)/(M(P_{25},P_{75}))	1.00(0.82,1.21)	1.23(1.05,1.41)	−11.945	< 0.001
Low-density lipoprotein cholesterol (mmol)/(M(P_{25},P_{75}))	2.63(2.02,3.18)	2.89(2.43,3.41)	−6.484	< 0.001
Waist circumference (cm)/(M(P_{25},P_{75}))	94.00(87.00,102.00)	87.00(82.00,92.00)	−12.595	< 0.001
Blood potassium (mmol/L)/(M(P_{25},P_{75}))	3.94(3.70,4.21)	4.14(3.90,4.39)	−8.132	< 0.001
Blood sodium (mmol/L)/(M(P_{25},P_{75}))	140.90(138.70,143.00)	141.70(140.10,143.00)	−4.676	< 0.001
Blood chlorine (mmol/L)/(M(P_{25},P_{75}))	104.40(102.70,106.80)	103.90(102.30,105.70)	−3.755	< 0.001
Blood calcium (mmol/L)/(M(P_{25},P_{75}))	2.21(2.12,2.31)	2.34(2.27,2.42)	−14.778	< 0.001
Serum magnesium (mmol/L)/(M(P_{25},P_{75}))	0.85(0.80,0.91)	0.84(0.79,0.90)	−3.139	0.002
Serum phosphorus (mmol/L)/(M(P_{25},P_{75}))	1.10(0.95,1.22)	0.96(0.85,1.06)	−11.505	< 0.001
Serum creatinine (μmol/L)/(M(P_{25},P_{75}))	79.35(67.40,90.00)	80.74(71.93,89.60)	−1.753	0.080
ZJU index/(M(P_{25},P_{75}))	35.70(33.02,38.58)	34.77(32.38,37.04)	−4.421	< 0.001
TyG index/(M(P_{25},P_{75}))	8.67(8.36,8.99)	8.55(8.23,8.86)	−4.736	< 0.001
TG/HDL-c/(M(P_{25},P_{75}))	2.91(2.07,4.23)	2.35(1.62,3.24)	−7.830	< 0.001
METS-IR/(M(P_{25},P_{75}))	41.54(35.81,45.48)	38.51(34.75,42.26)	−6.366	< 0.001

HDL-c was 1.431 (95%CI:1.335–1.534), and the adjusted OR of METS-IR was 1.129 (95%CI:1.110–1.149). When NI-IR indices were analyzed as categorical variables, also in model 3, using Q1 as reference, the adjusted OR of ZJU index in Q5 was 15.592 (95%CI:10.809–22.492), the adjusted OR of TyG index in Q5 was 7.306 (95%CI:5.182–10.301), the adjusted OR of TG/HDL-c in Q5 was 4.790 (95%CI:3.459–6.632), and the adjusted OR of METS-IR in Q5 was 9.844 (95%CI:6.862–14.121).See Table 3.

Restricted cubic spline

The results of fitting the restricted cubic spline with four points are displayed in Fig. 1: With increasing ZJU index, TyG index, TG/HDL-c index and METS-IR index, the risk of PCa tended to be increased.

Interaction of NI-IR indices and MPV on the risk of developing PCa

We constructed interaction tests based on generalized additive model (GAM), to assess the interaction of four NI-IR indices with MPV on the risk of PCa. The results of the interactions indicated that: the value of the interaction between the ZJU index and MPV on the risk of PCa was $\chi^2=3.393(P=0.38)$. The value of the interaction between TyG index and MPV on the risk of PCa was $\chi^2=0.313(P=0.577)$. The value of the interaction

Table 2 Basic information of study population after inverse probability weighting

Variables	Case group ($n=354$)	Control group ($n=1498$)	test SMD/Z/^{2}	*P*
Age (years)/(xs)	61.56 ± 9.78	58.91 ± 13.87	0.221	0.085
Body mass index (Kg/m^2)/ (M(P_{25},P_{75}))	25.74(24.10,27.44)	24.22(22.49,26.22)	−13.686	< 0.001
Red blood cell (× 10^{12}/L)/ (M(P_{25},P_{75}))	4.60(4.18,4.92)	4.79(4.50,5.03)	−8.022	< 0.001
Hemoglobin (g/L)/(M(P_{25},P_{75}))	139.00(123.00,150.00)	148.00(140.00,155.00)	−15.824	< 0.001
Mean corpuscular volume (fl)/ (M(P_{25},P_{75}))	91.90(88.65,94.70)	93.20(90.80,95.00)	−8.984	< 0.001
Mean corpuscular hemoglobin (pg)/ (M(P_{25},P_{75}))	30.20(29.30,31.40)	30.50(29.60,31.40)	−2.705	0.007
Mean corpuscular hemoglobin concentration (g/L)/(M(P_{25},P_{75}))	333.00(327.00,340.00)	333.00(325.00,339.00)	−2.925	0.003
Red cell distribution width (%)/ (M(P_{25},P_{75}))	12.70(12.30,13.30)	12.60(12.20,13.20)	−1.866	0.062
Platelet count (× 10^9/L)/ (M(P_{25},P_{75}))	219.60(191.00,254.00)	215.00(183.00,253.72)	−1.491	0.136
Mean platelet volume (MPV) (f1)/ (M(P_{25},P_{75}))	9.50(8.90,10.40)	9.10(8.50,10.00)	−8.484	< 0.001
Plateletocrit (%)/(M(P_{25},P_{75}))	0.21(0.18,0.24)	0.20(0.17,0.23)	−5.807	< 0.001
Platelet distribution width (%)/ (M(P_{25},P_{75}))	15.70(11.10,16.40)	16.00(15.40,16.50)	−8.484	< 0.001
Aspartate aminotransferase (AST) (U/L)/(M(P_{25},P_{75}))	23.99(18.50,28.60)	20.30(17.30,23.80)	−12.495	< 0.001
Alanine aminotransferase (ALT) (U/L)/(M(P_{25},P_{75}))	25.12(18.19,37.13)	20.70(15.10,27.84)	−12.017	< 0.001
Lactate dehydrogenase (U/L)/(M(P_{25},P_{75}))	169.00(151.14,211.03)	169.315(155.30,182.31)	−5.592	< 0.001
γ-glutamyl transpeptidase (U/L)/(M(P_{25},P_{75}))	30.00(21.00,44.49)	24.30(18.02,35.60)	−9.156	< 0.001
Alkaline phosphatase (U/L)/(M(P_{25},P_{75}))	88.36(64.30,184.60)	73.40(62.93,88.00)	−12.299	< 0.001
Fasting glucose (FG) (mmol)/(M(P_{25},P_{75}))	5.41(4.92,6.59)	5.11(4.67,5.61)	−11.913	< 0.001
Fasting triglycerides (TG) (mmol)/(M(P_{25},P_{75}))	1.36(1.07,1.75)	1.20(0.90,1.63)	−7.982	< 0.001
Total cholesterol (mmol)/(M(P_{25},P_{75}))	4.04(3.45,4.75)	4.61(4.02,5.29)	−15.205	< 0.001
High-density lipoprotein cholesterol (mmol)/(M(P_{25},P_{75}))	0.99(0.84,1.26)	1.21(1.03,1.38)	−15.979	< 0.001
Low-density lipoprotein cholesterol (mmol)/(M(P_{25},P_{75}))	2.76(2.16,3.28)	2.82(2.40,3.35)	−5.289	< 0.001
Waist circumference (cm)/(M(P_{25},P_{75}))	94.00(90.00,104.00)	87.00(82.00,92.00)	−23.295	< 0.001
Blood potassium (mmol/L)/(M(P_{25},P_{75}))	3.98(3.70,4.26)	4.06(3.80,4.33)	−6.112	< 0.001
Blood sodium (mmol/L)/(M(P_{25},P_{75}))	140.90(139.10,142.79)	141.20(140.00,143.00)	−4.226	< 0.001
Blood chlorine (mmol/L)/(M(P_{25},P_{75}))	104.60(103.00,106.80)	104.30(102.50,106.30)	−1.948	0.051
Blood calcium (mmol/L)/(M(P_{25},P_{75}))	2.23(2.15,2.30)	2.32(2.21,2.40)	−15.705	< 0.001
Serum magnesium (mmol/L)/(M(P_{25},P_{75}))	0.85(0.82,0.91)	0.85(0.80,0.91)	−1.833	0.067
Serum phosphorus (mmol/L)/(M(P_{25},P_{75}))	1.15(1.01,1.27)	0.97(0.86,1.08)	−22.935	< 0.001
Serum creatinine (μmol/L)/(M(P_{25},P_{75}))	78.98(64.68,89.28)	79.50(70.00,88.60)	−3.505	< 0.001
ZJU index/(M(P_{25},P_{75}))	36.62(34.26,39.62)	34.11(31.57,36.68)	−17.987	< 0.001
ZJU index/(%)			279.252	< 0.001
Q1(≤ 31.57)	10.6%	26.2%		
Q2(31.58 −34.04)	13.5%	22.3%		
Q3(34.05—35.87)	15.9%	20.2%		
Q4(35.88—38.34)	28.2%	17.6%		
Q5(≥ 38.35)	31.7%	13.7%		
TyG index/(M(P_{25},P_{75}))	8.73(8.38,9.02)	8.51(8.15,8.85)	−12.306	< 0.001
TyG index/(%)			168.382	< 0.001
Q1(≤ 8.14)	11.6%	24.7%		
Q2(8.15—8.45)	18.0%	21.3%		
Q3(8.46—8.73)	19.6%	19.8%		
Q4(8.74—8.98)	19.9%	20.0%		
Q5(≥ 8.99)	30.9%	14.2%		
TG/HDL-c/(M(P_{25},P_{75}))	3.31(2.06,4.35)	2.37(1.64,3.34)	−14.596	< 0.001
TG/HDL-c/(%)			233.207	< 0.001
Q1(≤ 1.64)	10.4%	25.0%		
Q2(1.65—2.24)	18.7%	20.7%		
Q3(2.25—2.96)	16.6%	21.9%		

Table 2 (continued)

Variables	Case group ($n=354$)	Control group ($n=1498$)	test SMD/Z/^{2}	*P*
Q4(2.97—3.96)	21.5%	19.2%		
Q5(≥ 3.97)	32.8%	13.2%		
METS-IR/(M(P_{25},P_{75}))	42.61(37.79,46.90)	38.27(34.00,42.08)	−17.221	< 0.001
METS-IR/(%)			275.630	< 0.001
Q1(≤ 34.21)	9.3%	25.5%		
Q2(34.22—37.89)	16.4%	22.2%		
Q3(37.90—41.13)	17.5%	21.4%		
Q4(41.14—44.96)	23.6%	18.1%		
Q5(≥ 44.97)	33.2%	12.9%		

between TG/HDL-c and MPV on the risk of PCa was $\chi^2=6.924(P=0.009)$, see Fig. 2. The value of the interaction between METS-IR and MPV on the risk of PCa was $\chi^2=5.997(P=0.075)$. The risk of PCa progressively increases with higher TG/HDL-c and lower MPV.

Sensitivity analysis

The relationship between NI-IR indices and the risk of developing PCa after propensity score matching

To further validate the robustness of results from weighted logistic regression analyses after inverse probability weighting, we performed 1:1 propensity score matching with a caliper value of 0.05 using age as the matching variable. We chose 0.05 as the caliper value, to get the largest sample size while balancing the confounders. After propensity score matching, the results of the conditional logistic regression were essentially the same as those obtained after inverse probability weighting. Supplementary Table 1 for details.

Excluded participants with hyperglycemia (fasting blood glucose ≥ 100 mg/dL)

The participants who were potentially hyperglycemic were excluded to verify the stability of the NI-IR indices, because one of the characteristics of insulin resistance is elevated blood glucose. We conducted analyses by weighted logistic regression after excluding participants with hyperglycemia, with the aim of validating the stability of the results by adjusting for the study population. The results of the weighted logistic regression after inverse probability weighting were still consistent with the previous results. Supplementary Table 2 for details.

The correlation between NI-IR indices and the risk of developing PCa was evaluated by poisson regression

We applied another statistical method to demonstrate that the results of the logistic regression analysis after inverse probability weighting are robust. We performed the analysis by Poisson regression, with the aim of verifying the stability of the results by alternating statistical methods. The relationship between NI-IR indices and the risk of PCa was assessed by poisson regression, displayed consistent results. Supplementary Table 3 for details.

Discussion

Our study displayed that there were significant positive correlations between NI-IR indices and the risk of PCa. There was an interaction between insulin resistance and MPV, demonstrating that insulin resistance and platelets may have an important role in the mechanism of PCa development.

Connection of insulin resistance, hyperinsulinemia, and hyperlipidemia to obesity can create an environment conducive to tumors [36]. Insulin resistance and insulin-like growth factor-1 (IGF-I) abnormalities as emerging biological mechanisms linking obesity to PCa [9, 37]. IGF-1 promotes cell proliferation and inhibits apoptosis, and is considered an important growth factor in PCa, that may raise the risk of various cancers, including PCa [38–42]. Insulin/insulin-like growth factor (IGF) axis, hyperglycemia, and inflammatory cytokines provide a good environment for cancer cell proliferation and metastasis: insulin/IGF axis activates metabolic and mitogenic signaling pathways, hyperglycemia feeds cancer cell growth, and inflammatory cytokines influence cancer cell apoptosis [8, 43]. Meanwhile, there is cross-reactivity between insulin and IGF-1 receptor [44]. On the one hand, hyperinsulinemia and IGF-I are involved in tumor development and progression in insulin-resistant patients by promoting cell proliferation and inhibiting apoptosis. On the other hand, chronic hyperinsulinemia may stimulate carcinogenesis either directly through insulin receptors or indirectly through insulin-like growth factor receptors (IGF-1Rs). Insulin and IGF-1 can similarly promote PCa growth through trans-activation of the androgen receptor (AR) since PCa is a hormone-dependent cancer

Table 3 The correlation between NI-IR indices and the risk of developing PCa after inverse probability weighting

Variables	Model 1		Model 2		Model 3	
	OR(95%CI)	*P*	OR(95%CI)	*P*	OR(95%CI)	*P*
[a]ZJU index						
Continuous	1.206(1.181–1.232)	< 0.001	1.314(1.275–1.354)	< 0.001	1.337 (1.296–1.379)	< 0.001
Categories		< 0.001		< 0.001		< 0.001
Q1(≤ 31.57)	Reference		Reference		Reference	
Q2(31.58—34.04)	1.494(1.141–1.957)	0.003	2.377(1.650–3.424)	< 0.001	2.586 (1.799–3.717)	< 0.001
Q3(34.05—35.87)	1.942(1.491–2.528)	< 0.001	3.127(2.185–4.475)	< 0.001	3.555 (2.478–5.099)	< 0.001
Q4(35.88—38.34)	3.937(3.072–5.046)	< 0.001	9.297(6.537–13.223)	< 0.001	9.874(6.927–14.074)	< 0.001
Q5(≥ 38.35)	5.686(4.422–7.311)	< 0.001	12.749(8.917–18.227)	< 0.001	15.592 (10.809–22.492)	< 0.001
[b]TyG index						
Continuous	3.010(2.560–3.539)	< 0.001	4.880 (3.906–6.097)	< 0.001	5.300 (4.208–6.675)	< 0.001
Categories		< 0.001		< 0.001		< 0.001
Q1(≤ 8.14)	Reference		Reference		Reference	
Q2(8.15—8.45)	1.799(1.396–2.320)	< 0.001	1.448 (1.039–2.019)	0.029	1.749 (1.246–2.457)	0.001
Q3(8.46—8.73)	2.110(1.639–2.716)	< 0.001	2.101 (1.514–2.915)	< 0.001	2.686 (1.902–3.791)	< 0.001
Q4(8.74—8.98)	2.124(1.652–2.732)	< 0.001	2.483 (1.792–3.441)	< 0.001	3.087 (2.197–4.336)	< 0.001
Q5(≥ 8.99)	4.639(3.624–5.937)	< 0.001	6.052 (4.356–8.409)	< 0.001	7.306 (5.182–10.301)	< 0.001
[b]TG/HDL-c						
Continuous	1.520(1.438–1.607)	< 0.001	1.433 (1.339–1.533)	< 0.001	1.431 (1.335–1.534)	< 0.001
Categories		< 0.001		< 0.001		< 0.001
Q1(≤ 1.64)	Reference		Reference		Reference	
Q2(1.65—2.24)	2.168(1.673–2.809)	< 0.001	1.988 (1.445–2.734)	< 0.001	1.800 (1.296–2.499)	< 0.001
Q3(2.25—2.96)	1.813(1.394–2.358)	< 0.001	2.118 (1.535–2.922)	< 0.001	2.209 (1.587–3.074)	< 0.001
Q4(2.97—3.96)	2.682(2.076–3.463)	< 0.001	2.216 (1.610–3.050)	< 0.001	2.121 (1.529–2.943)	< 0.001
Q5(≥ 3.97)	5.975(4.637–7.700)	< 0.001	4.727 (3.445–6.486)	< 0.001	4.790 (3.459–6.632)	< 0.001
[b]METS-IR						
Continuous	1.119(1.104–1.133)	< 0.001	1.126 (1.107–1.145)	< 0.001	1.129 (1.110–1.149)	< 0.001
Categories		< 0.001		< 0.001		< 0.001
Q1(≤ 34.21)	Reference		Reference		Reference	
Q2(34.22—37.89)	2.011(1.535–2.634)	< 0.001	2.857 (2.002–4.077)	< 0.001	3.276 (2.276–4.715)	< 0.001
Q3(37.90—41.13)	2.229(1.705–2.914)	< 0.001	2.957 (2.070–4.224)	< 0.001	2.895 (2.018–4.155)	< 0.001
Q4(41.14—44.96)	3.552(2.735–4.613)	< 0.001	5.278 (3.719–7.491)	< 0.001	5.666 (3.962–8.102)	< 0.001
Q5(≥ 44.97)	6.991(5.385–9.077)	< 0.001	8.600 (6.048–12.229)	< 0.001	9.844 (6.862–14.121)	< 0.001

Model 1: Crude; unadjusted model

Model 2:

[a] Adjusted for red blood cell ($\times 10^{12}$/L), hemoglobin (g/L), mean corpuscular volume (fl), mean corpuscular hemoglobin concentration (g/L), red cell distribution width (%), plateletocrit (%), platelet distribution width (%), lactate dehydrogenase (U/L),γ-glutamyl transpeptidase (U/L), alkaline phosphatase (U/L), blood potassium (mmol/L), blood sodium (mmol/L), blood calcium (mmol/L), serum phosphorus (mmol/L), serum creatinine (μmol/L)

[b] Adjusted for red blood cell ($\times 10^{12}$/L), hemoglobin (g/L), mean corpuscular volume (fl), mean corpuscular hemoglobin concentration (g/L), red cell distribution width (%), plateletocrit (%), platelet distribution width (%), lactate dehydrogenase (U/L), γ-glutamyl transpeptidase (U/L), alkaline phosphatase (U/L), blood potassium (mmol/L), blood sodium (mmol/L), blood calcium (mmol/L), serum phosphorus (mmol/L), serum creatinine (μmol/L), aspartate aminotransferase (AST) (U/L), alanine aminotransferase (ALT) (U/L)

Model 3:

[a] Adjusted for red blood cell ($\times 10^{12}$/L), hemoglobin (g/L), mean corpuscular volume (fl), mean corpuscular hemoglobin concentration (g/L), red cell distribution width (%), plateletocrit (%), platelet distribution width (%), lactate dehydrogenase (U/L),γ-glutamyl transpeptidase (U/L), alkaline phosphatase (U/L), blood potassium (mmol/L), blood sodium (mmol/L), blood calcium (mmol/L), serum phosphorus (mmol/L), serum creatinine (μmol/L), mean platelet volume (MPV) (fl)

[b] Adjusted for red blood cell ($\times 10^{12}$/L), hemoglobin (g/L), mean corpuscular volume (fl), mean corpuscular hemoglobin concentration (g/L), red cell distribution width (%), plateletocrit (%), platelet distribution width (%), lactate dehydrogenase (U/L), γ-glutamyl transpeptidase (U/L), alkaline phosphatase (U/L), blood potassium (mmol/L), blood sodium (mmol/L), blood calcium (mmol/L), serum phosphorus (mmol/L), serum creatinine (μmol/L), aspartate aminotransferase (AST) (U/L), alanine aminotransferase (ALT) (U/L), mean platelet volume (MPV) (f1)

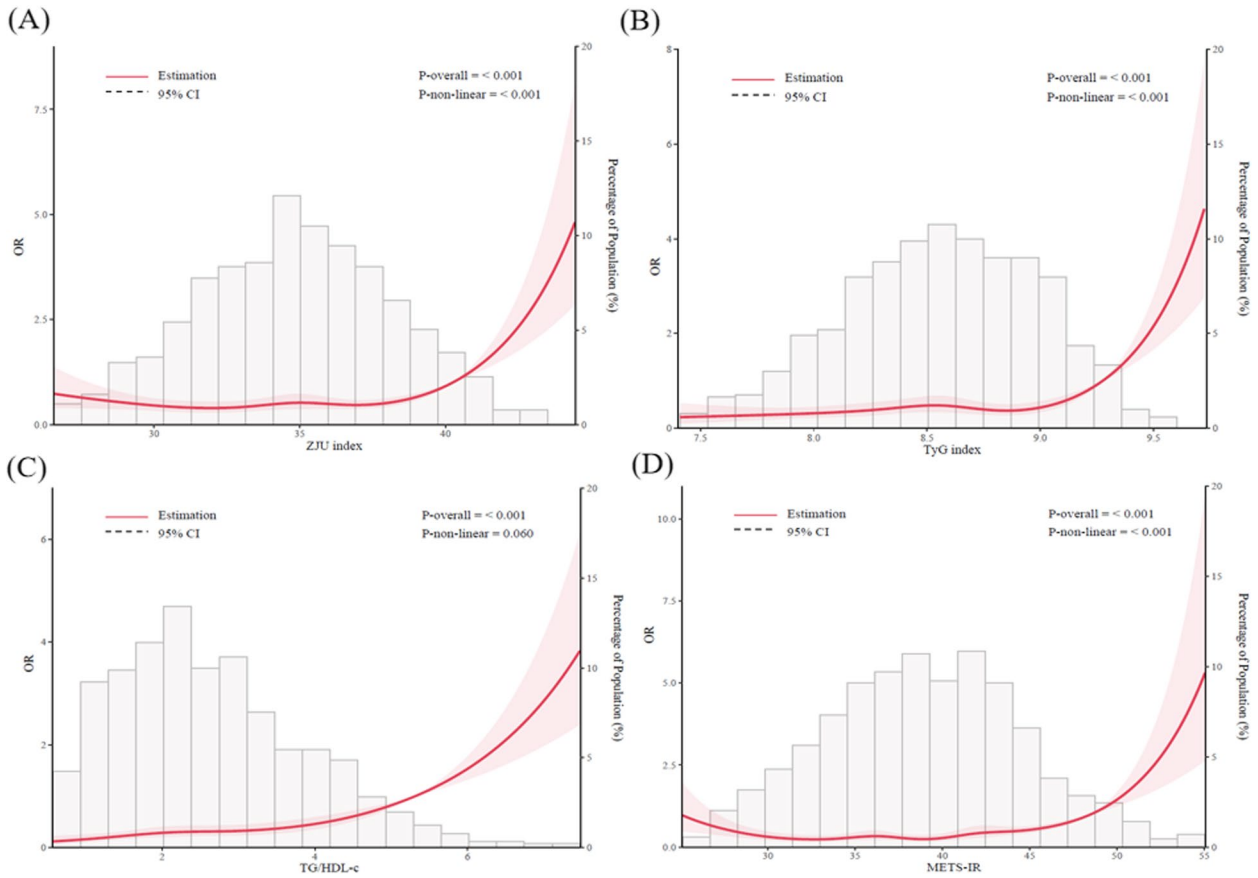

Fig. 1 Relationship between NI-IR indices and PCa

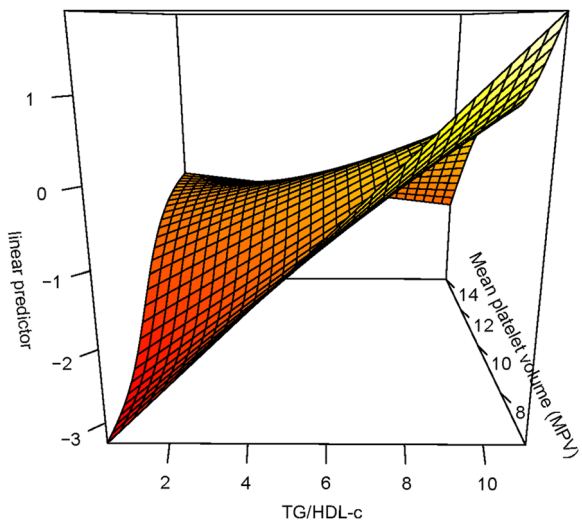

Fig. 2 Interaction test on the basis of GAM between NI-IR indices and MPV on PCa

[45]. Insulin resistance is often accompanied by chronic low-grade inflammation [46]. Meanwhile, inflammatory infections can lead to reduced platelet counts for several reasons: (1) Infections can directly damage or mediate through immune cells, causing destruction of bone marrow megakaryocytes or stromal cells, which reduces platelet production. (2) Platelets interact with neutrophils, leading to the decline of platelets due to rapid platelet consumption. (3) The activation of the complement system and the production of platelet autoantibodies during inflammation, causing an increase in platelet destruction, and the disruption of tubular wall integrity also leads to platelet loss [47, 48]. Inflammatory factors can cause platelet abnormalities, and platelets likewise participate in or exacerbate the inflammatory response [49]. Hyperinsulinism, inflammation work together in PCa development and progression [37, 50].

Within the tumor, tumor cells and various non-tumor cells form the tumor microenvironment. Tumor microenvironment is an important component of tumors, and plays an important role in tumorigenesis, metastasis and immunotherapy [51]. Platelets leak into the tumor microenvironment through tumor neovascularization.

Platelet-tumor cell interactions can influence the biological behavior of tumor cells, through platelet activation, surface receptors, and released factors, and play a key role in promoting tumor growth and dissemination [52, 53]. Platelets perform multiple roles in cancer biology, with the help of platelet-associated molecules in the tumor microenvironment: The endocytosis mechanism of platelets can regulate the tumor microenvironment, by taking up and storing proteins from the tumor [54]; platelets regulate vascular structure and maturation in the tumor microenvironment and promote tumor growth [53]; platelet-derived particles (PMPs) transfer RNA to tumor cells, modulate tumor cell gene expression, and influence tumor progression [55]. Platelet and tumor cell interactions promote tumor metastasis, playing an important role in all stages of tumor progression: to begin with, the tumor cells leave the primary growth site and enter the blood circulation system, and survived by platelet mediated protection. Subsequently, when circulating tumor cells (ctc) enter the blood circulation, platelets immediately combine with ctc and form TCIPA (i.e., platelet-platelet, platelet-tumor, tumor-platelet-leukocyte aggregation) around them, protects ctc from high shear stress and immune surveillance in the blood stream, promotes tumor metastasis, and increases the risk of thrombosis. At the same time, the complex interactions between platelets and tumor cells provide the underlying components for tumor growth and metastasis [56]. Platelets can release growth factors that stimulate tumor growth and angiogenesis, promote tumor cell survival, and contribute to adverse tumor-stroma interactions, leading to increased metastasis and contributing to tumor development [57, 58]. Platelets are protective against tumor cells. PCa cells co-cultured with platelets under stressful conditions have been shown to have significantly less cell death and apoptosis [59]. Consequently, in the presence of platelets, tumor cells and ctc may acquire a highly dynamic and invasive phenotype [59].

Metabolic disorders cause changes in platelet function that increase the risk of atherosclerosis [60]. Platelets mediate link between atherosclerosis and cancer [61]. Arterial stiffness increases in insulin-resistant states are associated with mechanisms related to endothelial cell (EC) and vascular smooth muscle cell (VSMC) sclerosis [62–64]. Hyperglycemia, hyperinsulinemia, and insulin resistance lead to impairment of endothelial function, endothelial dysfunction is also at the core of many cardiovascular diseases [65, 66]. The dysfunctional endothelium is exposed to an inflammatory tumour microenvironment that promotes tumour progression and metastasis [67]. On the one hand, IGF-I receptors are involved in metabolic homeostasis. On the other hand, they act directly on vascular smooth muscle cells (VSMCs) and are involved in some stages of the atherosclerotic process [68–70]. The prospective follow-up study revealed that a high risk score for atherosclerosis was associated with an increased risk of future cancers [71].

Hyperinsulinemia and inflammation may be potential mechanisms connecting dietary patterns to aggressive PCa risk [72]. For PCa patients, dietary patterns that limit chronic systemic inflammation and insulin hypersecretion may improve survival, especially when incorporated with an active lifestyle [73]. Insulin resistance is mediated by fat deposition in subcutaneous or peripheral areas, so prevention of adverse metabolic risk is achieved by preventing fat gain [74]. Those with a healthy lifestyle based on a low insulin diet and physical activity had a significantly lower rate of fatal PCa, compared to those with an unhealthy lifestyle [75–77]. Adhering to a dietary pattern dominated by red meat, processed meats, refined grains and sugar-sweetened beverages increases the risk of PCa, and adherence to a healthy diet that includes fruits, vegetables, and whole grains can reduce the risk of PCa [78]. The improved insulin sensitivity in patients with insulin resistance may lead to a significant reduction in platelet activation, thus reducing complications associated with platelet overactivation [22].

Strengths and limitations

The strength of this study is the application of the inverse probability weighting method, which balances the case and control groups for age. We adjusted as many confounding factors as possible to minimize interference. Moreover, the ZJU index and other widely used NI-IR indices were analyzed, and showed good agreement. The primary limitation is that our study was a cross-sectional design, a causal relationship could not be inferred. Our study is a single-center study in China, population sample is only from the First Affiliated Hospital of Xinjiang Medical University, and may be limited by regional and population characteristics, which may affect the universality of the results. The representativeness of the study population is relatively weak, and the extrapolation of the results is limited to some extent. Lifestyle and behavioral factors were not adequately investigated in our study. We will continue to enroll larger samples and follow up in the future.

Conclusions

In summary, ZJU index, TyG index, TG/HDL-c, as well as METS-IR were significantly related to PCa risk, suggesting that insulin resistance associated with PCa. By monitoring these indicators, healthcare decisions and risk management for PCa patients can be improved in advance. The interaction between MPV and insulin

resistance may further elevate the risk of PCa, further reflecting the complexity of the association with insulin resistance and PCa, and providing new strategies for targeted prevention and treatment of PCa.

Abbreviations

PCa	Prostate cancer
NI-IR	Non-insulin-based insulin resistance indices
MPV	Mean platelet volume
ZJU index	Zhejiang University index
TyG index	Triglyceride-glucose index
TG/HDL-c	Ratio of triglycerides to high-density lipoprotein cholesterol
METS-IR	Metabolic score for insulin resistance
GAM	Generalized additive model

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

Supplementary Material 6.

Supplementary Material 7.

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Authors' contributions
J.W. wrote the main manuscript text , prepared figures and tables. H.A. approved the final draft. N.T. authored or reviewed drafts of the article, and approved the final draft. All authors reviewed the manuscript.

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Data availability
The data were acquired by queries to the authors.

Declarations

Ethics approval and consent to participate
Our research adhered to the Declaration of Helsinki. This study was approved by Ethics Committee of First Affiliated Hospital of Xinjiang Medical University (Ethical Application: 20220308–166). All participants provided informed consent to participate in the study.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]College of Public Health, Xinjiang Medical University, Xinjiang Uygur Autonomous Region, Urumqi, China. [2]Department of Urology, The First Affiliated Hospital of Xinjiang Medical University, Xinjiang Uygur Autonomous Region, Urumqi, China.

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